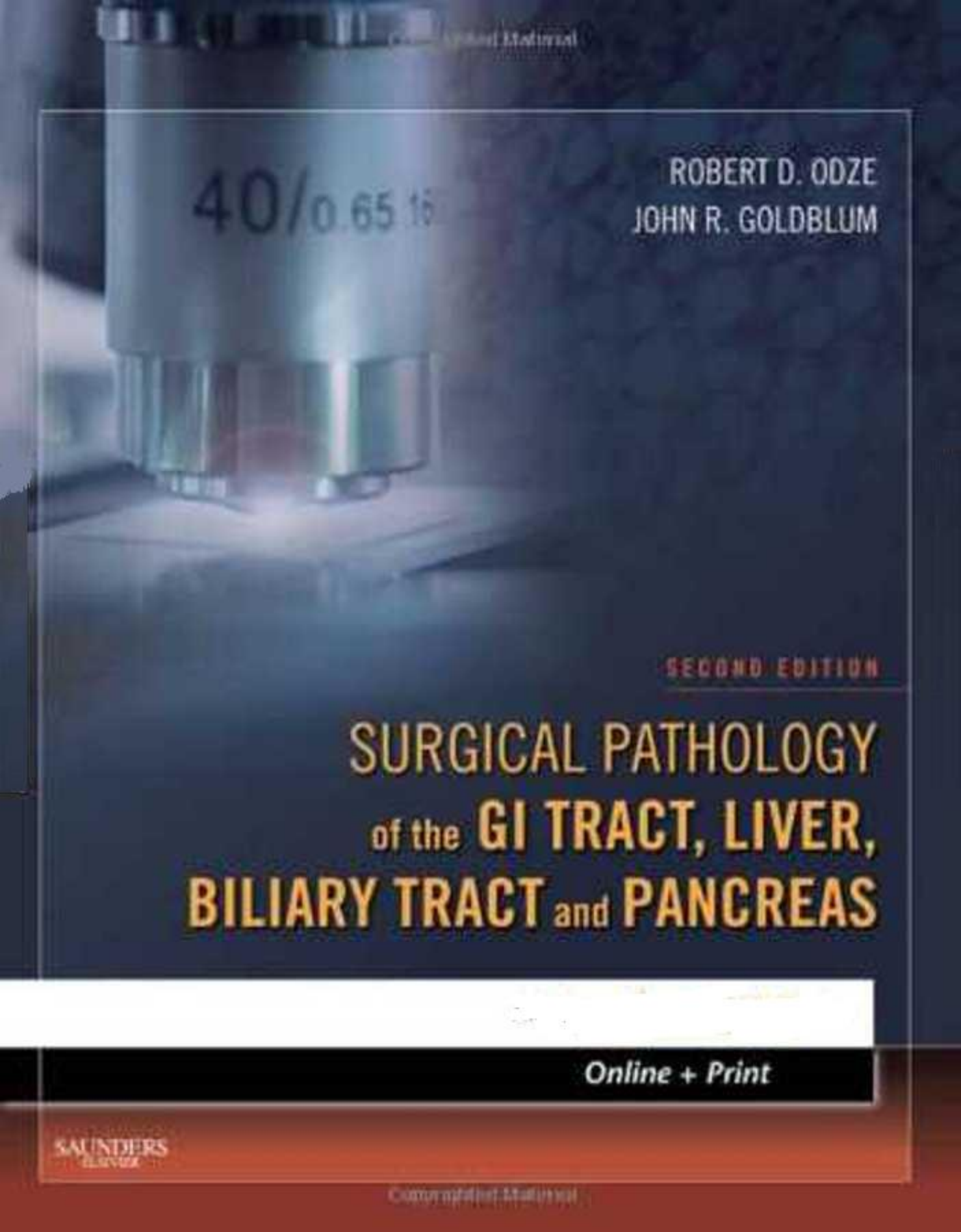
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JOHN R. GOLDBLUM
SECOND EDITION
SURGICAL PATHOLOGY
of the GI TRACT, LIVER,
BILIARY TRACT and PANCREAS
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SURGICAL PATHOLOGY OF THE GI TRACT, LIVER, BILIARY TRACT, AND PANCREAS

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To my family and particularly my late mother, Natasha, who is my hero in life.

ROBERT D. ODZE, MD, FRCP(C)

To those whom I hold most dear: my wife, Asmita; my children, Andrew, Ryan, Janavi, and Raedan; my dear mother, Bette; my late father, Raymond; and the rest of the Goldblum and Shirali families, whom I also cherish.

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Preface

Surgical Pathology of the GI Tract, Liver, Biliary Tract, and Pancreas was originally conceived on the basis of our perceived need in academic surgical pathology for a textbook that includes diseases of all organs traditionally considered part of the field of "gastrointestinal pathology"—the tubular gut, liver, gallbladder, biliary tract, and pancreas—all under one cover. The second edition represents a significant improvement over the first edition in many ways, outlined in the following few paragraphs:

1. Overall, the book is 40% larger. For instance, five new chapters have been added, and these are titled "Screening and Surveillance Guidelines in Gastroenterology," "Congenital and Developmental Disorders of the GI Tract," "GI Tract Enteropathies of Infancy and Childhood," "Vascular Disorders of the GI Tract," and "Fatty Liver Disease."
2. Additional sections on normal histology of the GI tract, pancreatico-biliary tract, and liver have been added to chapters 1, 29, and 36, respectively.
3. Tables to outline specific differential diagnostic points helpful for surgical pathologists at the level of the microscope have been increased in number and expanded.
4. The number (and quality) of color photographs have been increased by at least 30%.
5. A succinct and clinically relevant discussion of the key molecular aspects of tumor progression and risk assessment have been added to all chapters that cover neoplastic disorders.
6. An outline has been added to the beginning of all chapters in order to expedite searching for specific topics of interest.
7. All chapters have been updated to include the most current references, concepts, data, and controversies.
8. Diagnostic algorithms have been added to many chapters in order to simplify the evaluation of diagnostically challenging entities.
9. The new edition includes an online version that readers can access from any laptop computer, world-wide.

In the second edition, we have, once again, paid special attention to providing only the most relevant, up-to-date clinical, etiologic, and management information necessary for surgical pathologists to make clinically relevant diagnoses. This continues to be a morphology-based textbook with particular emphasis on histologic methods that can help differentiate diseases based on evaluation of biopsy and resection specimens. However, gastroenterologists, surgeons, and residents/fellows in training may also find this textbook of interest because of the accent on clinical-pathologic associations. The second edition is even more user friendly than the first edition, and it is organized in a method that helps pathologists gain access to diagnostic information quickly without having to waste time leafing through the index and turning pages. The overall organization of the textbook remains the same as in the first edition: part 1 represents disorders of the gastrointestinal tract; part 2, the gallbladder, extrahepatic biliary tract, and pancreas; and part 3, the liver. In each part, an introductory chapter on pertinent tissue processing techniques and normal histology, and a well-illustrated chapter on diagnostic cytology of each of the major organ systems, are included. Subsequent chapters in each section are separated into general disease categories, such as systemic disorders, inflammatory disorders, polyps, epithelial neoplasms, and other types of neoplasms, similar to the method used by pathologists to evaluate tissue specimens. In addition, the liver section is divided into chapters based on major patterns of injury, recapitulating the approach to liver biopsy assessment. Of course, all chapters were written by pathologists with a special interest or expertise in a particular field. Finally, the editors have paid careful attention to providing a consistent style of writing, structure, and content from chapter to chapter.

We are confident that the second edition represents a bigger, better, and, ultimately, state-of-the-art textbook on the pathology of the gastrointestinal system, liver, biliary tract, and pancreas that can be enjoyed by pathologists and clinicians worldwide.

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Acknowledgments

As in the first edition, many individuals contributed greatly to the conception, editing, and production of this textbook. The editors are appreciative of all the technical, administrative, and support staff involved in the production of this textbook and, particularly, Kendra Glueck-Abramson and Kathleen Ranney at the Brigham and Women's Hospital and Cleveland Clinic, respectively. We would also like to thank William Schmitt, Liliana Kim, and Linda Grigg for their patience, support, and endless dedication to helping us produce an excellent quality textbook, and John Alpert for his book cover layout.

From a professional point of view, I am greatly indebted to my longtime friends and mentors Dr. Donald Antonioli, who, unfortunately, has recently retired from academic pathology and Dr. Harvey Goldman, who continues to represent a pillar of knowledge in GI pathology. Their continued support and helpful advice during the long and sometimes tedious process of creating a textbook was very much appreciated. As all academic pathologists realize, creating a textbook of this magnitude requires a great deal of time and support, which was provided to me initially by Dr. Ramsy Cotran and later by Dr. Michael Gimbrone. For that, I am grateful. Similarly, Dr. Goldblum would like to acknowledge his mentor in gastrointestinal pathology, Dr. Henry Appelman.

On a personal level, I would like to thank all members of my family, Pilar, and my extended family in Boston, for their love, friendship, advice, and support in my personal and professional endeavors. In addition, I am eternally grateful and fortunate to have had the opportunity to benefit from the inspiration and love of my late dear mother, Natasha Odze, whose courage, wisdom, and outlook on life has always served as the basis for my own personal and academic endeavors. My heart goes out to all other individuals who have close family members or friends suffering from Alzheimer's disease or senile dementia.

Finally, we would like to thank all of the authors of the second edition for their excellent contributions and for the patience required to labor through the editorial process. We are particularly grateful to Dr. James Crawford for his role as Associate Editor of this textbook.

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SECTION I

General Pathology of the GI Tract

CHAPTER 1

GI Tract Endoscopic and Tissue Processing Techniques and Normal Histology

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Introduction

Endoscopy provides a unique opportunity to visualize the mucosal surface of the GI tract. When considered within the context of a specific clinical picture, endoscopic images may be all that is needed to make a specific diagnosis, or provide sound clinical management.[1] However, more often than not, endoscopists need to sample tissue. Examination by a qualified pathologist of specimens obtained at endoscopy is a routine and critical part of managing patients with disorders of the alimentary tract. The purpose of this opening chapter is to orient the pathologist to the clinical and technical considerations unique to specimens obtained endoscopically from the alimentary tract. This is followed by a discussion of the normal anatomy of the tubal gut.

Bowel Preparation

The effectiveness of endoscopy depends, in part, on the quality of bowel preparation.[2] Preparation of the upper GI tract for endoscopy consists, at minimum, of a 6-hour fast. Preparation for colonoscopy is achieved by use of oral purging agents, either with or without enemas. Most colonoscopy preparation regimens include the use of a clear liquid diet for 1 to 3 days, cleansing with oral polyethylene glycol (PEG)-electrolyte solution or sodium phosphate lavage solutions, and use of oral laxatives or prokinetic agents, such as magnesium citrate, metoclopramide, cisapride, and senna, as well as rectal enemas (Table 1-1). In general, vomiting is reported more frequently with oral PEG-based high-volume lavage regimens than with oral bowel prokinetics.[3] However, nausea, vomiting, and abdominal cramps are comparable between PEG lavage and oral sodium phosphate regimens.[4] PEG lavage regimens reportedly provide more consistent cleansing.[5,6] Purgative- and laxative-based regimens are more likely to cause flattening of surface epithelial cells, goblet cell depletion, and lamina propria edema; normo-osmotic electrolyte solutions, such as PEG-based solutions, are better agents for preserving mucosal histology.[7] In the most severe form of mucosal damage from purgatives, sloughing of the surface epithelium, neutrophilic infiltration of the lamina propria, and hemorrhage may be encountered, and the changes may even resemble mild pseudomembranous colitis.[8] Chemical-induced colitis, from inadequate cleansing of endoscopic instruments, also has been reported. Mucosal changes in this situation may resemble pseudomembranous colitis, both endoscopically and microscopically.[9]

TABLE 1-1 Common Preparation Methods for Colonoscopy

48-hr clear liquid diet, 240-mL magnesium citrate PO, senna derivative laxative (e.g., X-Prep), 12 hr NPO.
48-hr clear liquid diet, senna derivative laxative, rectal enema, 12 hr NPO.
24-hr clear liquid diet, 240 mL magnesium citrate PO, or 4 L PEG-electrolyte lavage,* 12 hr NPO.
24-hr clear liquid diet, 2 L PEG-electrolyte lavage, cascara-based laxative, 12 hr NPO.
24-hr clear liquid diet, oral sodium phosphate,† magnesium citrate PO, 12 hr NPO.
24-hr clear liquid diet, oral sodium phosphate, rectal enema.

**PEG-electrolyte solutions include CoLyte, GoLYTELY, NuLytely, Klean-Prep, and Norgine.*
†Oral sodium phosphate solutions include Fleets Phosphosoda, De Witt Phosphosoda.
NPO, nulla per os (nothing by mouth); PEG, polyethylene glycol; PO, per os (by mouth).

Methods for Obtaining Tissue Specimens

There is a limited number of methods available for obtaining tissue during endoscopy. This section describes several of these methods and the common situations in which they are used.

ENDOSCOPIC PINCH BIOPSY

Pinch biopsy, performed with the use of a biopsy forceps during endoscopy, is the most frequent form of tissue sampling; the biopsy site is usually fully visualized at the time of sampling. Suction capsule biopsy requires fluoroscopic guidance to position a long tube with the biopsy apparatus, and is done separately from endoscopy without visualization. Suction capsule biopsy, without bowel visualization, is still performed in some centers, but it is less successful than endoscopy-guided biopsies in obtaining tissue and, thus, has fallen out of favor.[10] Pinch biopsies may be small or large (the latter are referred to as "jumbo" biopsies) and can be obtained with or without use of electrocautery. Electrocautery has value for hemostasis and destruction of residual tissue, but introduces burn artifact into the harvested tissue.

All standard biopsy forceps have a similar design (Fig. 1-1). The sampling portion consists of a pair of small cups, or a paired set of teeth, that are in apposition when closed. In this manner, they can be passed through the 2.8-mm-wide channel of a standard gastroscope or colonoscope. Some biopsy forceps have a spike at the base of the cup or teeth to help seat the forceps against the mucosa. The spike also helps to impale multiple biopsy specimens before the forceps is removed from the endoscope.

After insertion into the endoscope and emerging from the distal end, routine biopsy forceps can be opened to a 4- to 8-mm width. The opened forceps is pressed against

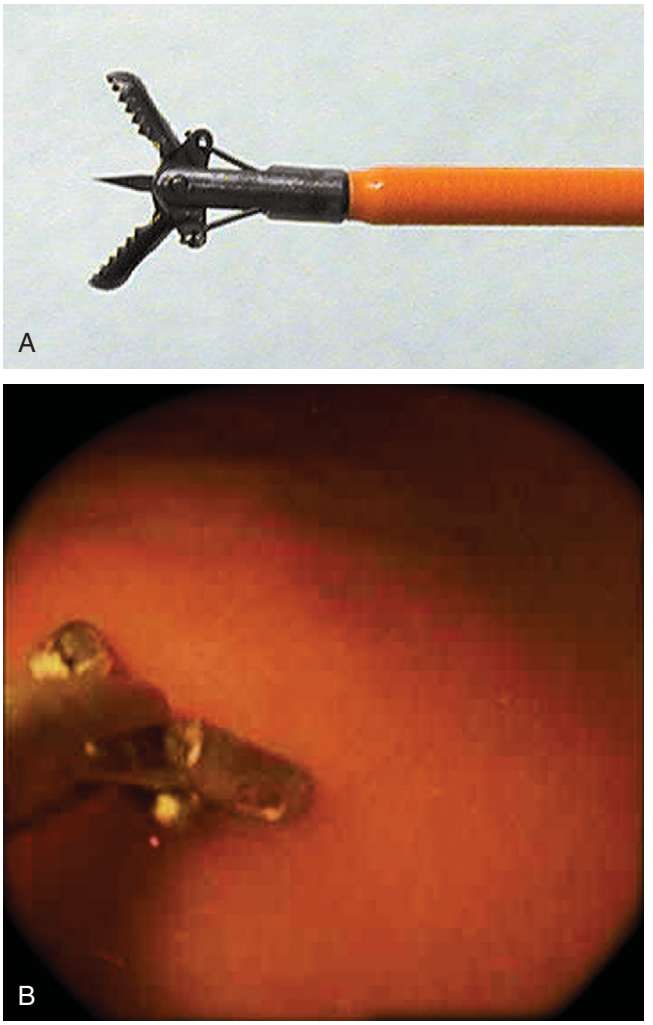

FIGURE 1-1 Endoscopic biopsy forceps. **A,** The biopsy forceps has been opened, revealing two sets of gripping "teeth" and a central spike used to impale the tissue. **B,** The biopsy forceps in use: the biopsy forceps is pressed against the mucosa and subsequently closed to obtain a tissue sample.

the mucosal surface for tissue sampling. Large-cup (jumbo) biopsy forceps have jaws that open to a width of 7 to 9 mm. The biopsy forceps is closed against the mucosal surface, and the endoscopist pulls the forceps away from the mucosa to remove the fragment of tissue. This method often yields samples that include muscularis mucosae, except in regions such as the gastric body, where the mucosal folds are quite thick.[11] The submucosa is sampled occasionally with either standard or jumbo forceps.[12] The sample size varies according to the amount of pressure the endoscopist applies to the forceps. In addition, application of a fully opened biopsy forceps flush against the mucosa before closure usually yields larger pieces of tissue, compared with those obtained by tangential sampling or incomplete opening of the forceps. In general, biopsy specimens are 4 to 8 mm in length.[13,14] The forceps shape does not impart a significant difference in either size or adequacy of biopsy specimens.[13] Single-use disposable biopsy forceps also have been shown to provide excellent samples.[15] In essence, there are no differences in the quality of tissue samples obtained among the dozen or more biopsy forceps currently available, so the primary considerations in the selection of an endoscopic biopsy forceps are usually related to cost and ease of use.[16]

After obtaining biopsy specimens and removing the forceps from the endoscope, an assistant dislodges the tissue fragments from the forceps with a toothpick or a similar small, sharp instrument. The tissue is then placed into a container containing appropriate fixative, and labeled according to instructions provided by the endoscopist.

Specimens obtained with a jumbo forceps often exceed 6 mm or greater in maximum diameter, but these are not necessarily deeper than standard biopsies. Rather, a jumbo forceps provides more mucosa for analysis. This is particularly useful during surveillance tissue sampling, such as in patients with Barrett's esophagus or ulcerative colitis. Jumbo biopsy forceps are as safe as standard biopsy forceps.[17] However, use of jumbo forceps is limited by its diameter because it cannot fit through a standard endoscope accessory channel. Jumbo forceps require a 3.6-mm-diameter channel characteristic of therapeutic endoscopes, which may be less comfortable for patients. In addition, although jumbo biopsy specimens are larger than standard biopsy specimens, this does not necessarily mean samples will be of greater diagnostic value.[18]

The most common indication for mucosal biopsy is for diagnosis of a mucosal abnormality at endoscopy. In addition, it is advantageous to sample normal-appearing mucosa during the evaluation of many conditions to establish "background" features of the mucosa, such as in gastroesophageal reflux disease, nonulcer dyspepsia, diarrhea, and surveillance of premalignant conditions, including Barrett's esophagus and inflammatory bowel disease. The ampulla of Vater may be sampled during surveillance for adenomatous change in familial adenomatous polyposis because the lifetime incidence of ampullary adenomas in these patients exceeds 50%.[19] Biopsy of biliary or pancreatic strictures may be carried out under fluoroscopic guidance during endoscopic retrograde cholangiopancreatography (ERCP) with the use of either standard or specially designed small biopsy forceps.[20] Even gallbladder lesions noted at ERCP may be amenable to endoscopic biopsy.[20] Endoscopy-directed biopsies are extremely safe. In one study of 50,833 consecutive patients who had an upper endoscopy, none had any biopsy-associated complications.[17]

Occasionally, an endoscopist uses a specialized insulated biopsy forceps to sample a small polyp ("hot biopsy"). Remaining tissue is then ablated in situ using electrocautery.[21] Unfortunately, cautery artifact in such small tissue samples often makes histologic interpretation difficult (or impossible).[11,22] In addition, the electrocautery technique carries an excessive risk of perforation due to

deep tissue burn, particularly in the cecum and ascending colon.[23,24] Finally, destruction of residual dysplastic tissue by electrocautery may be incomplete in as many as 17% of cases.[25]

ENDOSCOPIC SNARE POLYPECTOMY

During endoscopy, a loop of wire may be placed around a polypoid lesion that protrudes into the lumen of the gut for the purpose of removing the polyp (Fig. 1-2). This technique is used primarily for colonic polyps, but polyps throughout the alimentary tract may be excised in this manner. Depending on their size, excised polyps are either retrieved through the suction channel of the endoscope, or held by the snare after resection while the colonoscope is removed from the patient. Loss of excised polyps in recesses of the intestinal lumen is an infrequent occurrence.

Many endoscopists have reported successful removal of diminutive polyps (<0.5 cm in diameter) during both "hot" (with electrocautery) and "cold" (without electrocautery) snare polypectomy.[26,27] These endoscopists use small metal snares, termed *mini-snares*, that open to a size of either 1 to 2 cm or 2 to 3 cm. Polyps greater than 0.5 cm in diameter are amenable to snare polypectomy, although the size of the polyp that can be excised may be limited by the size of the loop placed around it (and the endoscopist's estimation of perforation risk). Alternatively, large polyps may be removed in a piecemeal fashion and submitted to pathology in several parts. This usually requires multiple transections of the lesion until the entire polyp has been removed.[21] One caveat with this technique is that identifiable tissue margins may be lost, so that the pathologist is often unable to determine the status of the resection margins.

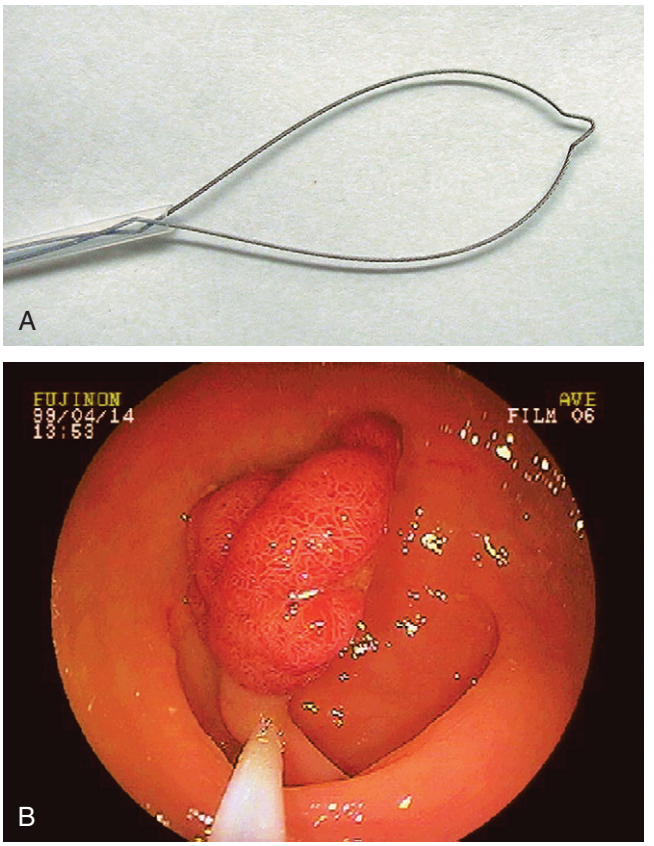

FIGURE 1-2 Endoscopic snare polypectomy. **A,** An open metal snare extends out of a protective plastic sheath. **B,** A polypectomy snare has been placed over a pedunculated polyp and tightened around the polyp stalk. Electrical current is applied through the metal loop of the snare, which helps cut through the stalk and cauterize blood vessels.

A hot snare allows the endoscopist to apply current to a metal wire that cuts through pedunculated polyps at the base. This assists tissue cutting and coagulation. Electrocautery also minimizes bleeding from larger blood vessels located in the stalk of the polyp. Cold polypectomy, without electrical current, avoids use of cautery, thereby limiting the amount of burn artifact in the specimen and minimizing the risk of perforation. In general, the risk of perforation from either mechanical or electrical injury is minimal, but is greater in portions of the colon that are covered by a free serosal surface, such as the transverse colon. Information on the relative risk of clinically significant hemorrhage after "hot" polypectomy is limited, but the risk is generally considered low (0.4%).[28,29] A recent large cross-sectional study from South Korea established that loop polypectomy is only rarely performed without electrical current ("cold"), and this is usually inadvertent owing to failure of application of electrical current.[30] Absence of electrical current is associated with an increased risk of clinically significant postpolypectomy hemorrhage. A higher risk of postpolypectomy hemorrhage also occurs in patients with pedunculated polyps larger than 1.7 cm or with a stalk diameter larger than 0.5 cm, sessile polyps, and malignant lesions.[31]

For polyps excised in one piece, by either hot or cold polypectomy, the polyp base constitutes the surgical margin of resection. This is true for both pedunculated and sessile polyps. For polyps removed by hot snare polypectomy, the cauterized portion of the specimen constitutes the surgical margin. An artificial stalk can be created when large sessile lesions are loop-excised. A true pedunculated polyp, with a stalk, has a narrow base that persists after removal; the base of a sessile polyp is usually as wide as the mucosal surface that is sampled.

Snares are available in a variety of shapes and sizes. Newer types of snares can be rotated, which provides the endoscopist with greater control of snare placement. The choice of snare size is typically based on the size of the lesion being removed. The selection of a particular snare shape usually reflects personal choice.

Snare polypectomy is performed in a similar fashion, whether colonic, esophageal, gastric, or small bowel lesions

are removed. In fact, the ampulla of Vater may be resected by standard snare techniques when an ampullary lesion is noted.[32] The risk of perforation during snare polypectomy is less than 0.1%,[33,34] and perforation generally results from transmural burn secondary to cautery. One technique aimed at decreasing the risk of perforation is to pull the snared polyp away from the mucosa so that less cautery is applied to the underlying tissue.

Another commonly used method is saline-assisted polypectomy.[35,36] A small needle is passed through the endoscope and is inserted into the gut wall adjacent to the polyp. A bolus of normal saline is then injected. Fluid collects within the submucosal plane, thereby "lifting" the mucosal-based polyp away from the muscularis propria. A standard snare polypectomy is then performed, but the cushion of saline insulates the deeper tissue layers from electrical current. Saline-assisted polypectomy is usually reserved for large sessile polyps and, theoretically, results in a decreased rate of polypectomy-associated perforation.

ENDOSCOPIC MUCOSAL RESECTION

The use of a liquid cushion to expand the submucosa and minimize transmural cautery damage is a principal component of endoscopic mucosal resection (EMR). This technique is commonly used to resect premalignant and malignant lesions confined to the mucosa.[37] In general, EMR requires some measure of confidence that a lesion is, in fact, confined to the mucosa or submucosa. Many endoscopists now rely on endoscopic ultrasonography (EUS) to determine the depth of a particular lesion before EMR. The accuracy of high-frequency EUS (15 or 20 MHz) may be as great as 95% for determining whether a lesion is limited to the mucosa,[37] but the availability of EUS and variation in operator experience may limit its general utility.

Several variations of the EMR technique are currently used. Many rely on submucosal injection of liquid, but there is currently no agreement as to the type or quantity of liquid that should be injected.[38] Some endoscopists advocate the use of saline alone. Others add diluted epinephrine to saline in an attempt to constrict small blood vessels at the base of the lesion. Submucosal fluid collections are absorbed. Hence, to lengthen the time that the submucosal cushion lasts, and thus maximize the time available for performing a safe resection, investigators have used hypertonic solution of 3.5% saline or 50% dextrose. Others advocate the use of sodium hyaluronate instead of saline. The quantity of liquid injected also varies. In general, there is agreement that the target lesion should appear endoscopically to be raised by the cushion of liquid before EMR. In fact, failure to lift the lesion despite the generous use of submucosal saline (the so-called nonlifting sign) may be a sensitive indicator that a lesion has spread deeper into the bowel wall.[39]

Two major types of resection techniques are used—those that do not use suction and those that do. When suction is not used, the endoscopist uses a dual-channel endoscope. A snare, passed through one instrument channel, is opened and placed around the lesion. A biopsy forceps passed through the second channel is used to grab the lesion and pull the mucosa through the snare even farther away from the muscularis propria. The snare is then closed around the base of the tented lesion, and electrocautery is applied (Fig. 1-3). This method is referred to as a *lift-and-cut technique*, or a *strip biopsy*.[37,40]

Suction methods of EMR incorporate the use of a cap fitted onto the tip of an endoscope. The cap presents an open surface to the mucosa and creates a short chamber into which the target lesion can be aspirated and held by suction, with the latter applied through a single-channel endoscope. A specialized snare is opened in the cap before aspiration of the lesion. Once the mucosa has been drawn into the cap, the snare may be closed around the lesion and cautery applied in the usual fashion.[37] This technique, also called *aspiration mucosectomy*, has been widely successful for removing lesions throughout the GI tract.[41]

A newer EMR technique is similar to aspiration mucosectomy. However, once a lesion is suctioned into the cap, a tiny rubber ring is released around the base of the lesion, similar to the method used during endoscopic variceal ligation. Once suction is released, the lesion appears contained within a "pseudopolyp" that can be removed by snare cautery. This is known as *band-ligation EMR* (Fig. 1-4).

EMR allows the endoscopist to attempt an en bloc resection and thus potentially completely resect an early malignant lesion. En bloc resection is limited, however, to small lesions (1.5 to 2 cm in largest diameter).[40] If deep margins are positive for neoplasia, surgical resection of the affected region is advocated.[42] Current indications for EMR include superficial carcinoma of the esophagus, or stomach, in patients who are nonoperative candidates, unifocal high-grade (or low-grade) dysplasia in Barrett's esophagus, and large, flat colorectal adenomas regardless of the degree of dysplasia (which might otherwise require piecemeal resection). EMR as a form of primary therapy for small, superficial cancer has not gained popularity in the United States, but is often used in Japan.[37,40,42] EMR may also be indicated as a form of primary therapy for small submucosal lesions, such as rectal carcinoid tumors or leiomyomas. In many cases, the submucosal lesion can be completely resected[43] (Fig. 1-5).

Major complications of EMR include bleeding and perforation. Bleeding occurs in less than 1% to 20% of cases and varies depending on the size of the lesion and its location.[37,40,42] Clinically significant bleeding is rare and usually amenable to endoscopic hemostatic cauterization. Perforation rates are generally lower than 2%. EMR also provides large specimens for pathologic analysis even in the absence of complete resection. Success rates of en bloc resection of early gastric cancers range from 36% to 74%.[40,42]

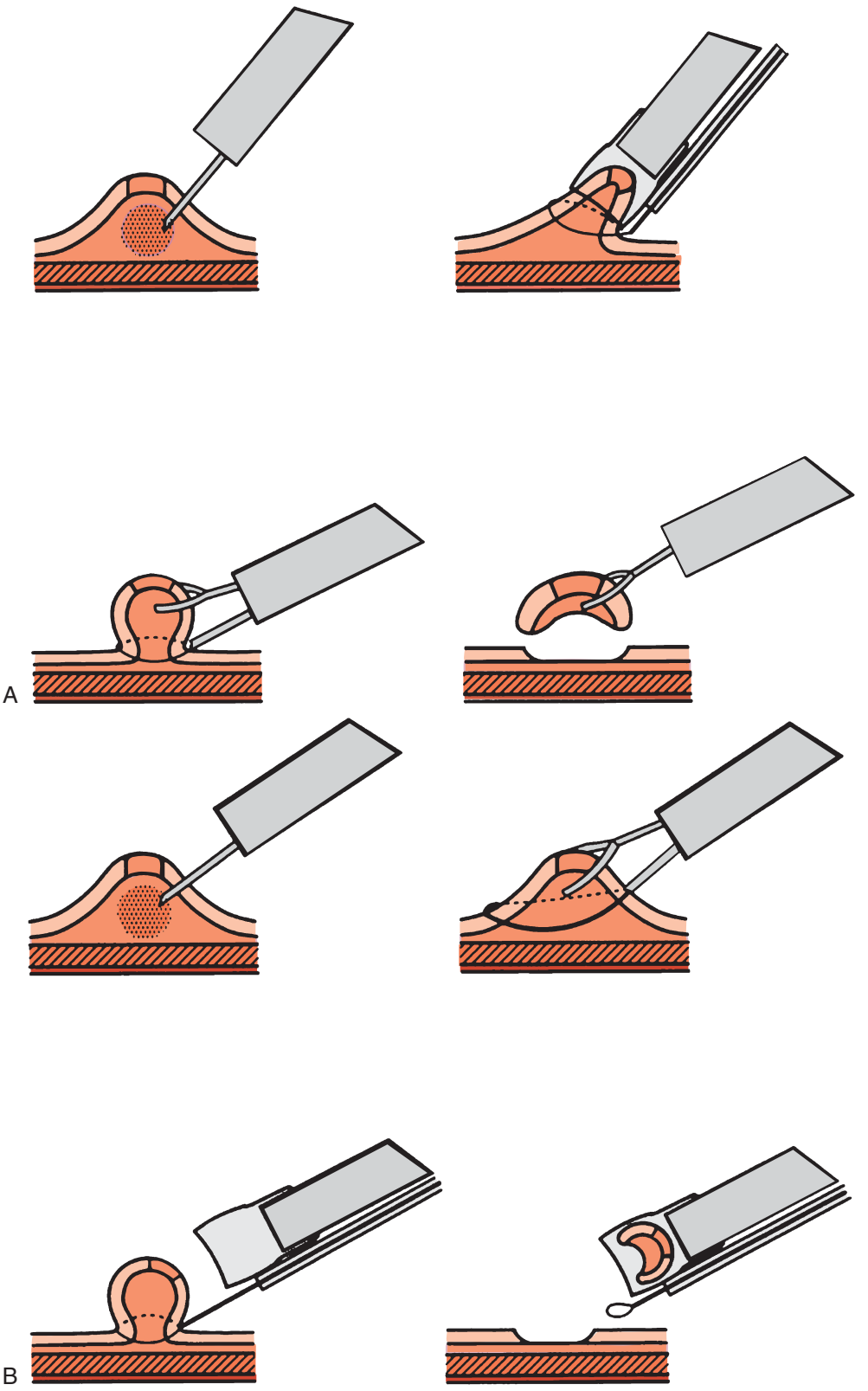

FIGURE 1-3 Endoscopic mucosal resection (EMR). **A,** EMR by strip biopsy: saline is injected into the submucosal layer, and the area is elevated (1). The top of the mound is pulled upward with forceps, and the snare is placed at the base of the lesion (2 and 3). Electrosurgical current is applied through the snare to resect the mucosa, and the lesion is removed (4). **B,** EMR by aspiration: saline is injected into the submucosa, and the tissue is elevated (1). The lesion is aspirated into a plastic cap at the end of the endoscope, and the snare is closed around the lesion (2). The ensnared lesion is released from the cap (3). Electrosurgical current is applied, and the resected lesion is trapped within the cap by aspiration (4). (**A** and **B** reused by permission of the publisher. From Tanabe S, Koizumi W, Kokutou M, et al: Usefulness of endoscopic aspiration mucosectomy as compared with strip biopsy for the treatment of gastric mucosal cancer. Gastrointest Endosc 50:819-822, 1999.)

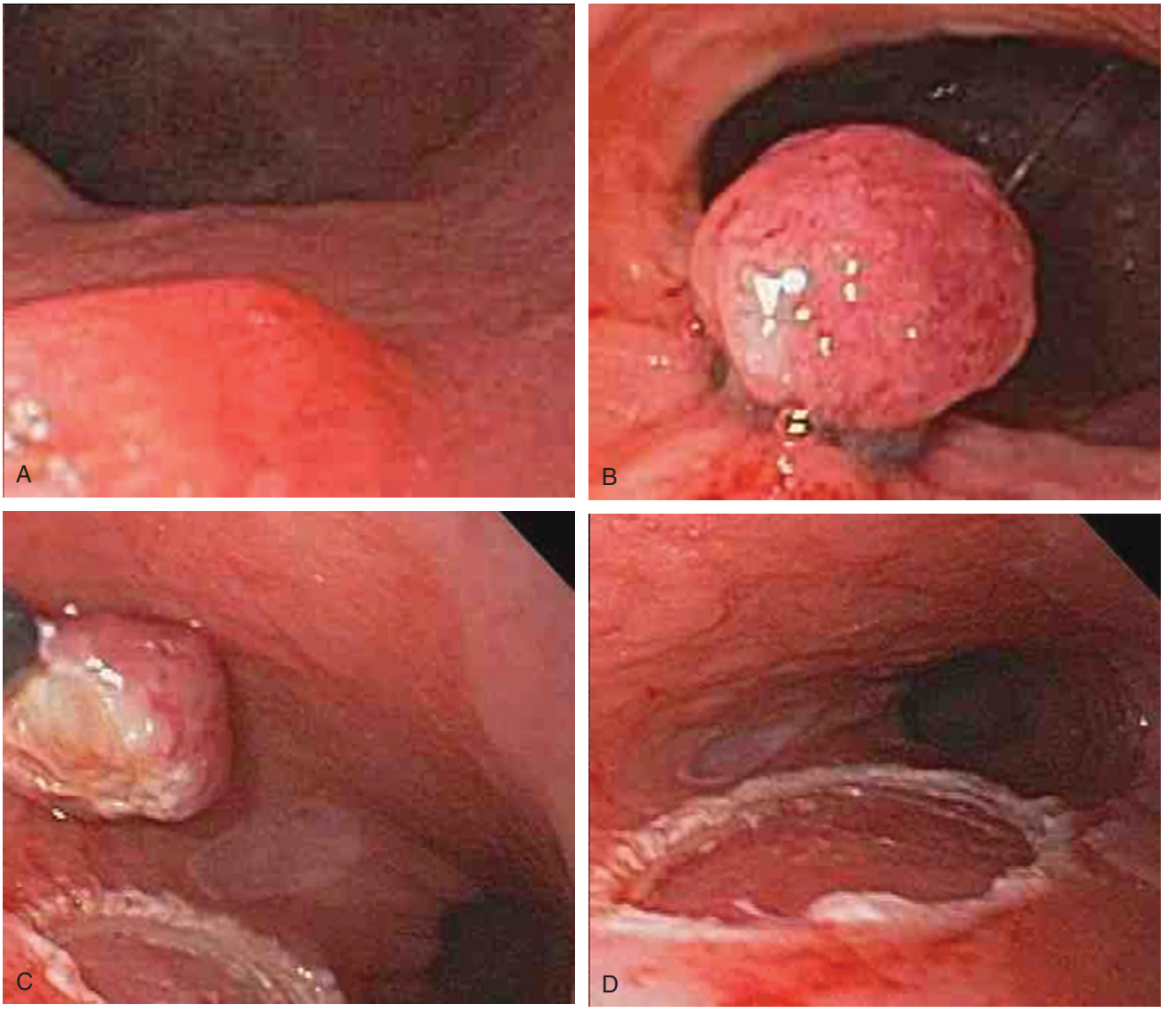

FIGURE 1-4 Band-ligation endoscopic mucosal resection. **A,** A region of endoscopically visible high-grade dysplasia in the esophagus. **B,** A rubber band ligator has been applied to the base of the lesion after aspiration of the mucosa and submucosa into a cap affixed to the end of the endoscope. The result is a polypoid area containing the dysplastic tissue. **C,** The pseudopolyp has been resected by snare cautery and can be retrieved for tissue processing. **D,** The region where dysplasia was present has been removed, leaving a clean-based ulcer.

Methods of Processing Tissue for Pathologic Evaluation

A general framework for processing biopsy specimens is provided in Table 1-2.

FORMALIN

Of the many types of fixatives used for human tissue, 10% buffered formalin remains the standard and is well suited for mucosal biopsies of the gastrointestinal tract. It is inexpensive, harmless to the tissue specimen even after long periods of time, and is compatible with most of the stains commonly used for morphologic assessment. Hollende's solution, B5, and Bouin's fixative have been used for mucosal biopsies because of better preservation of nuclear morphology compared with formalin. However, the heavy metal content of these fixatives creates biohazard disposal problems that are greater than those of formaldehyde-based fixatives. These fixatives also interfere with isolation of nucleic acid from tissue; finding substitute fixatives and new tissue processing techniques are active areas of scientific investigation.

On occasion, the formaldehyde in formalin may be irritating to the eyes and upper respiratory tract of personnel.

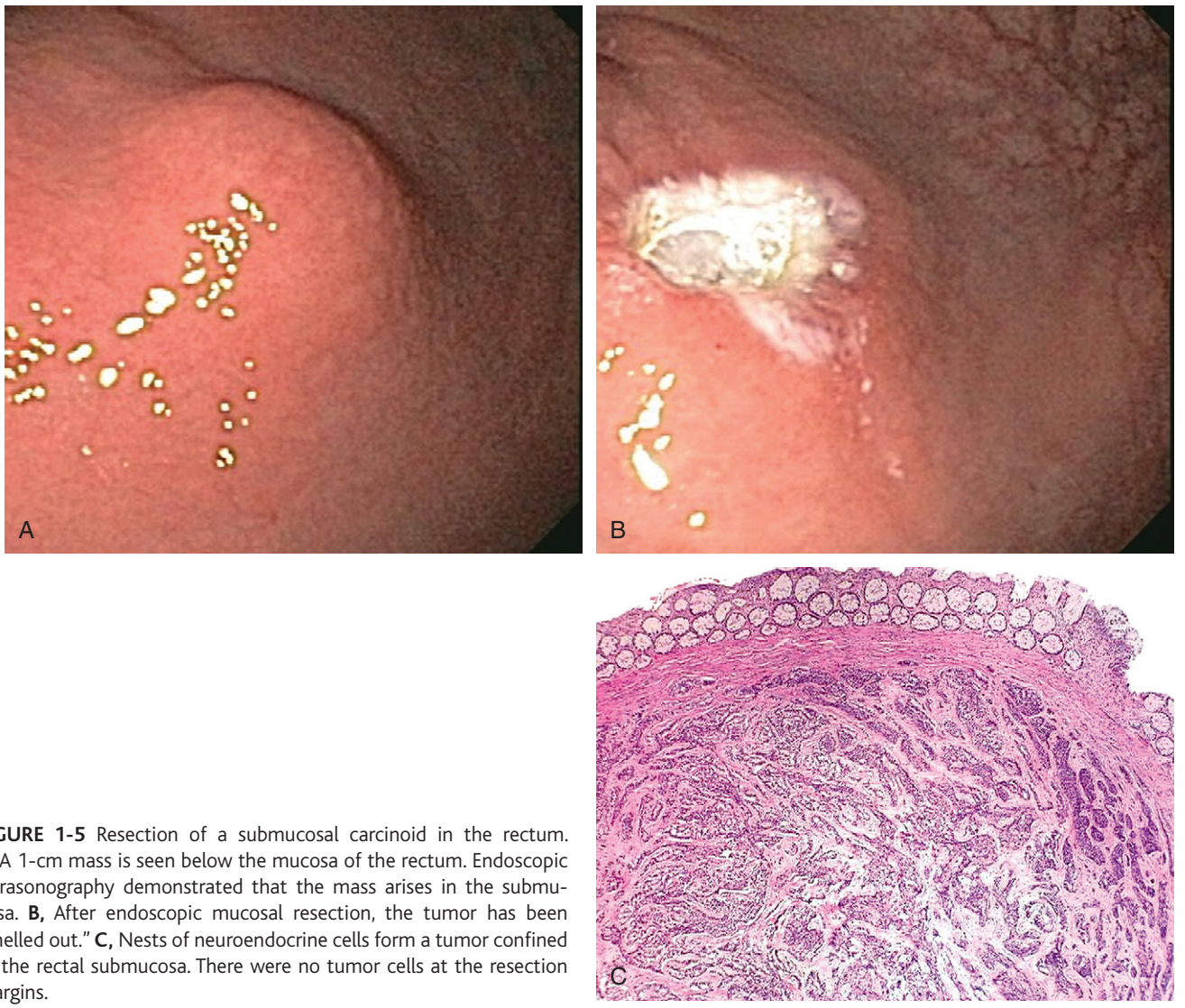

FIGURE 1-5 Resection of a submucosal carcinoid in the rectum. **A,** A 1-cm mass is seen below the mucosa of the rectum. Endoscopic ultrasonography demonstrated that the mass arises in the submucosa. **B,** After endoscopic mucosal resection, the tumor has been "shelled out." **C,** Nests of neuroendocrine cells form a tumor confined to the rectal submucosa. There were no tumor cells at the resection margins.

TABLE 1-2 Techniques of Processing Tissue Specimens Obtained by Endoscopy

Technique	Comment
Formalin fixation	Routine processing of all alimentary tract biopsies; immediate immersion in fixative. Permits immunohistochemistry, molecular analysis.
Flow cytometry	Suspected hematologic malignancy; fresh tissue in sterile culture medium.
Electron microscopy	Suspected poorly differentiated malignancy, infection (e.g., Whipple's disease, microsporidiosis); immediate immersion in electron microscopy fixative.
Electron microscopy fixative only	Suspected systemic mastocytosis, for which plastic-embedded thick sections with toluidine blue staining are optimal for identifying mast cells.
Microbial culture	Suspected viral, fungal, or parasitic infection; sterile tissue.
Biochemical analysis	Suspected metabolic deficiency (e.g., disaccharidase deficiency); frozen tissue.
Cytogenetics*	Suspected neoplasm (benign or malignant); fresh tissue in sterile culture medium.
Cell culture*	Suspected neoplasm (benign or malignant); fresh tissue in sterile culture medium.

**Usually for investigational purposes only.*

There also is public debate over its potential as a carcinogen.[44] However, the level at which formalin is considered carcinogenic is considered well above the level that causes sensory irritation, which has a threshold of 1.0 part per million (ppm).[45] Proper ventilation should be used to maintain exposure below 1.0 ppm. This is the lowest concentration that may exert a cytotoxic effect in humans.[44,46] This consideration applies to pathology suites. Typical occupational exposure in endoscopy suites is exceedingly brief, so that special ventilation is not usually required in that hospital area.

Alimentary tract biopsy specimens should be placed in a volume of formalin fixative that is at least 10 times greater than that of the tissue, and the fixative should surround the specimen completely. For routine processing, it is a common mistake to place specimens on saline-soaked gauze for delivery to the pathology suite because severe drying may occur. Complete fixation of these biopsies should always occur at the bedside. Formaldehyde diffuses into tissue at a rate of approximately 1.0 mm per hour at room temperature.[47] Thus, up to 1 hour is often needed adequately to fix a specimen with a diameter greater than 1.0 mm. More time is needed for larger specimens. Controlled microwave fixation at 63° to 65°C can greatly speed the process and is useful for rapid processing of specimens.[48]

Orientation of Formalin-Fixed Tissue Obtained at Endoscopy

Esophageal, gastric, and colonic mucosal biopsies do not require precise orientation before tissue processing and embedding. Until the mid-1980s, most peroral small intestinal biopsies were obtained by either a Crosby suction capsule or a Quinton hydraulic assembly.[49,50] These two methods were performed fluoroscopically and therefore did not permit direct visualization of the alimentary tract. Biopsies obtained by these methods were carefully oriented under a dissecting microscope before fixation and embedding. Direct endoscopic biopsy of the small intestine replaced the fluoroscopy with suction capsule biopsy procedure by the late 1980s[51,52]; biopsies obtained by this technique are not usually oriented before immersion in fixative, processing, and embedding. Rather, microscopic examination of multiple tissue sections usually permits identification of portions of the small intestinal mucosa that are well oriented and thus can be assessed satisfactorily for tissue architecture.

In contrast, processing of an endoscopic polypectomy specimen in the pathology suite requires diligent effort.[53] The size and surface configuration (bosselated or villiform) of the polyp should be noted, and the base of the polyp should be identified and described as to whether it is sessile or contains a cylindrical stalk. Regardless of the configuration of the stalk, the base of the polyp should always be inked. Ink and cautery artifact on a microscopic slide are valuable landmarks for locating the relevant resection margins. Small polyps (<1 cm in diameter) should be bisected along the vertical plane of the stalk so that the surgical margin is included. Both halves of the specimen can then be submitted in one cassette.

Section levels should be numbered consecutively; the first level is the one normally located closest to the middle of the polyp stalk. Large polyps (≥1 cm in diameter) may be sectioned differently if the polyp head is too wide to fit into a single cassette. First, the polyp should be bisected along its long axis and fixed overnight in formalin.. Once fixed, the sides of the polyp may be trimmed away from the stalk on a vertical axis and submitted in separate cassettes that are labeled accordingly. The middle of the polyp, including the base, should be sectioned vertically and submitted in an appropriate number of cassettes. If a stalk is identified histologically, the status of the margins should always be noted in the surgical pathology report.

If the polyp has been excised in a piecemeal fashion, the size, color, surface configuration (bosselated or villiform), and aggregate dimensions of the tissue fragments should be noted. It is important to note the number of tissue fragments received in the pathology suite.

FLOW CYTOMETRY

Gastrointestinal lesions suspected of representing a lymphoproliferative process are usually submitted for histology, but should also be processed for flow cytometry.[54] Biopsy specimens intended for flow cytometric analysis, such as gastric biopsies of a mass lesion, should be placed in sterile culture medium and delivered as rapidly as possible to the flow cytometry laboratory. Ideally, this should occur within several hours, but storage of specimens at 4°C overnight is an acceptable alternative.

Upon receipt in the laboratory, the tissue specimen is disaggregated and a cell suspension is prepared. Cocktails of fluorescently labeled antibodies appropriate to the diagnostic question are applied to the cell suspension. Current flow cytometry machines can analyze 5000 to 10,000 cells per second, measuring multiple wavelengths of laser-induced fluorescence simultaneously, thus permitting rapid and highly efficient analysis of cell populations. This technique cannot be performed on fixed tissue. It is, therefore, incumbent on the endoscopist to consider the possibility of a lymphoproliferative disorder at the time of endoscopy to ensure that tissue is preserved in a fresh state.

ELECTRON MICROSCOPY

For the uncommon instances in which electron microscopy of an alimentary tract biopsy is contemplated, tissue samples should be placed directly into the appropriate fixative, which usually consists of a mixture of

paraformaldehyde and glutaraldehyde. Unlike formaldehyde-based fixatives, bifunctional glutaraldehyde fixatives penetrate only about 0.5 mm into the tissue. Thus, tissue fragments to be placed in fixative for subsequent electron microscopy should, ideally, measure less than 1.0 × 1.0 × 1.0 mm^3 in maximal dimension. Indications for electron microscopy of endoscopic biopsy specimens are now largely limited to examination of unusual tumors.[55] However, this technique is also helpful in cases of unknown diarrhea in children, and in patients with AIDS, for detection of parasitic organisms.

Endoscopy-Induced Artifacts

Many types of tissue artifacts may be introduced into tissues as a result of bowel preparation, endoscopic trauma, or tissue handling. Some of these are listed in Table 1-3. Histologic features of artifacts are provided in Table 1-4.

TABLE 1-3 Endoscopic Events that May Affect Tissue Analysis

Event	Comment
Trauma (tissue hemorrhage)	"Scope trauma" (due to mechanical damage from endoscope) or excessive mechanical manipulation for access before biopsy
Cautery artifact	Excessive use of electrical current during "hot" biopsy
Crush artifact	Excessive use of mechanical force during pinch biopsy
Inadequate sampling depth	Absence of submucosa (e.g., evaluate submucosal lesion, rule out amyloid)
Inadequate sampling location	Absence of muscularis mucosa (for evaluation for Hirschsprung's disease)
	Insufficient regional sampling (e.g., of "normal-appearing" mucosa)
Chemical colitis[56,57]	Inadequate rinsing of cleaning solution from the endoscope
Laxative-induced changes[58]	Edema, damage to surface epithelium from exposure to oral and rectal laxatives
Air-drying	Failure to immerse specimen promptly in fixative
Postbiopsy healing	Sampling of a previous biopsy site during subsequent endoscopy
Wrong fixative	Formalin rather than fixative for electron microscopy; suboptimal but not irretrievable
No fresh tissue	Failure to preserve fresh tissue; precludes flow cytometry, cytogenetics

The most common type of artifact (or effect) is lamina propria edema and intramucosal hemorrhage ("scope trauma"), as illustrated in Figure 1-6. Other effects include aggregation and clumping of inflammatory cells in the lamina propria, surface flattening, mucin depletion, and even erosion and influx of air into the tissue (pseudolipomatosis).[56-58] The most common histologic artifacts include cautery and crush artifacts (Fig. 1-7). Cautery artifact as a result of hot biopsies is, in fact, a normal and expected component of endoscopic polypectomy with electrocautery. Specifically, the region of cauterization may provide a useful landmark of the surgical margin.

Pathologic Features of a Healing Biopsy Site

After endoscopic biopsy, the tissue healing process takes a considerable amount of time (Table 1-5). Blood clot and granulation tissue form within several hours after biopsy,[59]

TABLE 1-4 Histologic Artifacts Related to Endoscopy

Event	Feature
"Scope trauma"	Mucosal lamina propria hemorrhage or edema
Bowel prep-related changes	Clumping of inflammatory cells, mucin depletion, epithelial degenerative changes, focal neutrophilic infiltration, hemorrhage, edema, air in mucosa (pseudolipomatosis)
Insufflation of air at endoscopy	Air spaces within mucosa or submucosa (pseudolipomatosis)
Cautery artifact	Coagulated, eosinophilic tissue without cellular or nuclear detail
Crush artifact	Compressed tissue with markedly elongated, wavy nuclear remnants and no identifiable architecture
Chemical colitis from inadequate cleaning of the endoscope	Degenerative damage to, or sloughing of, surface epithelium, intraepithelial neutrophils and congestion, focal intramucosal hemorrhage
Laxative-induced changes	Lamina propria edema and neutrophilic infiltration, flattening or sloughing of mucosal surface epithelium, decreased goblet cell numbers
Air-drying	Eosinophilic and compressed tissue and loss of nuclear detail at edge of tissue fragment
Postbiopsy healing	See Table 1-5

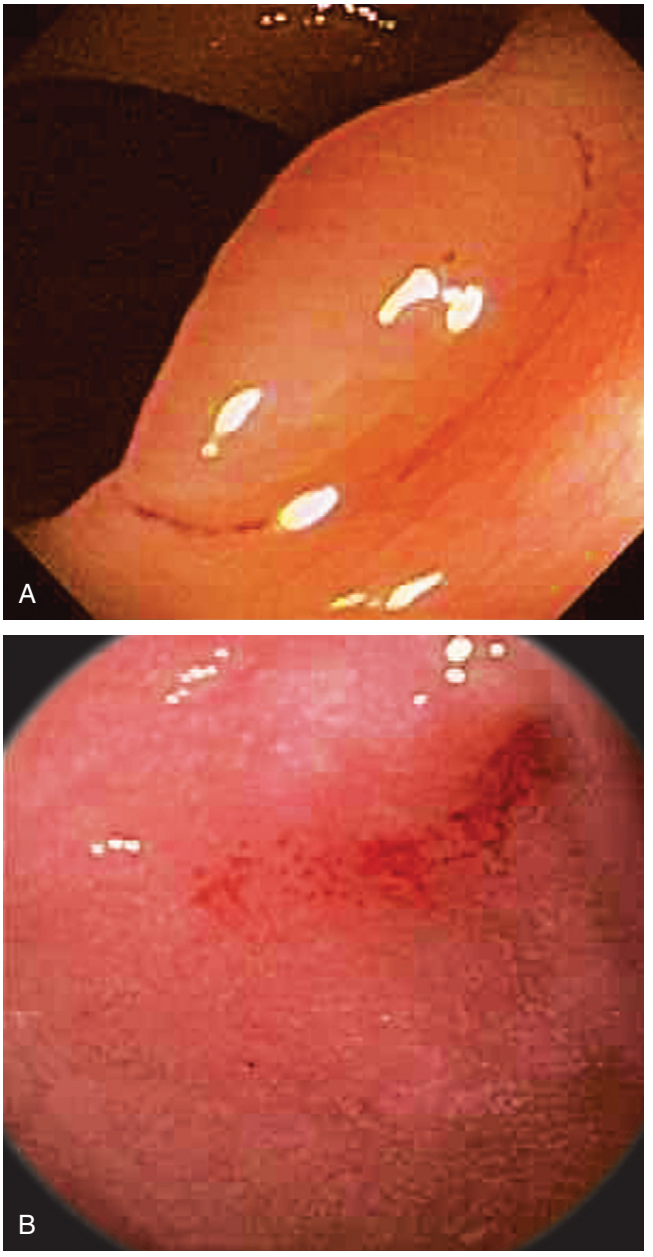

FIGURE 1-6 Endoscopic appearance of "scope trauma." **A,** A duodenal fold is swollen owing to lamina propria edema induced by passage of an endoscope; the region shows a subtle ring of mucosal hemorrhage. **B,** The colonic mucosa demonstrates multifocal areas of mucosal hemorrhage after withdrawal of the colonoscope; these were not present during initial advancement of the colonoscope into the colon. (Photographs courtesy of Dirk Van Leeuwen, Dartmouth Mary Hitchcock Medical Center, Lebanon, NH.)

as illustrated in Figure 1-8A and B. Routine superficial biopsies that involve only mucosa and submucosa typically reepithelialize within 48 hours after biopsy (see Fig. 1-8C). Ulcers that penetrate into the muscularis propria often take 3 to 6 days to reepithelialize (see Fig. 1-8D). Notably, after superficial biopsy, there is no increased risk of perforation during subsequent insufflation (as from repeat endoscopy or from barium enema), even immediately after the biopsy. The risk of perforation after a deep biopsy, one that involves the muscularis propria, returns to baseline after 3 to 6 days.[59] Regardless of the maximum depth of biopsy penetration (submucosa or muscularis propria; pinch biopsy or loop resection of a polyp), after several weeks a residual submucosal scar may remain, either with (see Fig. 1-8E) or without (see Fig. 1-8F) atrophy of the mucosa.

Pathologists should be aware of changes associated with colonic biopsy site repair in order not to misinterpret architectural distortion of the mucosa as evidence in favor of inflammatory bowel disease.

TABLE 1-5 Pathologic Features of a Healing Mucosal Biopsy Site

Time	Feature
Immediate	Blood clot with coagulum
Hours	Acute inflammation; granulation tissue reaction
2 days*	Reepithelialization of inflamed biopsy site by ingrowth of epithelial cells from adjacent preserved epithelium; early formation of submucosal scar
1-4 wk	Restoration of mucosa with rudimentary glandular architecture, maturation of submucosal scar
Months	Residual minimal mucosal architectural distortion, submucosal scar

**Longer with deep biopsies that involve the muscularis propria.*

Methods for Obtaining Cytology Specimens

See also Chapters 3, 30, and 37.

BRUSH CYTOLOGY

Brush cytology is a method used for broad sampling of the mucosal surface.[60,61] Cytology brushes, whether reusable or disposable, have a common design. A cytology brush consists of bristles, usually composed of nylon fibers, that branch off a thin metal shaft that runs lengthwise within a protective plastic sheath. The various cytology brushes that are currently available do not seem to vary in terms of performance characteristics.[62] The cytology brush is passed through an accessory channel of an endoscope. The end of the sheath is passed out of the tip of the endoscope, and the bristle portion of the brush is then extended from the sheath. The brush is rubbed back and forth several times along the surface of the lesion, or stricture, and is then pulled back into the sheath. The sheath is then withdrawn from the endoscope, and the

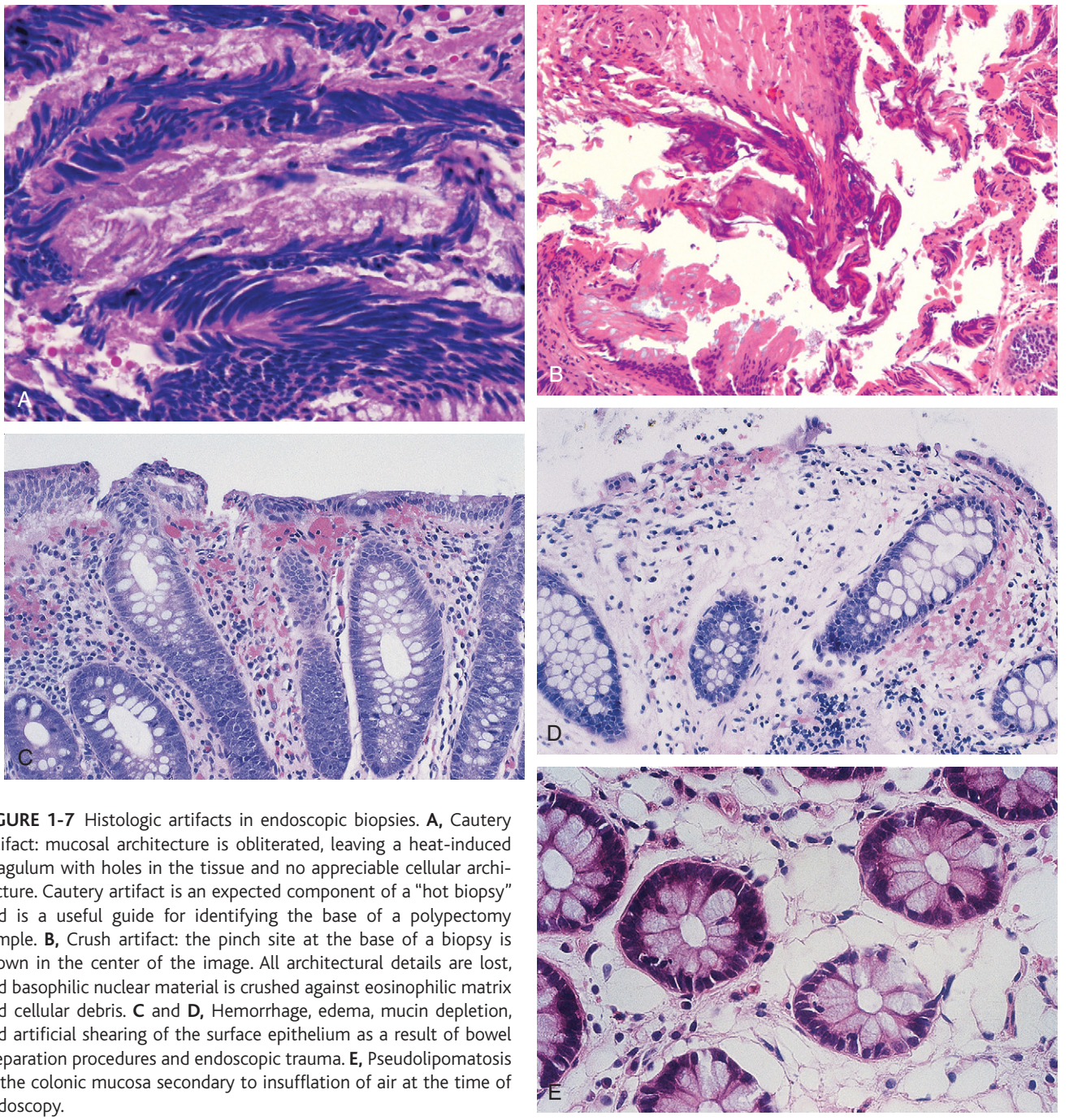

FIGURE 1-7 Histologic artifacts in endoscopic biopsies. **A,** Cautery artifact: mucosal architecture is obliterated, leaving a heat-induced coagulum with holes in the tissue and no appreciable cellular architecture. Cautery artifact is an expected component of a "hot biopsy" and is a useful guide for identifying the base of a polypectomy sample. **B,** Crush artifact: the pinch site at the base of a biopsy is shown in the center of the image. All architectural details are lost, and basophilic nuclear material is crushed against eosinophilic matrix and cellular debris. **C** and **D,** Hemorrhage, edema, mucin depletion, and artificial shearing of the surface epithelium as a result of bowel preparation procedures and endoscopic trauma. **E,** Pseudolipomatosis of the colonic mucosa secondary to insufflation of air at the time of endoscopy.

brush is pushed out of the sheath, thus exposing the bristles. The bristle portion of the brush may be cut off, placed into fixative, and sent in its entirety to the cytopathology laboratory. Alternatively, the bristles can be rolled against a glass slide in the endoscopy suite. The slides should be sprayed with fixative immediately, or submerged within it, and subsequently delivered to the cytopathologist. If smears are made in the endoscopy suite, little additional benefit is derived from inclusion of the bristles for cytopathologic analysis.[63]

FINE-NEEDLE ASPIRATION

Fine-needle aspiration (FNA) is another method used for obtaining tissue for cytology.[64-66] FNA needles may be used during standard endoscopy or during EUS. EUS provides endoscopists with the ability to sample tissue from parenchymal lesions and lymph nodes, as well as fluid from cystic lesions. EUS provides real-time imaging to ensure that the intended target is localized and sampled. The needles used for FNA during endoscopy are hollow 19- to

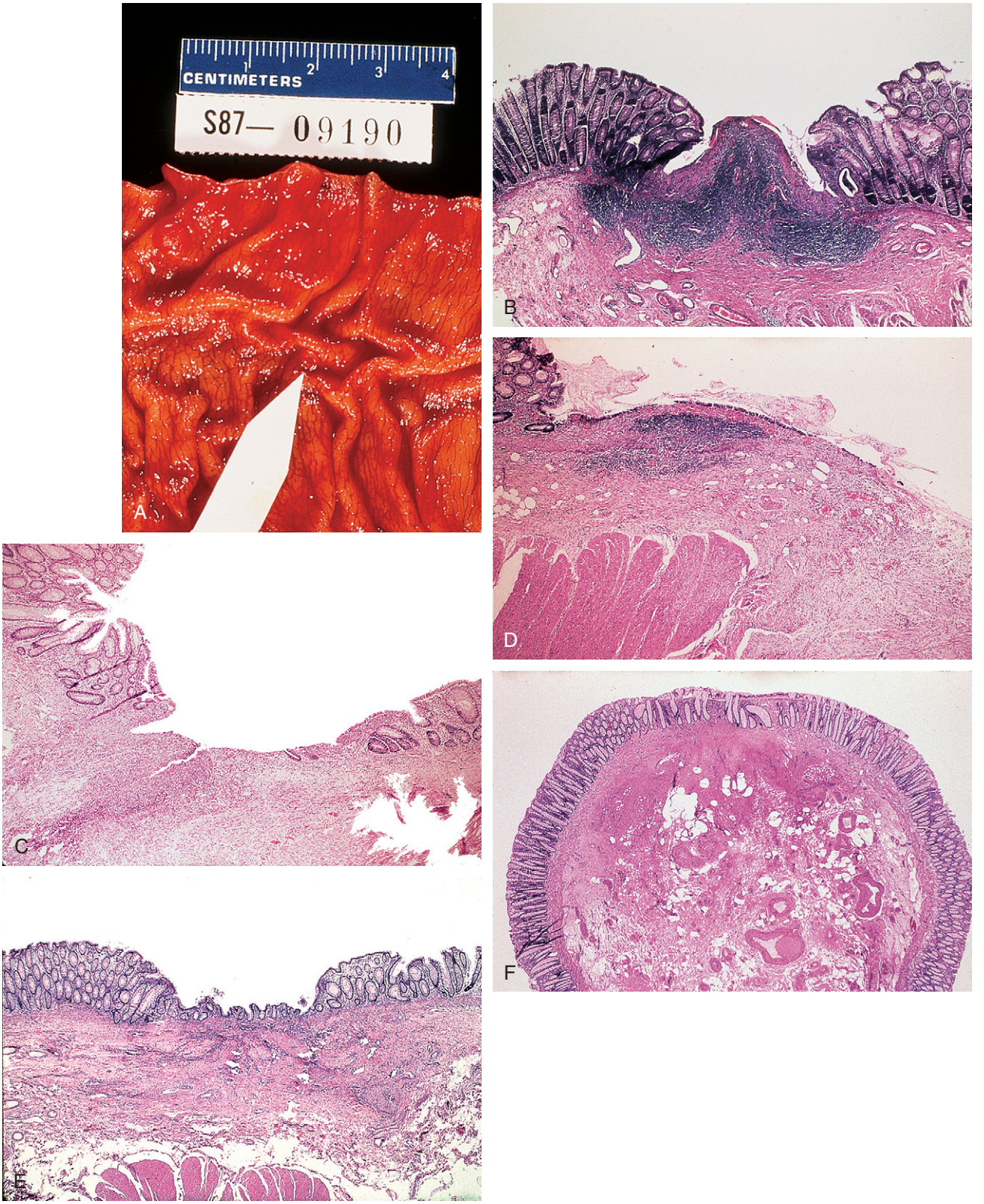

FIGURE 1-8 Healing mucosal biopsy sites. Healing of the colonic mucosa and submucosa after endoscopic biopsy is shown. **A,** Gross photograph of a resected colon specimen 2 days after endoscopic biopsy, with an arrow demonstrating the original biopsy site. **B,** Two days after endoscopic polypectomy, the biopsy site shows ulceration, inflammation, and granulation tissue reaction. **C,** Four days after biopsy, the mucosa shows architectural distortion and a thin, attenuated layer of surface epithelium. **D,** Four days after a loop polypectomy, an attenuated layer of epithelium covers portions of the biopsy site, but the ulcer is still present. **E,** Three weeks after biopsy, submucosal scarring and rudimentary crypt restoration are noted. **F,** One month after biopsy of a prominent mucosal fold, the submucosa shows scarring, and there is focal architectural distortion in the mucosa.

25-gauge needles, often fitted with a central stylet to avoid gathering of intervening tissue. Once the lesion of interest has been identified, the sheath is pushed out of the endoscope, and the needle is advanced into the target tissue either under fluoroscopic guidance (during ERCP) or under ultrasonographic guidance (during EUS). If a stylet is present, it is then removed, and suction is applied to a syringe at the proximal end of the needle. While suction is applied, the endoscopist moves the needle forward and backward within the lesion, thereby filling the distal needle lumen with tissue. The needle is then withdrawn into the sheath, and the entire apparatus is removed from the endoscope. Complications from FNA biopsy occur in less than 2% of cases and include bleeding and, in the setting of pancreatic mass FNA, acute pancreatitis.

Normal Histology of the Tubal Gut

ESOPHAGUS

The adult human esophagus measures about 25 cm in length. For the endoscopist, the length of the esophagus is measured as the anatomic distance from the incisor teeth. The esophagus usually begins at 15 cm, and the gastroesophageal junction (GEJ) is located at 40 cm. The 3-cm segment of the proximal esophagus (at 15 to 18 cm from the incisors), at the level of the cricopharyngeus muscle, is referred to as the *upper esophageal sphincter*. The 2- to 4-cm segment just proximal to the anatomic GEJ (at 36 to 40 cm from the incisors), at the level of the diaphragm, is referred to as the *lower esophageal sphincter*. Both "sphincters" are physiologic because there are no anatomic landmarks that outline these high-pressure regions in relationship to the underlying esophageal musculature.

In keeping with the structural organization of the entire alimentary tract (Fig. 1-9), the wall of the esophagus consists of a mucosa, submucosa, muscularis propria, and adventitia. The *mucosa* has a smooth, glistening, pink-tan surface. It has three components: a nonkeratinizing stratified squamous epithelial layer, and an underlying lamina propria and muscularis mucosae (Fig. 1-10). The basal cell zone of the squamous epithelium occupies 10% to 15% of the total thickness of the epithelial layer. A small number of specialized cell types, such as endocrine cells, Langerhans' cells, and lymphocytes, are typically present in the deeper portion of the squamous epithelium. The intraepithelial lymphocytes are T cells.[67] Melanocytes may be present in the esophagus in 3% to 8% of normal individuals.[68,69]

The lamina propria is the nonepithelial (mesenchymal) portion of the mucosa, located above the muscularis mucosae. It consists of areolar connective tissue and contains vascular and neural structures, and scattered inflammatory cells. Finger-like extensions of the lamina propria, termed *papillae*, extend into the epithelial layer. These papillae usually extend to one third to one half of the thickness of the epithelial layer. In esophagitis (e.g., reflux esophagitis), the papillae extend into the upper third of the epithelial layer.

The muscularis mucosae is a thick layer of longitudinally oriented smooth muscle bundles. The *submucosa* consists of loose connective tissue containing blood vessels, a rich network of lymphatics, and a sprinkling of inflammatory cells, with occasional lymphoid follicles, nerve fibers (including the ganglia of Meissner's plexus), and submucosal glands. Submucosal glands connect to the lumen of the esophagus by squamous epithelium–lined ducts. Submucosal glands are scattered along the entire esophagus but are more concentrated in the upper and lower portions. Submucosal glands are suspended within the delicate mesenchyme of the submucosa. They have a simple acinar structure, and resemble salivary glands in that they contain mucous cells surrounding a central lumen, in a radial fashion. Their mucin-containing fluid secretions help lubricate the esophagus. Submucosal glands also secrete biologically active peptides, such as those from the trefoil factor family 3 (TTF3)[70]; these peptides play a role in mucosal protection and repair. *Identification of a squamous duct and submucosal mucous glands is considered a definitive anatomic landmark of the tubular esophagus*. In the deep portion of the submucosa, the gland ducts contain two discrete layers of cuboidal cells, which become progressively more squamoid at higher levels of the submucosa and mucosa. A mild, concentric, chronic inflammatory infiltrate is commonly noted surrounding the gland ducts.

Endoscopic biopsies of the esophagus yield squamous epithelium, lamina propria, and muscularis mucosae. Sampling of the submucosa is variable. The anatomic landmarks change in patients with Barrett's esophagus: the lamina propria no longer lies only underneath the epithelial layer, but is also located between the glands. A newly developed muscularis mucosae lies directly underneath the glands. This layer of muscularis mucosae represents the superficial layer of a "double muscularis" in patients with Barrett's esophagus.[71]

STOMACH

The stomach is a large saccular organ with a volume of 1200 to 1500 mL, but it has a potential capacity of over 3000 mL. It extends from just left of the midline superiorly, where it is joined to the esophagus, to just right of the midline inferiorly, where it connects to the duodenum. The stomach begins at the GEJ, considered to be the most proximal point of the gastric folds. The stomach ends at the pylorus, where the muscularis propria thickens to create the *pyloric sphincter*. The concavity of the right, inner curve of the stomach is termed the *lesser curvature*, and the convexity of the left, outer curve is considered the *greater curvature*. The angle

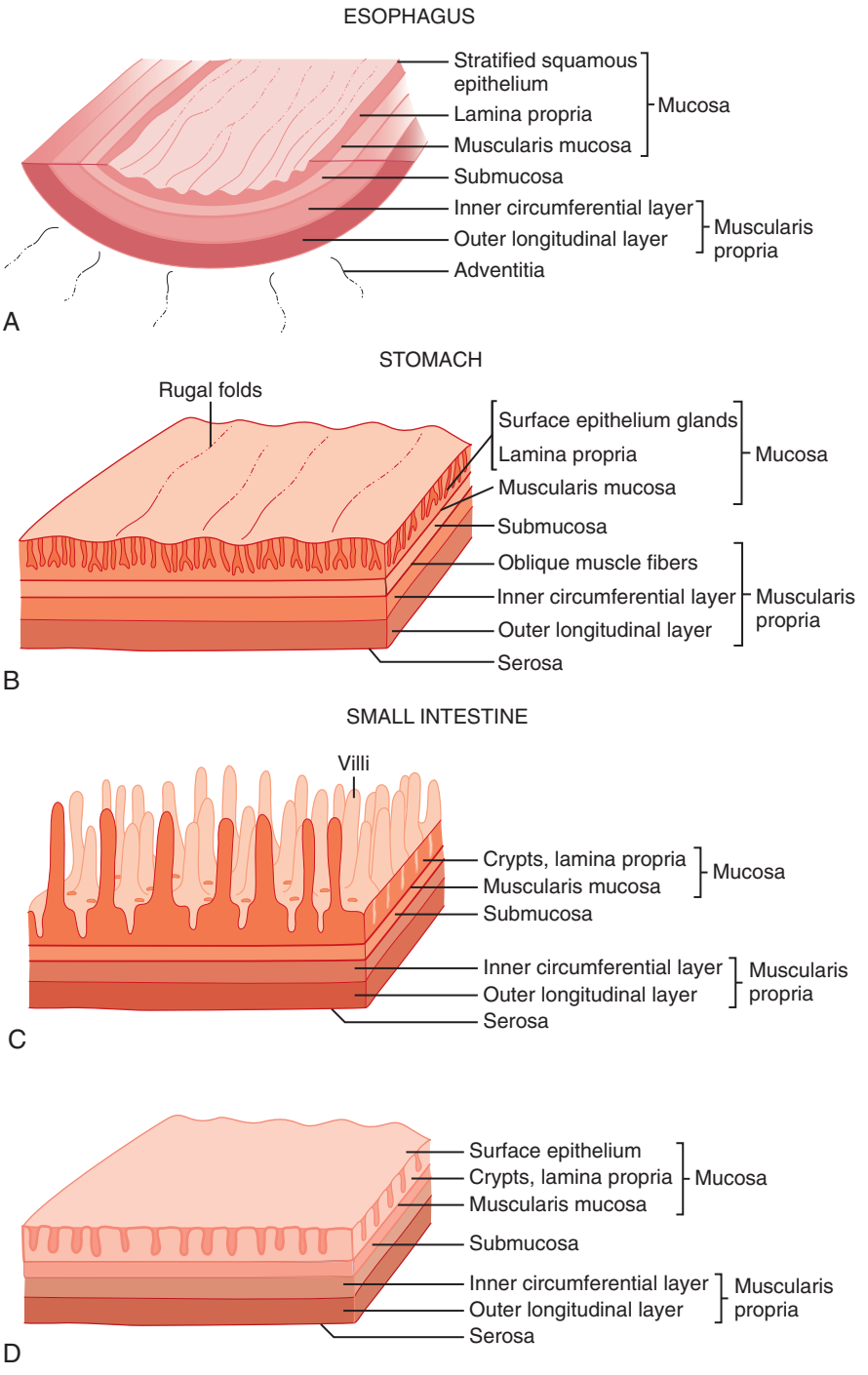

FIGURE 1-9 Microanatomy of the tubal gut. **A,** Esophagus. **B,** Stomach. **C,** Small intestine. **D,** Colon. (Reproduced with permission from Crawford JM: Principles of anatomy. In Rustgi AK, Crawford JM [eds]: Gastrointestinal Cancers: Biology and Clinical Management. Philadelphia, WB Saunders, 2003, pp 121-131.)

along the lesser curve, termed the *incisura angularis*, marks the approximate point at which the stomach narrows before its junction with the duodenum. The stomach is divided into five anatomic regions. The *cardia* is a narrow (0.1 to 0.4 cm in length) conical portion of the stomach located immediately distal to the GEJ. The *fundus* is the dome-shaped portion of the proximal stomach that extends superolateral to the GEJ. The *body*, or *corpus*, comprises the remainder of the stomach proximal to the incisura angularis. The stomach distal to the incisura is considered the *antrum*, which is demarcated from the duodenum by the pyloric sphincter.

The gastric wall consists of mucosa, submucosa, muscularis propria, and serosa. The interior surface of the stomach exhibits coarse *rugae* ("folds"). These infoldings of mucosa and submucosa extend longitudinally and are most prominent in the proximal stomach. The rugae flatten when the stomach is distended. A finer, mosaic-like pattern is delineated by small furrows within the mucosa. Finally, the delicate texture of the mucosa is punctuated by

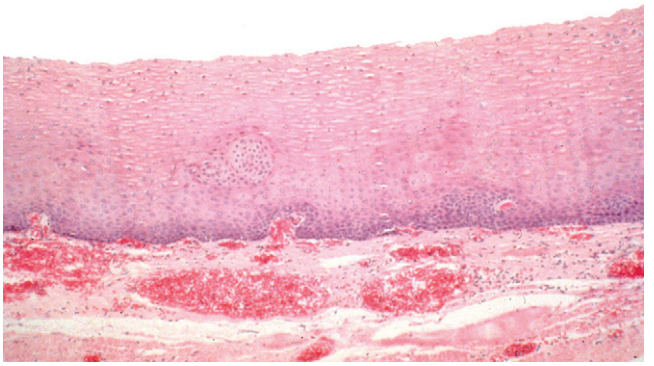

FIGURE 1-10 Normal histology of the esophageal mucosa. Stratified nonkeratinizing squamous mucosa rests on loose lamina propria, which contains supporting vasculature and scattered inflammatory cells.

millions of gastric foveolae, or "pits," which lead to the mucosal glands.

The normal gastric mucosa has two main epithelial compartments: the superficial foveolar (meaning "leaf-like") compartment and the deeper glandular compartment. The foveolar compartment is relatively uniform throughout the stomach. In contrast, the glandular compartment exhibits major differences in thickness and composition in different regions of the stomach (Fig. 1-11). The foveolar compartment consists of mucous cells that line the entire mucosal surface, and gastric pits (*foveolae*). The tall, columnar mucin-secreting foveolar cells contain basal nuclei and crowded, small, relatively clear mucin-containing granules in the supranuclear region of the cytoplasm. Deep in the gastric pits are the so-called *mucous neck cells*, which have a lower content of mucin granules and are thought to be the cell progenitors of both the surface epithelium and the gastric glands. Mitoses may be identified in this region because the entire gastric mucosal surface is normally replaced completely every 2 to 6 days. The glandular compartment consists of gastric glands, which vary between the different anatomic regions of the stomach:

- In the cardia, the glands contain either pure mucous cells, or a mixture of mucous and oxyntic cells, for a length of 0.1 to 0.4 cm in most individuals (see Chapter 12). In a small proportion of individuals, a portion of the circumference of the cardia may contain only pure oxyntic glands.
- *Oxyntic glands* (also called *fundic glands*) are found in the fundus and body, and contain parietal cells, chief cells, and scattered endocrine cells. The term *oxyntic* is derived from the Greek *oxynein*, and means "acid-forming."
- *Antral* and *pyloric glands* are identical and contain both mucus-secreting cells and endocrine cells. At the proximal junction of the antrum with the gastric corpus, the glands usually show a mixture of mucous and oxyntic glands. This histologic junction migrates proximally a few centimeters with age. Distally, where the pyloric mucosa enters the proximal duodenum,

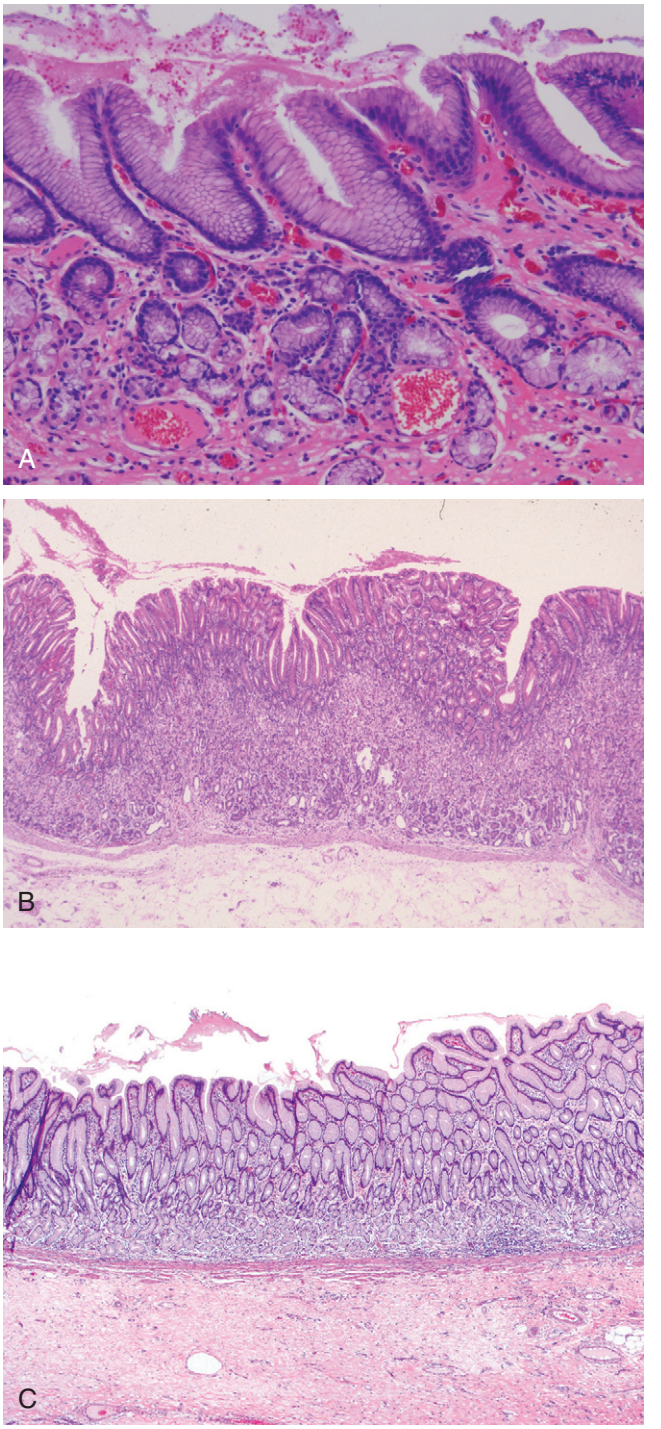

FIGURE 1-11 Normal histology of the stomach. **A,** Cardiac mucosa, high-power view, showing simple mucous glands (and some oxyntic glands) underlying the surface epithelium. **B,** Oxyntic mucosa, low-power view, showing the thickness of the glandular mucosa. **C,** Antral mucosa, low-power view, showing a slightly thinner mucosa, with mucous glands only.

the small intestinal mucosa (see later) appears to override the mucous glands. In turn, the mucous glands quickly transition to a location below the level of the muscularis mucosae, to form the duodenal Brunner's glands.

Gastric gland cell types include the following:

- *Mucous cells* populate the mucous glands of the cardia and antral regions and secrete mucus and pepsinogen II. The mucous neck cells in the oxyntic glands of the body and fundus secrete mucus as well as group I and II pepsinogens.
- *Parietal cells* line mainly the upper half of the oxyntic glands in the fundus and body. They are recognizable by their bright eosinophilia on H&E stain, which is attributable to the abundance of mitochondria. Scattered parietal (and chief) cells can be seen in the antrum as well, particularly in the proximal transition zone with the true antrum.
- *Chief cells* are concentrated at the base of oxyntic glands in the fundus and body, and are responsible for secretion of the proteolytic proenzymes *pepsinogen I and II*. Chief cells are notable for their basophilic cytoplasm, and, ultrastructurally, are classic protein-synthesizing cells, having an extensive subnuclear rough endoplasmic reticulum, a prominent supranuclear Golgi apparatus, and numerous apical secretory granules.
- *Endocrine* (or *enteroendocrine*) *cells* are scattered among the epithelial cells of the oxyntic and mucous glands (see Chapter 25 for details). The cytoplasm of these triangle-shaped cells contains small, brightly eosinophilic granules that are concentrated on the basal aspect of the cell. These cells can act in an "endocrine" fashion by releasing their products into the circulation, or in a "paracrine" fashion through secretion directed into the local tissue. In antral mucosa, most endocrine cells consist of gastrin-producing *G cells*. In the body, the endocrine cells produce histamine, which binds the H_2 receptor on the parietal cells, and leads to an increased acid production. These cells are also referred as *enterochromaffin-like cells*. Other enterochromaffin-like cells in the oxyntic glands include *D cells* (which produce somatostatin) and *X cells* (which produce endothelin). These cells play an important role in modulating acid production.

The Gastric Cardia

The stomach begins at the most proximal aspect of the gastric folds. The gastric cardia is viewed as an anatomic region of the stomach of approximately 0.1 to 0.4 cm in length located at the proximal cone of the gastric cavity, just distal to the squamocolumnar mucosal boundary (the "Z"-line) in normal individuals. Traditionally, the gastric cardia is viewed as having "cardiac" mucosa, which is a mucinous, glandular mucosa typically lacking oxyntic glands (which contain chief and parietal cells) (see Fig. 1-11A). However, some individuals may show a mixture of both types of glands (mucous and oxyntic; see later; see also Chapter 12 for details).

The strict (physiologic) definition of the GEJ is actually manometric, in that the high-pressure zone of the lower esophageal sphincter defines the true distal end of the esophagus. Because manometry is not a normal part of routine endoscopy and the GEJ passes through the diaphragmatic orifice, the performance of endoscopy on a live, breathing patient makes it difficult to identify precisely the true anatomic location of the GEJ region. The flaring of the gastric cavity on retroflexion of the endoscope is considered a reliable indicator of the beginning of the stomach. However, an axial hiatal hernia, or the proximal migration of the squamocolumnar mucosal junction in the setting of gastroesophageal reflux (whether physiologic or pathologic), also makes it very difficult to identify the anatomic site of the most proximal stomach at the time of endoscopy.

The origin and nature of epithelium in the cardia region of the stomach is controversial. In 1997, Öberg and colleagues[72] found that endoscopic biopsies obtained at and below the GEJ in 334 patients showed absence of cardia-type mucinous glands in 26% of patients. Patients who did have cardiac mucosa were also significantly more likely to have gastroesophageal reflux disease. Chandrasoma and coworkers[73] reported that the presence of cardia-type gastric mucosa or "oxyntocardiac mucosa" (combined oxyntic and mucous glands) in the GEJ correlated with acid reflux. These authors concluded that all cardia-type mucosa in the GEJ region represents metaplastic transformation of the squamous epithelium as a result of reflux. In another autopsy study by the same group,[74] the entire circumference of the GEJ was examined histologically in 18 patients, and cardia-type mucosa was completely absent in 10 (56%). These findings were contradicted by Kilgore and associates,[75] who found cardia-type mucosa at the GEJ in all 30 pediatric autopsies examined, a population considered to be at low risk for gastroesophageal reflux disease. Other investigators also have found either mucous glands or mixed mucous glands in most, if not all, patients at the GEJ, even in patients without any gastroesophageal reflux disease history (Table 1-6).

A summary of the objective evidence and the controversies surrounding the nature of the cardia was reported by Odze in 2005.[83] In that evidence-based review, the preponderance of evidence indicates that the true gastric cardia is an extremely short segment (<0.4 cm) of mucosa that is typically composed of pure mucous glands, or mixed mucous/oxyntic glands. Notably, these glands are histologically indistinguishable from metaplastic mucinous columnar epithelium of the distal esophagus characteristic of Barrett's esophagus. In patients with gastroesophageal reflux disease, the length of cardia-type

TABLE 1-6 The Gastric Cardiac Mucosa: Key Publications

Author	Study Design	Findings	Conclusions
Öberg et al,[72] 1997	Endoscopic biopsies; 334 patients	No cardiac mucosa detectable in 88 (26%)	Cardiac mucosa is the result of GERD
Chandrasoma et al,[73] 2000	Endoscopic biopsies with acid reflux measurement	Cardiac/oxyntocardiac mucosa is related to GERD in all 71 patients	Cardiac mucosa is not a normal anatomic structure
Chandrasoma et al,[74] 2000	Autopsy study, adults	Cardiac mucosa is absent in 10/18 cases (56%)	Cardiac mucosa is not a normal anatomic structure
Kilgore et al,[75] 2000	Autopsy study, pediatric	Cardiac mucosa is present in all 30 cases	Cardiac mucosa is a normal anatomic structure
Sarbia et al,[76] 2002	Esophagogastric resection specimens	Cardiac mucosa or oxyntocardiac mucosa is present in all 20 cases	Cardiac and oxyntocardiac mucosa is a dynamic structure
Park et al,[77] 2003	Autopsy study, fetal and pediatric	Transitional zone is present in the proximal fetal stomach	Cardiac mucosa composed of pure mucous cells is not a normal developmental structure
Glickman et al,[78] 2002	Biopsy study, 74 pediatric patients	Pure mucous or mixed mucous/oxyntic glands present in 100% of patients	Cardiac mucosa is present in most pediatric patients, may increase in length with GERD
Chandrasoma et al,[79] 2003	Endoscopic biopsies, 959 patients	Abnormal columnar epithelium present in 811 (84.6%) of patients	A histologic system for classifying columnar mucosa of the cardiac region is proposed
Marsman et al,[80] 2004	Endoscopic biopsies, 198 patients	Cardiac mucosa present in 62% of patients, oxyntocardiac mucosa in 38% of patients	Cardiac mucosa is uniformly present adjacent to the squamous epithelium of the esophagogastric junction
De Hertogh et al,[81] 2005	Autopsy study, fetal	Simple columnar epithelium identified in distal esophagus of 48 fetal autopsy specimens	At least a part of the adult cardiac mucosa has a congenital origin
Lord et al,[82] 2004	Endoscopic biopsies, after esophageal resection	Cardiac mucosa identified in 10 of 20 patients in cervical esophagus	Cardiac mucosa can be acquired, likely related to reflux of acid into remnant esophagus

GERD, gastroesophageal reflux disease.

Adapted from Odze RD: Unraveling the mystery of the gastroesophageal junction: A pathologist's perspective. Am J Gastroenterol 100:1853-1867, 2005.

mucosa increases and extends proximally above the level of the anatomic GEJ into the distal esophagus. Thus, intestinal metaplasia of either the true gastric cardia or esophageal metaplastic columnar epithelium may occur. For a more detailed discussion of the gastric cardia and intestinal metaplasia of the GEJ region, the reader is referred to Chapter 12.

SMALL INTESTINE

The adult *small intestine* is approximately 6 m in length. The *colon* (large intestine) is about 1.5 m in length. The first 25 cm of small intestine, the duodenum, is retroperitoneal; the jejunum marks the entry of the small intestine into the peritoneal cavity. The remainder of the small intestine is intraperitoneal until it enters the colon at the ileocecal valve. The demarcation between the jejunum and ileum is not a clearly defined landmark; the jejunum arbitrarily constitutes the proximal third of the intraperitoneal portion, and the ileum the remainder.

The most distinctive feature of the small intestine is its mucosal lining, which is designed to provide maximal surface area for the purpose of food absorption. It is studded with innumerable *villi* (Fig. 1-12A,B). These extend into the lumen as finger-like projections covered by epithelial lining cells. The central core of lamina propria contains blood vessels, lymphatics, a small population of lymphocytes, eosinophils, and mast cells, and scattered fibroblasts and vertically oriented smooth muscle cells. Between the bases of the villi are the pitlike crypts of Lieberkühn, which contain stem cells that replenish and regenerate the epithelium. The crypts extend down to the muscularis mucosae. The muscularis mucosae is a smooth, continuous sheet that serves to anchor the configuration of villi and crypts alike. In normal individuals, the villus-to-crypt height ratio is about 4:1 to 5:1, but this is variable. For instance, in the proximal duodenum, the villus-to-crypt height ratio may reach only 2:1 to 3:1. Within the duodenum are abundant submucosal mucous glands, termed *Brunner's glands*. They can be observed immediately distal to the pyloric channel.

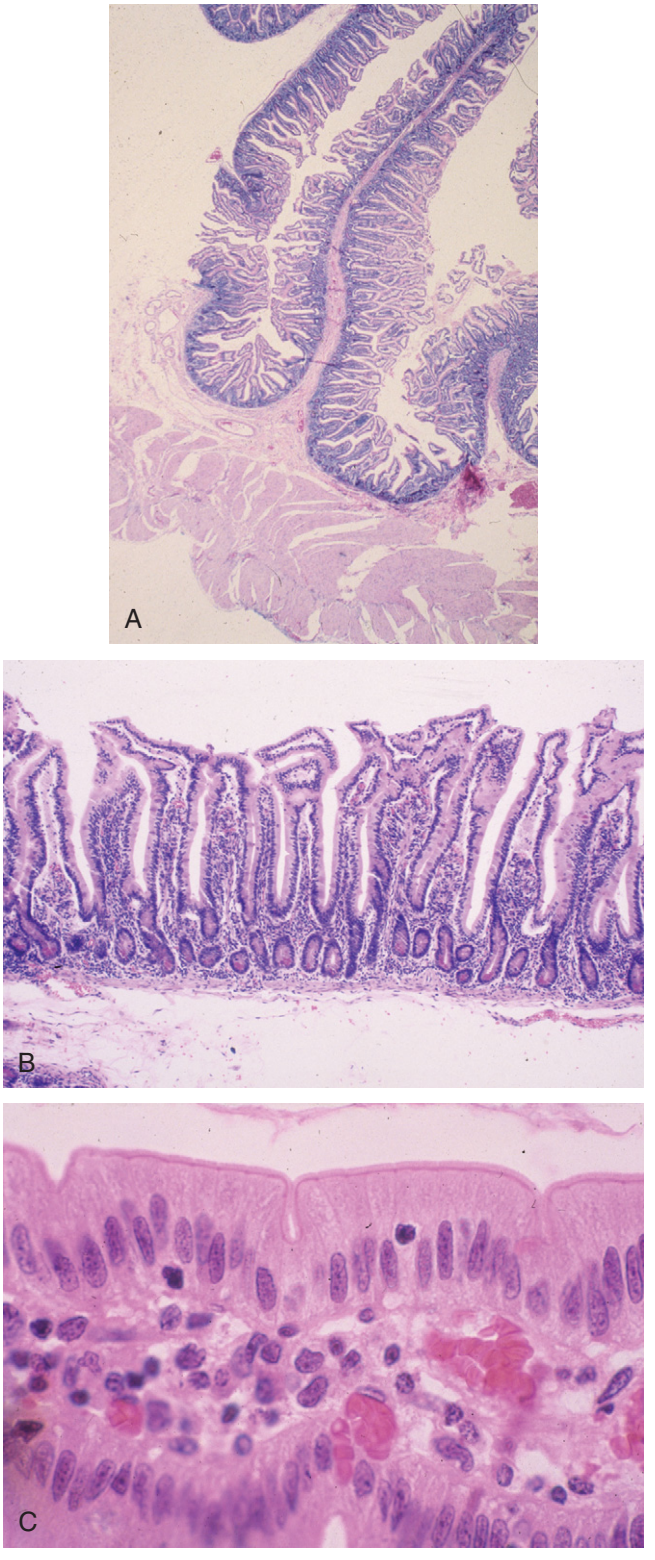

FIGURE 1-12 Normal histology of the small intestine. **A,** Low-power image, showing the plica circulares protruding into the lumen, lined by mucosa. **B,** Medium-power image, showing tall villi and short crypts. **C,** High-power image of a villus, showing enterocytes with basal nuclei and an apical "brush border."

These glands secrete bicarbonate ions, glycoproteins, and pepsinogen II, and, except for their submucosal location, are virtually indistinguishable from the mucous glands of the distal stomach.

The surface epithelium of the small intestinal villi contains three principal cell types. *Columnar absorptive cells* are recognized by the dense array of *microvilli* on their luminal surface (the "brush border"), and an underlying mat of microfilaments (the "terminal web"; see Fig. 1-12C). Interspersed regularly between absorptive cells are mucin-secreting *goblet cells*, and a few *endocrine cells*, described later. Goblet cells in the small intestine contain mainly acidic sialated mucins, identifiable by the Alcian blue stain performed at pH 2.5 (acidic). Within the crypts reside stem cells, goblet cells, more abundant endocrine cells, and scattered *Paneth cells*. Paneth cells contain apically oriented, bright eosinophilic granules that contain growth factors and a variety of antimicrobial proteins (such as *cryptdins*, also called *defensins)* which play a role in mucosal innate immunity against bacterial infection.[84] Paneth cells are located throughout the small intestine and in the proximal portion of the colon, including the cecum, ascending colon, and proximal portion of the transverse colon. They normally are absent from the distal transverse colon, the descending and sigmoid colon, and rectum.

Endocrine Cells

A diverse population of *endocrine cells* is scattered among the epithelial cells that line the small intestinal villi and small and large intestinal crypts (see also Chapter 25). Comparable cells are present in the epithelium lining the pancreas, biliary tract, lung, thyroid, and urethra. Gut endocrine cells exhibit characteristic morphologic features. In most cells, the cytoplasm contains abundant fine eosinophilic granules that harbor secretory products. The main portion of the cell is located at the base of the epithelium, and the nucleus resides on the luminal side of the cytoplasmic granules. The number of endocrine cells in the small intestine is greater than in the colon. The greatest diversity of endocrine cell types is in the duodenum and jejunum, becoming less diverse distally.[85] 5-Hydroxytryptamine–containing endocrine cells are present in all regions of the intestine (small and large) and comprise the single largest endocrine cell population. A minor proportion of these cells contain substance P. The second largest cell population is glicentin cells, which are more numerous in the ileum and colon. Somatostatin cells occur throughout the alimentary tract. Cells that store cholecystokinin, motilin, secretin, or gastric inhibitory polypeptide are more numerous in the duodenum and jejunum compared with the ileum. *Gastrin cells* are few, and occur exclusively in the proximal duodenum. There are many other peptides and bioactive compounds released by endocrine cells in the small intestine and colon, including β-endorphin, pro-gamma-melanocyte–stimulating hormone, β-lipotropin, neurotensin, glicentin, glucagon, and pancreatic polypeptide (see Chapter 25 for details).

Histologic distinction between endocrine cells and Paneth cells is based on the size and color of the eosinophilic cytoplasmic granules. Although both cell types are pyramidal in shape, with broad bases that narrow toward the crypt lumen, endocrine cells are small (about 8 μm in height), do not extend to the surface of the epithelial layer, and contain abundant small deeply eosinophilic granules. Paneth cells are larger (about 20 μm in vertical height) with a luminal apical plasma membrane, and contain a population of larger, coarse, and brightly eosinophilic granules.

The Intestinal Mucosal Immune System

Humans are exposed to an enormous load of environmental antigens through the GI tract, and the ultrastructural surface area of the GI tract exposed to environmental antigens far exceeds that of the skin and pulmonary tract. The immune system must balance antigenic tolerance against immune defense. The function of the intestinal immune system is best addressed on the basis of its anatomy, almost all features of which can be identified by routine light microscopy (Fig. 1-13; see also Chapter 27). Throughout the small intestine and colon are nodules of *lymphoid tissue*, which lie either within the mucosa or within both the mucosa and the submucosa. Lymphoid nodules distort the surface epithelium to produce broad domes rather than villi; within the distal ileum confluent areas of dense lymphoid tissue become macroscopically visible as *Peyer's patches*. The surface epithelium overlying lymphoid nodules contains both columnar absorptive cells and *M (membranous) cells*, the latter found only in the small and large intestinal lymphoid sites. These cells cannot be readily identified by light microscopy. M cells are capable of transporting antigenic macromolecules, intact, from the lumen to the underlying lymphocytes, thus serving as an important afferent limb of the *intestinal immune system*.

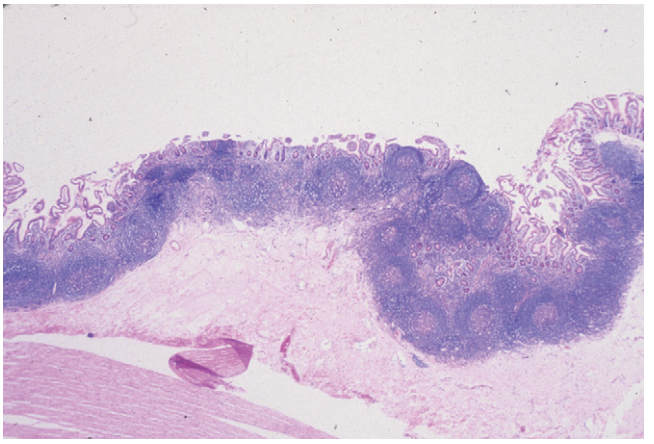

FIGURE 1-13 Normal mucosa-associated lymphoid tissue from the ileum, in which confluent lymphoid aggregates in the mucosa and submucosa form Peyer's patches.

Throughout the intestines, T lymphocytes are scattered within the surface epithelium, usually at the base of the epithelial layer. These T cells are referred as *intraepithelial lymphocytes (IELs)*, and are generally of the cytotoxic $CD8^+$ phenotype. However, there is remarkable diversity of T-cell subtypes, some unique to the intestine.[86] In normal small intestinal villi, IELs normally decrease in number from the base toward the tip.[13] CD3 immunohistochemistry can aid in the detection of IELs, particularly because some lymphocytes have irregular nuclear borders, which makes their identification on H&E stain more difficult.[87] In healthy individuals, the duodenum normally contains less than 26 to 29 IELs per 100 epithelial cell nuclei, with a mean of 11 and 13 IELs per 100 epithelial nuclei in H&E- and CD3-stained sections, respectively.[88] The range of IEL counts among healthy individuals can vary widely, between 1.8 to 26 per 100 epithelial nuclei, and there is no correlation between IEL counts and the villus-to-crypt height ratios.[89] The mean number of IELs decreases progressively in the distal small intestine and colon.[90,91] Normal villus IEL counts in the terminal ileum are in the range of 2 IELs per 100 epithelial nuclei.[92] A normal IEL count in the ileum does not preclude abnormality in the duodenum.[93] A modest elevation in IEL counts accompanies many types of inflammatory conditions of the colon.[92]

The lamina propria contains helper T cells ($CD4^+$), educated B cells, and plasma cells. The lamina propria plasma cells secrete dimeric IgA, IgG, and IgM, which enter into the splanchnic circulation. IgA is transcytosed directly across enterocytes, or across hepatocytes, for secretion into bile; both are mechanisms for delivering IgA into the intestinal lumen. Finally, other antigen-presenting cells located in the lamina propria include macrophages and dendritic cells. The intestinal lymphoid nodules and mucosal lymphocytes, together with isolated lymphoid follicles in the appendix and mesenteric lymph nodes, constitute the mucosa-associated lymphoid tissue (MALT). Although most prominent in the small intestine, the concept of MALT has relevance to both the stomach (as an acquired anatomic compartment) and the colon (in which it also is normally present; see Chapter 27 for details).

COLON

The colon is subdivided into the cecum and the ascending, transverse, and descending colon. Unlike the jejunum and ileum, whose anatomic location and mechanical attachment to the posterior abdomen are entirely dictated by the mesentery, the anatomic locations of the colonic segments are established by other means. The bulbous cecum and the ascending colon constitute the entire portion of the colon on the right side of the abdomen, and are fixed in location. Although peritoneal membrane covers their ventral surfaces, the dorsal aspect of both the cecum and

ascending colon adhere directly to the posterior abdominal wall. (The appendix, which inserts into the cecum just below the insertion of the ileum into the cecum, is an intraabdominal viscus, being entirely covered with peritoneum.) The transverse colon begins at the hepatic flexure, and swings across the most ventral aspect of the abdominal cavity to reach the splenic flexure. The transverse colon is suspended by the lesser omentum, which reflects off the greater curvature of the stomach. In turn, the greater omentum hangs from the transverse colon. The descending colon is adherent to the left posterior abdominal wall, similar to its counterpart (the ascending colon) on the right side of the peritoneal cavity. The sigmoid colon begins at the pelvic brim and loops ventrally into the peritoneal cavity. The sigmoid colon is the only portion of the colon suspended entirely by mesentery. Thus, it may be subject to redundancy that may, rarely, lead to volvulus. Distally, the colon is adherent to the posterior wall of the pelvis beginning at the rectum, at about the level of the third sacral vertebra. Halfway along the 15-cm length of rectum, it passes between the crura of the peroneal muscles to exit the abdominal cavity.

In normal adults, the length of the colon is quite variable, but generally measures in the range of 0.8 to 1.1 m. From the endoscopist's perspective, the rectal canal is approximately 15 cm in length, beginning at the anal verge. The variable length of the sigmoid colon makes identification of further landmarks less reliable, but the splenic flexure is located about 0.4 m proximal to the anal verge, and the hepatic flexure about 0.7 m proximal.

The anatomy of the wall of the colon is unique in that the external layer of the muscularis propria is discontinuous. Instead, three longitudinal strips of smooth muscle lie on top of the inner continuous circumferential smooth muscle layer of the muscularis propria. These longitudinal strips are termed the *tinea coli*. One strip is located at the attachment of the mesentery to the colon. The second and third strips are located equidistantly at about 120 and 240 degrees around the circumference of the colon. Each strip is approximately 0.5 cm in width, and becomes more prominent distally. The tinea coli begin at the cecum, so that the bulbous end of the cecum is creased by the outer two tinea coli as they arc to their respective locations on the opposite sides of the cecal wall. Notably, throughout the entire length of colon, arteries and veins penetrate through the continuous inner muscle layer at the edges of the tinea coli. These blood vessels constitute the circumferential ramifications of the mesenteric vasculature. Hence, there are three double tracks of holes in the inner muscle coat, owing to the orifices created by the penetrating vasculature. It is through these holes that diverticula usually protrude (see Chapter 8). Small tags of adipose tissue, the *epiploic appendages*, also are attached to the colon, at the edges of the nonmesenteric tinea coli 120 and 240 degrees around the circumference of the colon. Two double tracks of intermittent epiploic appendages are thus created along the entire length of the colon. Protruding diverticula can be difficult to identify because they are in the same circumferential location as the epiploic appendages and may, in fact, protrude *into* epiploic appendages.

The cecum has the widest diameter of the colon, as well as the highest wall tension. Despite this fact, the mural thickness of the normal cecum is only about 0.2 cm. The mural thickness increases gradually over the length of the colon, and reaches about 0.4 cm in the sigmoid colon, which corresponds to the increasingly solid nature of the luminal contents. The lack of a continuous outer longitudinal muscle layer in the muscularis propria implies that the circumferential inner smooth muscle layer dictates the real diameter of the colon. The diameter varies irregularly from mildly pinched constrictions to intervening dilated segments, each about 2 to 4 cm in length. From the luminal aspect, the constrictions are termed *haustral folds*, and are prominent anatomic features during endoscopy.

The ileum inserts into the cecum at the *ileocecal valve*. This is a prominent circumferential lip of mucosa and fatty submucosa, which extends about 0.5 to 1 cm into the cecal lumen. The luminal opening may be slit-shaped or oval. The thickness of the "lip" is about 0.3 cm, but it may be thicker in some individuals. The proximal aspect of the ileocecal valve contains small intestinal mucosa, and the distal aspect has colonic mucosa. The mucosal transition occurs at the level of the abrupt luminal convexity of the valve. This structure represents the mechanism that minimizes reflux of cecal contents into the ileum. Whether the "valve" restricts flow of ileal contents into the cecum has never been established; it does not constitute a real muscular sphincter.

The function of the colon is to reclaim luminal water and electrolytes. Unlike the mucosa of the small intestine, the colonic mucosa has no villi, and is flat. The mucosa is punctuated by numerous straight, nonbranching tubular crypts that extend down and touch the muscularis mucosae (Fig. 1-14A). The surface epithelium is composed of columnar absorptive cells, which have shorter and less abundant microvilli than those in the small intestine, and goblet cells. The crypts contain abundant goblet cells, endocrine cells (see the discussion of small intestine, previously), and undifferentiated crypt cells. Paneth cells are occasionally present at the base of crypts in the cecum and the ascending and proximal transverse colon. IELs are present throughout the colonic mucosal epithelium. Normal counts are less than 5 IELs per 100 epithelial nuclei.[91]

Two sources of potential diagnostic error arise from the normal variation in colonic mucosal microanatomy. First, on occasion, the normal colonic mucosa exhibits undulation of the surface, so-called *anthemic folds* (see Fig. 1-14C). This is a normal variant. A particular feature of this variant is that crypts that arise at the base of the

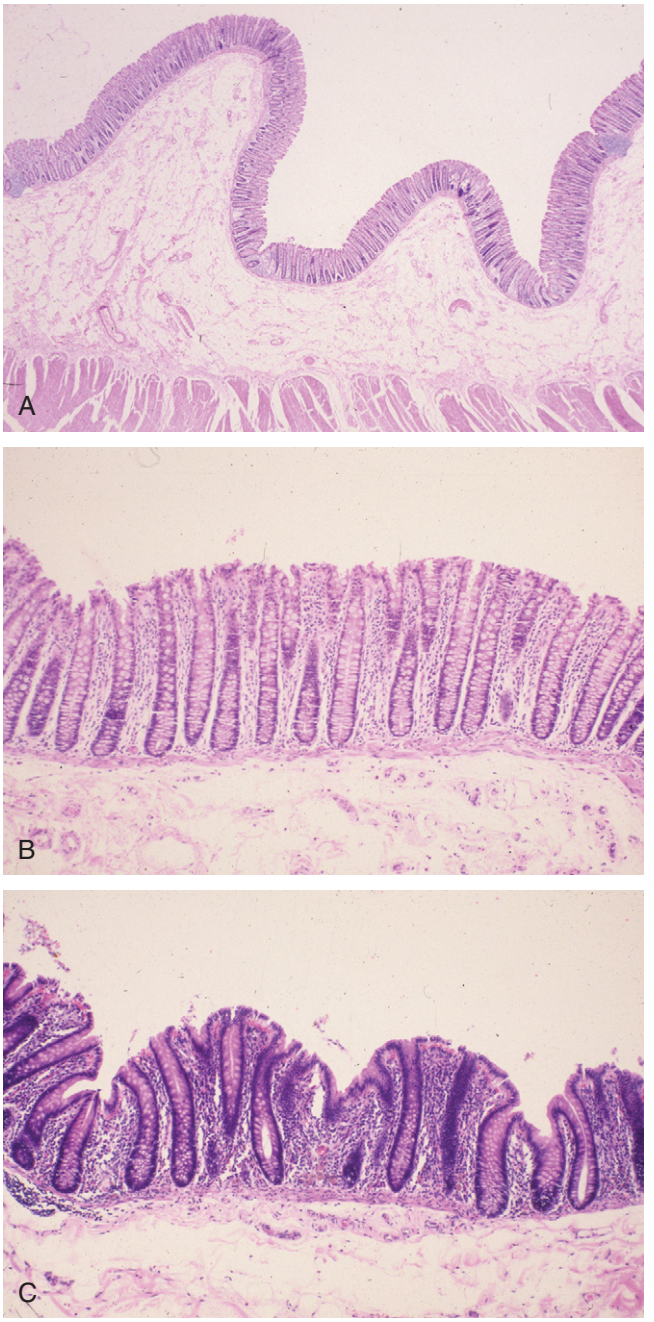

FIGURE 1-14 Normal histology of the colon. **A,** Low-power view, showing the mucosa overlying the submucosa and muscularis propria. **B,** Medium-power view, showing characteristic flat colonic mucosa. **C,** Medium-power view, showing colonic mucosa with anthemic folds.

undulations appear to branch into the upper third of the mucosal layer. Confusion arises when these crypts are interpreted as evidence of "architectural distortion" characteristic of chronic colitis. Thus, crypt branching is considered definitive only when it occurs in the lower third of the mucosal layer. Second, in the immediate vicinity of a mucosal lymphoid nodule, the crypts are typically

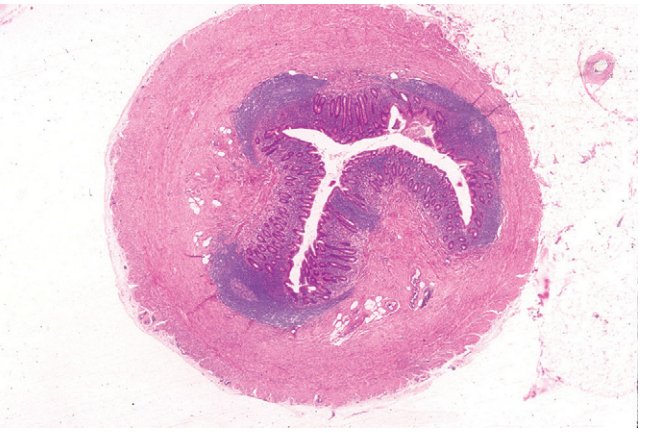

FIGURE 1-15 Normal histology of the appendix, low-power view. Mucosa-associated lymphoid tissue in the mucosa and submucosa is visible.

distorted.[94] Although this may be obvious if the tissue section transects a lymphoid nodule, a tissue section near, but not through, a lymphoid nodule will reveal only disorganized crypts. Scanning multiple serial sections helps identify the lymphoid nodule.

APPENDIX

The vermiform appendix is a narrow, worm-shaped structure that protrudes from the posteromedial aspect of the cecum, 2 cm (or less) below the insertion of the ileum into the cecum. The appendix is located at the proximal root of the outer tinea coli of the cecum. Because the anterior tinea coli of the cecum is generally quite prominent, it serves as a guide to locate the appendix. The length of the normal appendix is quite variable, from 2 to 20 cm in length. Its diameter is quite consistent and uniform along its length, about 0.3 to 0.5 cm. It has a rudimentary mesentery only on a portion of its length. The intraperitoneal location of the appendix also is variable. The appendix may lie behind the cecum, hang over the brim of the pelvis, or lie in front or behind the ileum. However, in any individual, the location is relatively fixed.

The appendix is completely invested by peritoneum, and has both an inner circumferential and a fully circumferential, outer longitudinal muscle layer of the muscularis propria. The mucosa of the appendix is colonic in type. However, the most prominent feature is the abundance of lymphoid tissue that lies within both the lamina propria and submucosa (Fig. 1-15). The lymphoid tissue is particularly prominent in younger individuals, and dissipates gradually over the person's lifetime. The concept that the appendix undergoes normal "fibrous obliteration" late in life has long been postulated. More likely, alterations to the lumen of the appendix reflect a life of clinically silent inflammatory conditions (see Chapter 15).

RECTUM AND ANUS

The rectum begins within the abdominal cavity and tapers rapidly to the base of the pelvis. The discontinuous tinea coli converge, unite, and again constitute a complete outer longitudinal smooth muscle layer of the muscularis propria. Where the rectum exits the peritoneal cavity to enter the anal canal, it is completely invested by both inner and outer smooth muscle coats of the muscularis propria, and acquires an adventitia rather than a serosal covering.

There are subtle differences in the normal histology of the distal rectal mucosa.[94] Compared with nonrectal colonic mucosa, distal rectal mucosa exhibits crypts that are not as closely spaced and are slightly shorter (Fig. 1-16). Unlike the rest of the colon, the crypts do not extend directly down to the muscularis mucosae. The crypts may be slightly dilated or tortuous, and somewhat less numerous. The surface epithelium may be slightly cuboidal rather than tall columnar. The intervening lamina propria contains a moderate number of lymphocytes, plasma cells, macrophages, and occasional neutrophils. Scattered muciphages are common in the lamina propria of the rectum, particularly in older adults. Presumably, they represent the vestiges of previous mucosal injury. It is important to recognize the simplified and somewhat distorted mucosal architecture of the distal rectal columnar mucosa as normal, and not indicative of true "architectural distortion" characteristic of chronic inflammatory bowel disease.

The anal canal is a complex anatomic structure that shows considerable individual variation of mucosal histology[95] (discussed in detail in Chapter 28). First, it is critical to understand the macroscopic anatomy of the anal canal (Fig. 1-17). The rectal vault descends into the muscular anal canal, which is composed of the muscularis propria of the anal canal (the internal anal sphincter), and the anorectal skeletal musculature (the external anal sphincter). The external anal sphincter is a complex arrangement of perineal muscle fibers, the most proximal of which is the puborectalis muscle (sling). The puborectalis muscle loops from the pubis bone around the upper portion of the anal canal and back to the pubis, and imparts a sharp

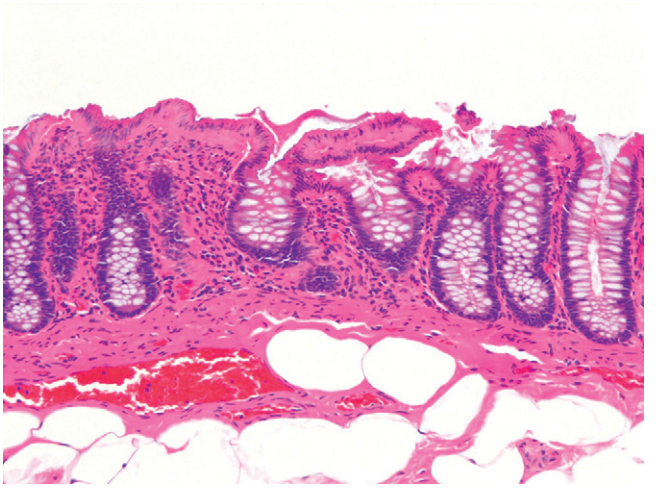

FIGURE 1-16 Normal histology of the rectum, showing the more rudimentary glands, lack of extension down to the muscularis mucosae, and mild crypt distortion.

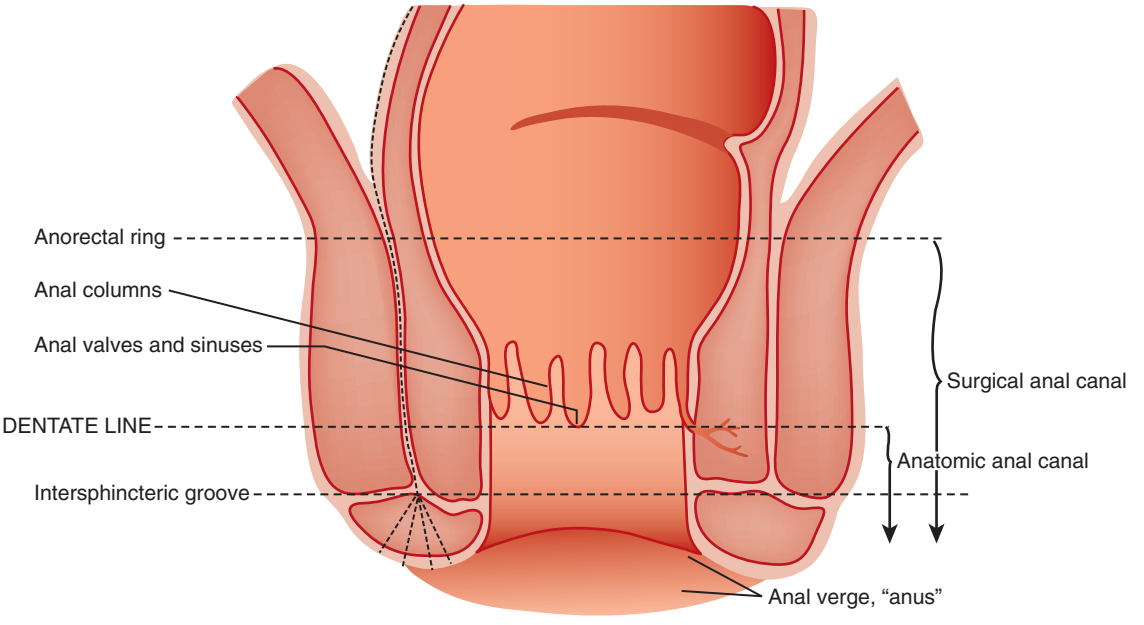

FIGURE 1-17 Macroscopic anatomy of the anal canal.

mucosal angle to the posterior aspect of the rectal vault. As the rectum enters the anal canal, the transverse folds of the colorectal mucosa end, and the mucosa aligns along the long axis into 6 to 10 vertical *anal columns*. The anal columns terminate about halfway down the anal canal, with interconnecting semicircular *anal valves* that delineate discrete mucosal recesses termed the *anal sinuses*. Anal mucin-producing glands empty into the anal sinuses. These anal valves and sinuses are particularly prominent in children, but become less pronounced with age. The anal columns may actually protrude into the lumen, earning the name *anal papillae*. The circumferential ring of anal valves and sinuses is termed the *dentate line*. Immediately below the dentate line is a zone of smooth mucosa, which flares at the *anal verge* to become anal skin, which is visible upon external examination. The overall distance of the anal canal, in vivo, averages 4.2 cm in normal adults.

The mucosa of the anal canal is divided into three zones according to the type of epithelial lining. The upper third, above the anal columns, is rectal columnar mucosa. Next is the *anal transitional zone*, which spans the distance of the anal columns down to the dentate line, about 1 cm in length. Distal to the dentate line is a nonkeratinizing stratified squamous mucosa; at the anal verge this becomes keratinized skin, and contains adnexal structures typical of perineal skin.

It is the mucosa of the anal transitional zone that is the most variable (Fig. 1-18). In some instances, nonkeratinizing anal squamous mucosa may extend up the anal columns and transition directly into the columnar rectal mucosa at its most proximal extent. However, in many individuals, a *transitional mucosa* is present that consists of four to nine cell layers that are neither squamous nor columnar, but rather stratified cuboidal or polygonal and overlie a basal cell layer. Occasional mucin goblet cells may be present as well. Transitional mucosa may be present, especially in the anal sinuses, extending proximal from the nonkeratinizing squamous mucosa of the lower anal canal and transitioning to rectal columnar mucosa proximally. Regardless of whether the anal canal mucosa is columnar, transitional, or nonkeratinizing squamous, this region retains the designation of the *anal transitional zone*.

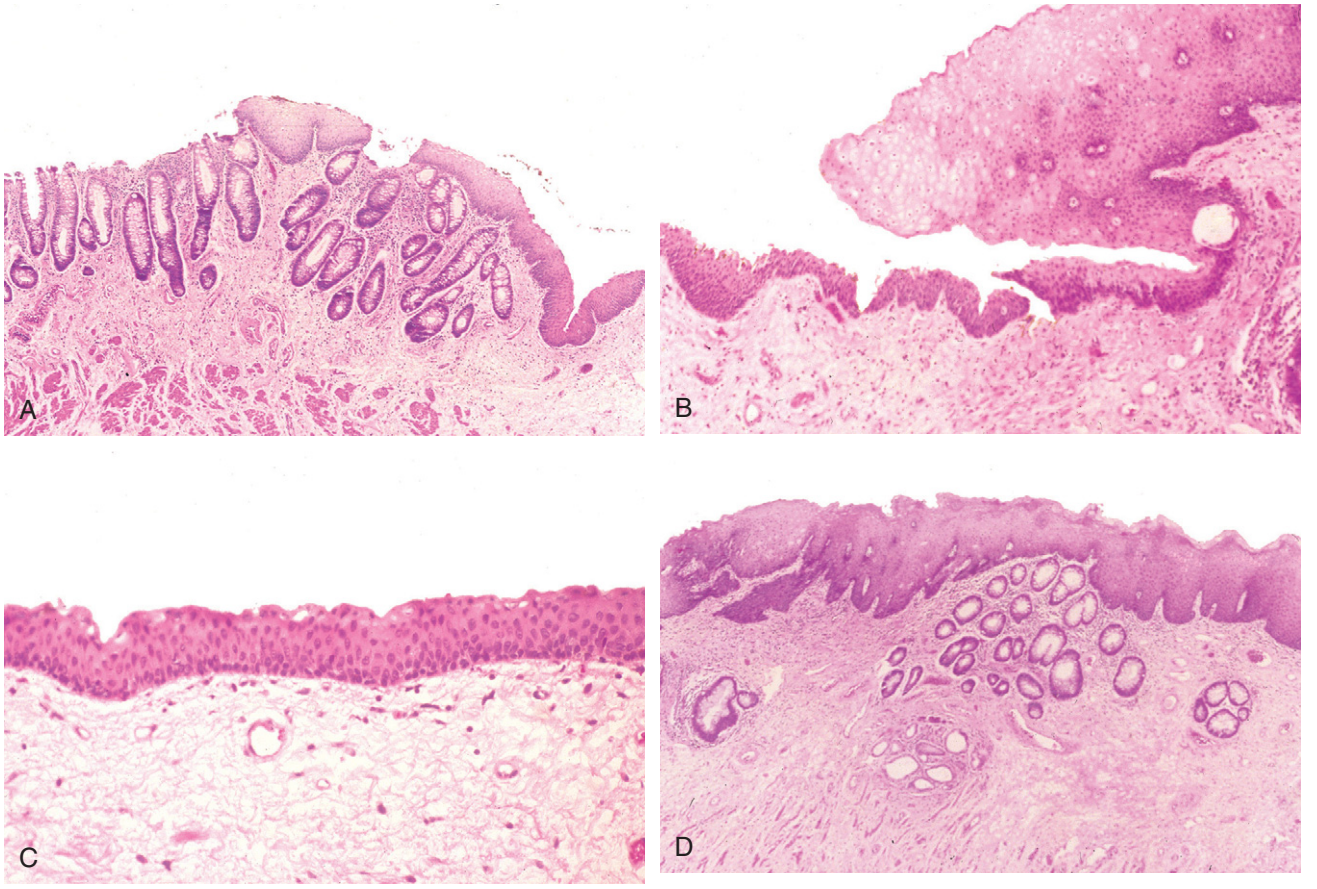

FIGURE 1-18 Normal histology of the anal canal. **A,** Mucosal squamocolumnar transition at the top of an anal column. **B,** Mucosal transition from transitional mucosa *(left)* to anal squamous mucosa *(right)*, at the lip of an anal sinus. **C,** Anal transitional mucosa. **D,** Anal verge, with epidermis overlying dermal sebaceous glands.

LYMPH NODE PRAINAGE AND LYMPHATICS OF THE TUBAL GUT

General principles of lymphatic drainage are straightforward[96]: lymphatics in the mucosa or submucosa drain through the muscularis propria, then either enter into larger lymphatic channels located in the perivisceral adventitia, or into a pedicle or mesentery. There are, however, key anatomic features in each segment of the tubal gut.

Esophagus

The mucosal anatomy of the esophagus bears one key difference from the remainder of the tubal gut, in that the squamous mucosa overlies a definitive layer of lamina propria, which is supported by the muscularis mucosae and submucosa. In the stomach, small intestine, and colon, the lamina propria is intimately interdigitated between the epithelium, so that the base of epithelial glands or crypts lies directly on the muscularis mucosae. Hence, unlike elsewhere, in the esophagus there is a rich mucosal plexus of lymphatics in the lamina propria oriented predominantly in a longitudinal direction.[97] This plexus connects with less extensive plexuses in the submucosa and muscularis propria, and eventually drains to regional lymph nodes. Because of this arrangement, esophageal cancers can display early and extensive intramucosal, submucosal, and mural spread along the axis of the esophagus, well beyond the margins of grossly visible tumor.

Stomach

In the stomach, lymphatic channels are absent from the superficial lamina propria but are present in the interglandular region of the deeper portions of the mucosa.[98] They converge into thicker channels that pierce the muscularis mucosae and enter a submucosal plexus. From there, they drain into the lymphatic plexus between the circular and longitudinal layers of the muscularis propria, which runs along the muscle fibers to form a polygonal meshwork. Valves are present in this intramural network. From there, larger lymphatic channels track along the major arteries and veins into the gastric and colonic mesenteries.

Small Intestine

The lymphatic drainage of the small intestine is distinct.[99] In the lamina propria of each villus are three or more lymphatic channels that run parallel to one another along the long axis. Given the heavy flow of chylomicrons and fatty droplets from the absorptive epithelium to the lymphatic space, the endothelial lining typically contains numerous gaps. These lymphatic channels collect into central lacteals located within the deeper part of the villi, which have a continuous endothelial lining and a reticulin fiber sheath to which smooth muscle fibers attach. The smooth muscle fibers are oriented longitudinally in the villi as well, and intermittently contract to force lymph along the channels. The lacteals anastomose with each other at the base of each villus, and form an expanded sinus network, the intravillous lymphatic sinus. Penetrating lymphatic channels then traverse the muscularis mucosae to enter an extensive submucosal lymphatic plexus. This latter plexus drains through lymphatics in the muscularis propria to large conducting lymphatics in the mesentery and, thence, to the major lymphatic ducts located mainly parallel to the larger vascular structures and at the mesenteric root.

Colon

In the colon, a lymphatic plexus lies just underneath the muscularis mucosae. This plexus sends small branches into the deep mucosa at the level of the bases of the colonic crypts.[100] The submucosal plexus drains to an intramural lymphatic plexus located between the inner circular and outer discontinuous longitudinal layers of the muscularis propria (Fig. 1-19). Intramucosal, submucosal, and mural lymphatic channels may be sites for microscopic metastasis. However, unlike in the esophagus, extensive longitudinal microscopic spread of colon cancer is exceedingly rare because there is a virtual absence of microscopic colonic cancer more than 2 cm proximal or distal to the macroscopic tumor mass.[101] As in the small intestine, lymphatic channels exiting the colonic wall enter into a predominantly radial pattern of drainage in the mesocolon.

The existence of lymphatic channels located immediately above the muscularis mucosae is often overlooked by pathologists, particularly in light of the fact that there are abundant data to suggest that carcinomas confined to the mucosa (intramucosal) are not at significant risk of lymphatic metastasis.[102] Indeed, these lymphatic channels are

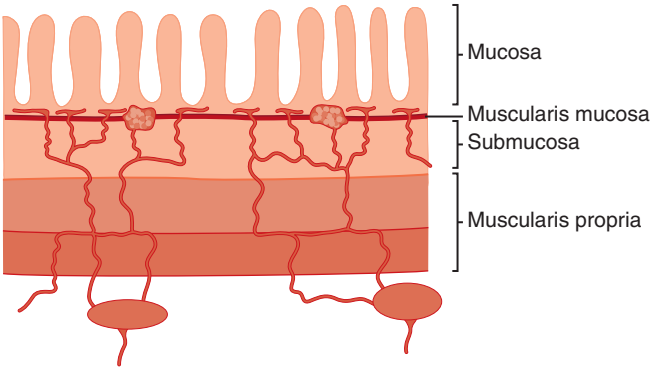

FIGURE 1-19 Schematic of lymphatic system that drains the colon wall. Terminal twigs of the lymphatics lie just above the muscularis mucosae, at the base of the lamina propria. There are occasional dilated lymphatic spaces that span the muscularis mucosae. There is a limited submucosal lymphatic plexus, and plexuses within the muscularis propria. Immediately adjacent to the muscularis propria are epicolic lymph nodes, which drain towards the mesenteric root through paracolic, intermediate, and principal lymph nodes *(not shown)*. (Reproduced with permission from Crawford JM: Principles of anatomy. In Rustgi AK, Crawford JM [eds]: Gastrointestinal Cancers: Biology and Clinical Management. Philadelphia, WB Saunders, 2003, pp 121-131.)

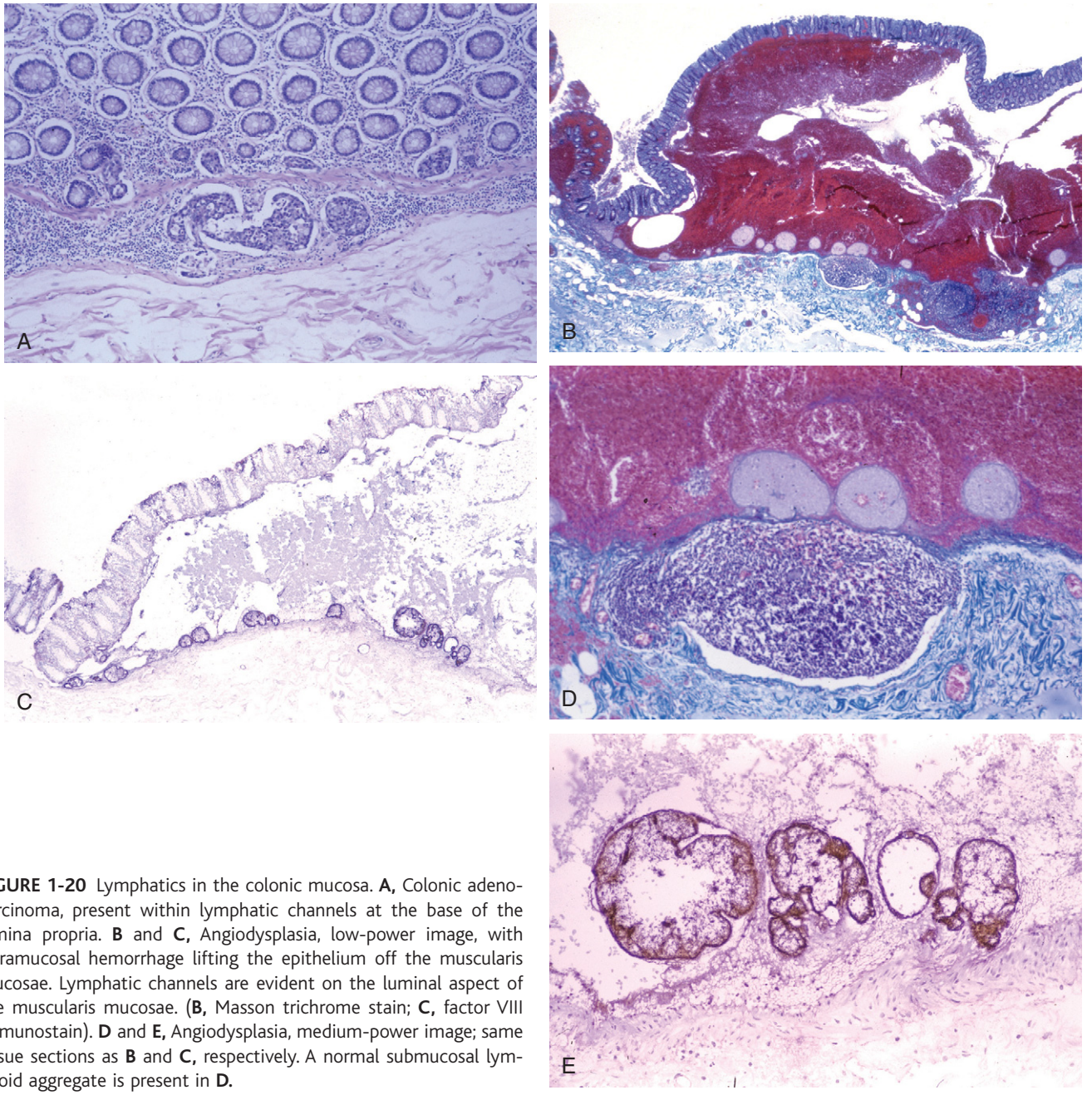

FIGURE 1-20 Lymphatics in the colonic mucosa. **A,** Colonic adenocarcinoma, present within lymphatic channels at the base of the lamina propria. **B** and **C,** Angiodysplasia, low-power image, with intramucosal hemorrhage lifting the epithelium off the muscularis mucosae. Lymphatic channels are evident on the luminal aspect of the muscularis mucosae. (**B,** Masson trichrome stain; **C,** factor VIII immunostain). **D** and **E,** Angiodysplasia, medium-power image; same tissue sections as **B** and **C,** respectively. A normal submucosal lymphoid aggregate is present in **D.**

very difficult to identify on routine H&E-stained tissue sections. However, invasive adenocarcinomas may be visible within intramucosal lymphatic channels (Fig. 1-20A), and other striking examples of intramucosal lymphatics may also be encountered (see Fig. 1-20B–E). The reason why pure intramucosal carcinomas almost never metastasize through lymphatics is therefore unknown.

Lymph Nodes

The esophagus drains into numerous lymph node groups: five directly adjacent to the esophagus in paratracheal, parabronchial, paraesophageal, pericardial, and posterior mediastinal locations (Fig. 1-21). The cervical esophagus also drains into the internal jugular and cervical lymph nodes, upper tracheal lymph nodes, and potentially supraclavicular lymph nodes. The infradiaphragmatic portion of the esophagus drains into the left gastric nodes along the lesser curvature, and the ring of lymph nodes surrounding the cardia.

Lymphatics from the gastric wall drain into numerous lymph nodes distributed in chains along the greater and lesser curvatures, in the cardia region, and in the splenic hilum (Fig. 1-22). As detailed by Fenoglio-Preiser and colleagues,[97] the drainage patterns are as follows:

- Lesser curvature and lower esophagus: left gastric lymph nodes
- Pylorus: right gastric and hepatic lymph nodes along the course of the hepatic artery
- Cardia: pericardial lymph nodes surrounding the GEJ and left gastric lymph nodes
- Proximal portion of the greater curvature: pancreatosplenic lymph nodes in the hilum of the spleen

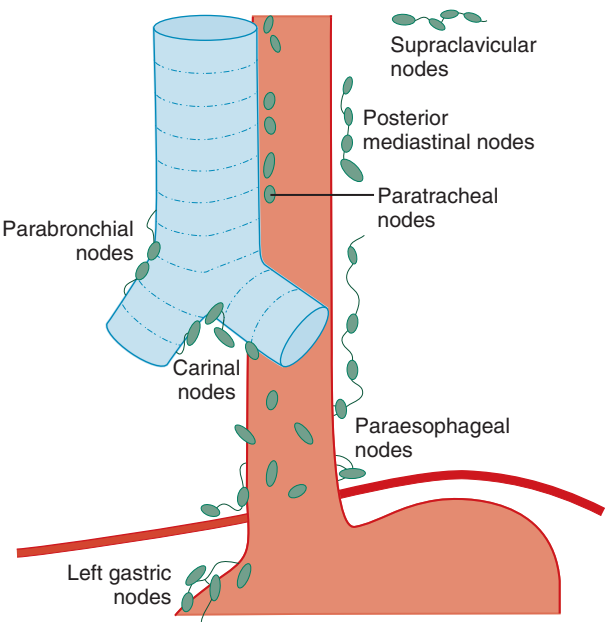

FIGURE 1-21 Lymph nodes of the esophagus are separated into six regional node systems. (Reproduced with permission from Crawford JM: Principles of anatomy. In Rustgi AK, Crawford JM [eds]: Gastrointestinal Cancers: Biology and Clinical Management. Philadelphia, WB Saunders, 2003, pp 121-131.)

- Distal part of the greater curvature: right gastroepiploic lymph nodes in the greater omentum, and to the pyloric lymph nodes at the head of the pancreas

Effluents from all lymph node groups ultimately pass to the celiac nodes surrounding the main celiac axis.

There are about 200 mesenteric lymph nodes in the small and large intestinal mesentery. Small mesenteric lymph nodes lie along the radial and arcuate ramifications of the distal mesenteric vasculature subjacent to the bowel wall (Fig. 1-23). Larger ones lie along the primary arcades and major intestinal arteries, especially near the bifurcation of major vessels. The major lymph node groups are located at the root of the superior and inferior mesenteric arteries. These lymphatics converge in lymph nodes located at the mesenteric root. Lymph fluid passes from there to the *cisterna chyli*, a lymphatic sac that lies in the retroperitoneum behind the aorta and immediately below the diaphragm (Fig. 1-24). The cisterna chyli gives rise to the thoracic duct, which tracks alongside the aorta into the thorax. From there, it runs between the aorta and azygos vein, and receives lymphatic branches from the posterior mediastinal structures, intercostals, jugular, subclavian, and bronchomediastinal ducts before emptying into the angle between the left internal jugular and left subclavian veins.

Distal rectal lymphatics drain laterally along the course of the inferior hemorrhoidal vessels, and from there into para-aortic lymph nodes to end in the hypogastric, obturator, and internal iliac nodes. Alternatively, they follow the superior rectal artery to drain into lymph nodes in the sigmoid mesocolon near the origin of the inferior mesenteric artery. Lymphatic drainage from the anus is into the endopelvic fascia along the lateral aspect of the ischiorectal

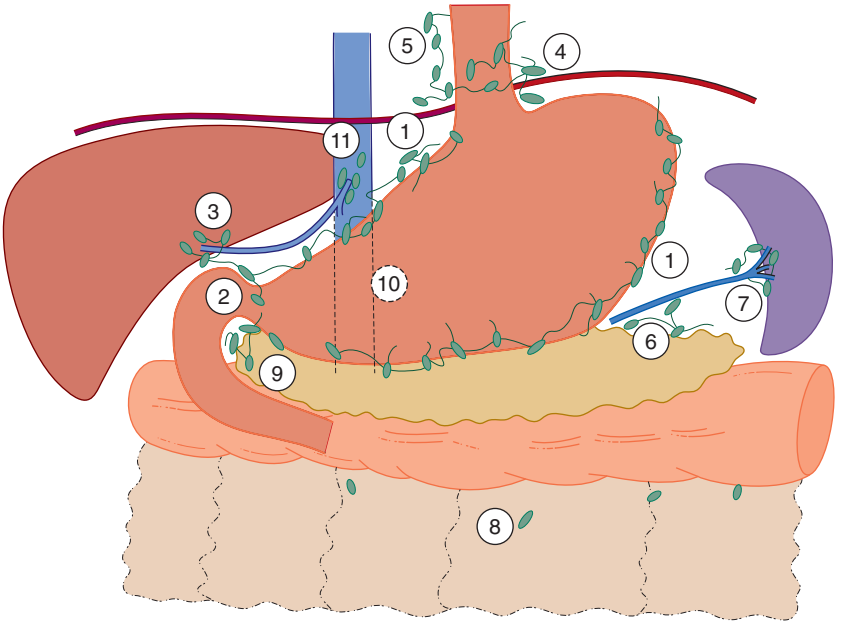

FIGURE 1-22 Lymph nodes that drain the stomach and pancreas are separated into (1) lesser curvature and left gastric lymph nodes; (2) right gastric lymph nodes; (3) hepatic hilar lymph nodes; (4) pericardial and (5) paraesophageal lymph nodes; (6,7) pancreatosplenic lymph nodes; (8) gastroepiploic lymph nodes in the greater omentum; (9) pancreaticoduodenal lymph nodes; (10) para-aortic lymph nodes; and (11) celiac lymph nodes. The celiac lymph nodes drain into the cisterna chyli *(not shown)*, and from there into the thoracic duct. (Reproduced with permission from Crawford JM: Principles of anatomy. In Rustgi AK, Crawford JM [eds]: Gastrointestinal Cancers: Biology and Clinical Management. Philadelphia, WB Saunders, 2003, pp 121-131.)

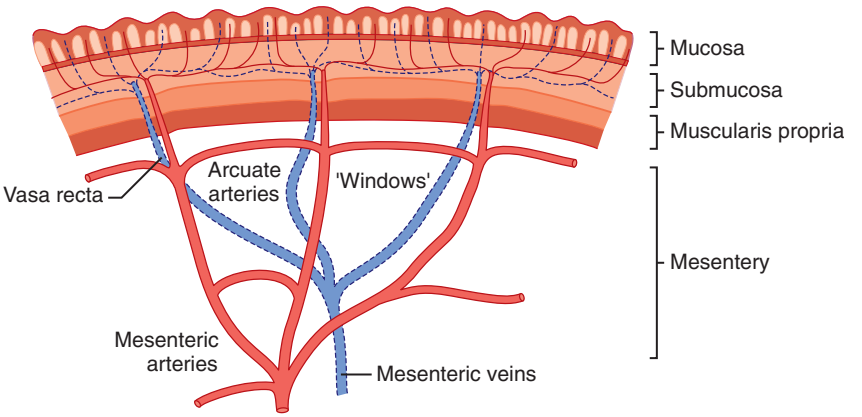

FIGURE 1-23 Diagrammatic representation of the vascular supply of the small intestine and colon. Radially oriented mesenteric arteries are interconnected by arcuate arteries, providing extensive anastomoses between regions of the arterial circulation. Terminal arteries penetrate the muscularis propria and ramify in an extensive arteriolar network in the submucosa. Terminal arterioles enter the mucosa to supply intramucosal capillary arcades. Mucosal blood exits through venules back into the submucosa and then by veins through the muscularis propria into the mesenteric venous system. Unlike the mesenteric arterial system, there are only limited anastomotic connections between mesenteric veins, and drainage is essentially linear into the portal venous system. Not shown are the lymphatic channels that accompany the major blood vessels of the mesentery; the vascular architecture provides orientation for location of small mesenteric lymph nodes lying along the radial and arcuate arteries, especially at the bifurcations of the arteries. (Reproduced with permission from Crawford JM: Principles of anatomy. In Rustgi AK, Crawford JM [eds]: Gastrointestinal Cancers: Biology and Clinical Management. Philadelphia, WB Saunders, 2003, pp 121-131.)

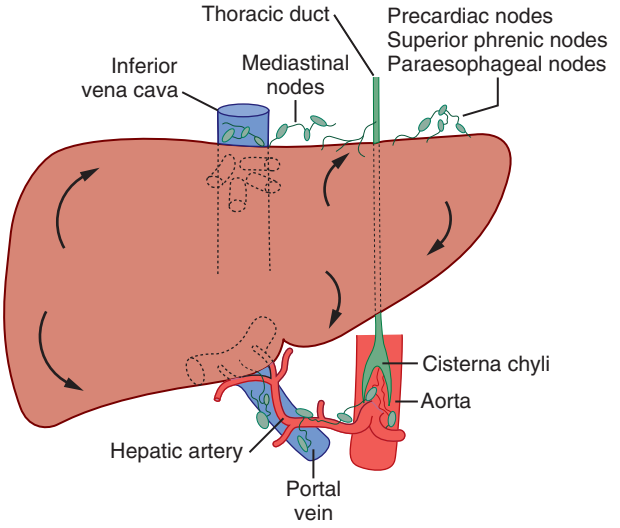

FIGURE 1-24 Lymph node drainage of the splanchnic root and liver. Lymph from the intestines gathers along the mesenteric roots *(not shown)* and travels immediately cephalad to the *cisterna chyli*, at the celiac root on the ventral aspect of the aorta, and then to the thoracic duct. The hepatic corpus drains primarily through lymphatics in the portal tree *(not shown)* and then exits through the hepatic hilum, into lymph nodes adjacent to the hepatic artery. These drain toward the celiac root and cisterna chyli. There is limited lymphatic drainage of the corpus into lymphatics that are situated along the hepatic veins, which collect into lymph nodes alongside the inferior vena cava. The liver capsule collects lymph from the superficial portions of the liver corpus, draining anteroinferiorly toward the hilum and hepatic artery lymph nodes, and posterosuperiorly toward lymph nodes of the inferior vena cava, mediastinum, and the paraesophageal/diaphragmatic region. (Reproduced with permission from Crawford JM: Principles of anatomy. In Rustgi AK, Crawford JM [eds]: Gastrointestinal Cancers: Biology and Clinical Management. Philadelphia, WB Saunders, 2003, pp 121-131.)

space, thence to the genital femoral sulcus on either side, and ultimately to the inferomedial group of superficial inguinal lymph nodes. Some anal canal lymphatics connect with the rectal lymphatics, whereas others may drain to the common iliac, middle and lateral sacral, lower gluteal, external iliac, or deep inguinal lymph nodes.

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CHAPTER 2

Screening and Surveillance Guidelines in Gastroenterology

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FRANCIS A. FARRAYE

This chapter focuses on clinical gastroenterologic issues of interest to pathologists, including the endoscopic diagnosis and management of Barrett's esophagus, the management of intestinal metaplasia in the setting of chronic gastritis, and surveillance in patients with inflammatory bowel disease, colonic polyps, and colon cancer.

Surveillance in Patients with Barrett's Esophagus

Most authorities recommend that patients with chronic reflux symptoms of 5 years or longer undergo an upper endoscopy to screen for Barrett's esophagus. The benefits of screening programs for Barrett's esophagus are controversial because of a lack of sufficient evidence to support an improvement in survival rates or cost-effectiveness of such programs.[1] Furthermore, there is only indirect evidence to suggest that patients diagnosed with adenocarcinoma while undergoing surveillance have an increased chance of survival. Nevertheless, the current standard of care dictates that if Barrett's esophagus is diagnosed, the patient should be entered into an endoscopic surveillance program for early detection of dysplasia and adenocarcinoma.[2] In the recent past, endoscopic surveillance was undertaken only in patients medically fit to undergo esophagectomy. However, with the advent of nonsurgical ablative endoscopic techniques (e.g., photodynamic therapy, multipolar electrocautery, argon plasma coagulation) and endoscopic mucosal resection, the number of patients eligible for surveillance has increased. Recent experience with endoscopic mucosal resection suggests that it may, in fact, represent the treatment of choice in patients with high-grade dysplasia or intramucosal adenocarcinoma in the setting of Barrett's esophagus.[3-5] Aggressive treatment of reflux with proton pump inhibitors is warranted prior to surveillance endoscopy because active inflammation with repair can mimic dysplasia. Endoscopic surveillance is performed by obtaining four-quadrant biopsies at 2-cm intervals with the use of jumbo biopsy forceps. In addition, specific attention is paid to mucosal abnormalities such as ulcers, irregular lesions, nodules, and polyps. In the future, newer imaging modalities, including narrow band imaging and chromoendoscopy, may also allow more targeted biopsies.[6,7]

The recommended interval of surveillance for dysplasia in patients with Barrett's esophagus is every 3 years after two negative endoscopies 1 year apart. In the presence of biopsy-proven low-grade dysplasia, repeat endoscopy is recommended within 6 months. If no dysplasia is found, then yearly endoscopy is recommended until no dysplasia is present on two consecutive examinations. Patients with flat high grade dysplasia confirmed by an expert GI pathologist should undergo a repeat endoscopy within 3 months. The prevalence of cancer in resection specimens of patients who have undergone an esophagectomy for high-grade dysplasia ranges from 5% to 41%, and the rate of progression to cancer in patients with high-grade dysplasia approaches 30% at 10 years. Options for patients with flat high grade dysplasia include intensive surveillance (every 3 months), esophagectomy, or ablative therapies. High grade dysplasia with mucosal irregularity should undergo endoscopic mucosal resection. A summary of recommendations from the American College of Gastroenterology on endoscopic surveillance intervals in patients with Barrett's esophagus is presented in Table 2-1.

TABLE 2-1 Dysplasia Grade and Surveillance Interval

Dysplasia	Documentation	Follow-up
None	Two EGDs with biopsy within 1 yr	Endoscopy every 3 yr
Low Grade	• Highest grade on repeat EGD with biopsies within 6 mo • Expert pathologist confirmation	1 yr interval until no dysplasia × 2
High Grade	• Mucosal irregularity • Repeat EGD with biopsies to rule out EAC within 3 mo • Expert pathologist confirmation	ER Continued 3 mo surveillance or intervention based on results and patient

EGD, esophagogastroduodenoscopy; ER, endoscopic resection; EAC, esophageal adenocarcinoma.

Wang KK, Sampliner RE: Updated guidelines 2008 for the diagnosis, surveillance, and therapy of Barrett's esophagus. Am J Gastroenterol. 103:788-797, 2008.

Surveillance in Patients with Chronic Gastritis and Intestinal Metaplasia or Dysplasia

The most common causes of chronic gastritis include *Helicobacter pylori*, environmental exposures including smoking, and autoimmune processes. Endoscopically obtained biopsies from patients with chronic gastritis may reveal intestinal metaplasia. A study from the United States revealed that 13% of patients at low risk for gastric cancer, and 50% of patients at higher risk, had intestinal metaplasia on biopsies from normal-appearing gastric mucosa.[8] Although gastric intestinal metaplasia (incomplete type) is considered a premalignant lesion, the overall risk of gastric cancer in patients with gastric intestinal metaplasia is very low. However, those with dysplasia have an approximately 100-fold increased risk of gastric cancer.[8]

Currently, in the United States where the incidence of gastric cancer is low, endoscopic surveillance of patients with gastric intestinal metaplasia is not recommended in

those at low risk for gastric cancer.[9] Low-risk patients include those living in developed countries, whites without any family history of gastric cancer, and people without dysplasia on gastric biopsy. The likelihood that endoscopic surveillance of low-risk patients with intestinal metaplasia increases detection of curable gastric cancer is very low and thus not likely to be cost-effective. Furthermore, intestinal metaplasia is a histologic lesion, not visible endoscopically. This makes endoscopic surveillance difficult, as numerous biopsies mapping the stomach would be needed to obtain a significant yield.

Surveillance in patients with intestinal metaplasia at a high risk for gastric cancer is controversial. High-risk patients include those with a family history of gastric cancer, Hispanics, blacks, and immigrants from higher-risk geographic locations. No formal recommendations or data that support the implementation of an endoscopic surveillance program in high-risk patients with gastric intestinal metaplasia exist at this time. The American Society of Gastrointestinal Endoscopy concluded that patients at increased risk for gastric cancer on the basis of ethnic background or family history *may* benefit from surveillance, although there was no specific recommendation on the frequency of endoscopy.[9] If surveillance is performed, the American Society of Gastrointestinal Endoscopy recommends that endoscopic surveillance with gastric biopsies should incorporate a topographic mapping of the entire stomach histologically.[9]

More uniform consensus exists for the management of patients with dysplasia in gastric biopsies. These patients should be placed in an endoscopic surveillance program, although no recommendation has been issued on the frequency of surveillance endoscopy. The Society for Gastrointestinal Endoscopy recommends that patients with confirmed high-grade dysplasia on gastric biopsies be considered for gastrectomy or endoscopic mucosal resection.[9] Recent studies using magnification chromoendoscopy have shown that this technique is useful in identifying precancerous gastric lesions.[10] We expect that recommendations regarding appropriate intervals for surveillance endoscopy, and the use of new techniques, will be formalized in the near future.

Surveillance in Patients with Inflammatory Bowel Disease

Although no prospective randomized studies have been performed to evaluate the efficacy of surveillance colonoscopy to detect dysplasia or colorectal cancer in inflammatory bowel disease, it has become the standard of care to offer colonoscopy to these patients. The available data suggest a reduction in mortality from colorectal cancer in patients with inflammatory bowel disease who are undergoing surveillance.[11] Surveillance colonoscopy should optimally be performed when the patient is in remission, because active inflammation may hinder the histologic diagnosis of dysplasia. Current guidelines from the Crohn's and Colitis Foundation of America consensus group recommend that colonoscopic surveillance begin 8 to 10 years after the diagnosis of colitis in patients with pancolitis or left-sided colitis. A repeat colonoscopy should be performed within 1- to 2-years. After two negative examinations, the interval is every 1 to 3 years, as long as the duration of disease does not exceed 20 years. After 20 years of disease, colonoscopy should again be performed at 1- to 2-year intervals.[12-15] Patients with proctitis or distal proctosigmoiditis are not at an increased risk for the development of colorectal cancer and thus do not need to undergo surveillance.

Numerous studies have demonstrated that the risk of colorectal cancer is increased in patients with long-standing and extensive colitis, and in patients with primary sclerosing cholangitis. Recent studies have correlated the severity of colonoscopic macroscopic as well as histologic inflammation and the risk of colorectal cancer.[16] Patients with coexisting primary sclerosing cholangitis should begin surveillance colonoscopy at the time of diagnosis of liver disease, and then annually thereafter regardless of the extent of disease.[13,15] Although not included in formal recommendations, patients with a family history of colon cancer are also candidates for shorter surveillance intervals.

Accumulating evidence suggests that patients with extensive Crohn's colitis should also undergo endoscopic surveillance. Recent studies have shown an increased risk of colorectal cancer in patients with long-standing Crohn's disease, strictures, and fistulas involving the colon.[17-20] In one study, the cumulative probability of detecting dysplasia or cancer in patients with Crohn's colitis after a negative initial screening colonoscopy was 22% by the time of the third follow-up colonoscopy.[18] Recent guidelines recommend beginning surveillance colonoscopy 8 to 10 years after disease onset. Interval examinations should be performed according to the same time schedule as that proposed for patients with ulcerative colitis.[13]

There is wide variability in the practice of surveillance by gastroenterologists as well as inconsistency in the management of patients with dysplasia.[21,22] Current guidelines recommend obtaining 33 total colonic biopsies using jumbo forceps. This was based on a retrospective analysis that revealed a 90% positive predictive value for dysplasia with 33 biopsy specimens, and a 95% positive predictive value with greater than 56 specimens.[23] In practice, most endoscopists obtain four-quadrant biopsies at 10-cm intervals from the cecum to the rectum. It is also recommended that in patients with ulcerative colitis, four-quadrant biopsies should be taken every 5 cm in the distal sigmoid and rectum.[13] Other endoscopists obtain six specimens from each of the following sections: cecum and ascending colon, transverse colon, descending colon,

sigmoid, and rectum. Additional biopsies should be obtained of any suspicious mucosal lesions. A recent study found that in 79% to 89% of cases, dysplasia (e.g., irregular mucosa, strictures, polypoid lesions, or masses) in ulcerative colitis was visible to the endoscopist.[24] The finding of dysplasia of any grade needs to be confirmed by a pathologist with special expertise in GI pathology. For patients with indefinite dysplasia, colonoscopy should be repeated at a shorter interval of 3 to 6 months.[13] The Crohn's and Colitis Foundation guidelines recommend proctocolectomy in cases of high-grade dysplasia, but there is no formal consensus on the recommendation of proctocolectomy for patients with low-grade dysplasia.[22] Most authorities recommend proctocolectomy in patients with more than one focus of low-grade dysplasia, or a single repetitive focus on more than one colonoscopy. Many authorities now recommend proctocolectomy in patients with even a single focus of low-grade dysplasia, since this has been shown to be associated with concurrent adenocarcinoma in 20% of patients, and to progress to higher grades of dysplasia in 50% of cases.[25] Patients with low-grade dysplasia, who elect against colectomy, should undergo repeat surveillance colonoscopy on a 3- to 6-month basis. These guidelines apply to flat dysplasia.

The treatment of a dysplastic "polyp" in patients with ulcerative colitis or Crohn's colitis is evolving. If a well-circumscribed adenomatous polyp is found proximal to the highest extent of histologically demonstrable colitis, it should be managed as a simple adenoma. Dysplasia-associated lesions or masses (DALMs) were first identified by Blackstone and colleagues in 1981 and were associated with a high rate of colorectal cancer at colectomy.[26] More recently, a raised dysplastic lesion with the appearance of sporadic adenoma has been termed an adenoma-like DALM.[27] In contrast, poorly circumscribed lesions with indistinct borders and an irregular surface, or plaquelike lesions, have been termed nonadenoma-like DALMs. The endoscopist must make a distinction between an adenoma-like DALM and a nonadenoma-like DALM, since these lesions overlap histologically. Patients with ulcerative colitis who develop an adenoma-like DALM may undergo polypectomy and continued endoscopic surveillance if no other areas of flat dysplasia are detected in the adjacent mucosa or elsewhere in the colon, because the risk of adenocarcinoma is negligible.[13,28,29] It is recommended that at least four biopsies be taken immediately adjacent to the polyp to appropriately exclude flat dysplasia. Follow-up colonoscopy should be performed within 6 months, and thereafter at regular surveillance intervals if no dysplasia is found. In contrast, patients with nonadenoma-like DALM are generally referred for colectomy because of its high rate of association with synchronous or metachronous cancer. Recommendations for the management of flat and polypoid dysplasia are shown in Figure 2-1.

Three recent studies have demonstrated that the use of chromoendoscopy can greatly increase the detection rate of dysplasia in patients with ulcerative colitis who have been enrolled in a surveillance program. Chromoendoscopy with targeted biopsies revealed significantly more dysplastic lesions than conventional colonoscopy with random biopsies. The overall sensitivity of chromoendoscopy for predicting neoplasia was 93% to 97%.[30-32] Given these findings, the Crohn's and Colitis Foundation consensus guideline has endorsed the use of chromoendoscopy in surveillance colonoscopy by trained endoscopists.[13] As more data regarding chromoendoscopy become available and new techniques are developed, guidelines for surveillance endoscopy in patients with inflammatory bowel disease will no doubt be refined to reflect these advances.[27,33] It is also likely that molecular biology techniques may play a more important role in the future as an adjunct to endoscopic biopsy.[34]

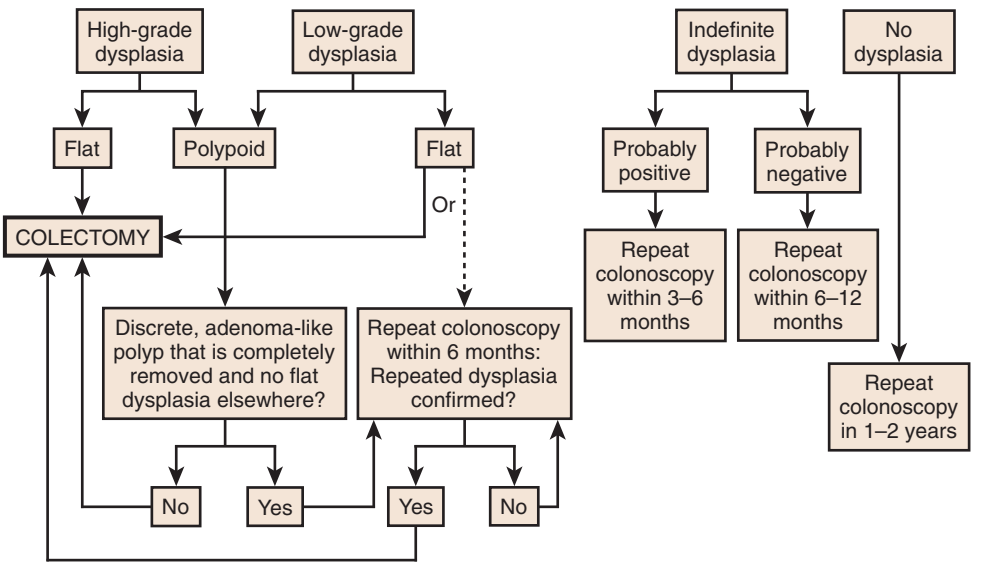

FIGURE 2-1 Suggested surveillance strategy in patients with inflammatory bowel disease and dysplasia. (From Itzkowitz SH, Harpaz N: Diagnosis and management of dysplasia in patients with inflammatory bowel diseases. Gastroenterology 126:1634-1648, 2004.)

Screening and Surveillance Guidelines for Colon Polyps

The following is a review of the management of colonic polyps in patients who do not have inflammatory bowel disease.[35,36] This summary includes surveillance after polypectomy and after resection for colorectal cancer, and the approach to the patient with a malignant polyp.

DEFINITION AND CLINICAL CONSIDERATIONS

Small (<1 cm) tubular adenomas are extremely common and have a low risk of becoming malignant. Only a small proportion of these develop histologic features of high-grade dysplasia or cancer. Advanced adenomas are defined as any polyp greater than 1 cm in diameter, and any polyp regardless of size that is villous or contains a focus of high-grade dysplasia. Efforts to reduce colon cancer are now shifting mainly to strategies to reliably detect and resect advanced adenomas before they become malignant rather than focusing on identifying small tubular adenomas. Currently, 70% of polyps removed at colonoscopy are adenomas. Approximately 70% to 85% of these are tubular, 10% to 25% are tubulovillous, and less than 5% are villous adenomas.[37]

INITIAL MANAGEMENT OF POLYPS

Colonoscopy is the most accurate method for detecting polyps and allows immediate biopsy and resection.[38] It has quickly replaced fecal occult blood testing, flexible sigmoidoscopy, and barium enema as the primary screening modality, although those remain approved methods to screen for colorectal cancer in the asymptomatic patient. Most patients who have a polyp detected by barium enema or flexible sigmoidoscopy, especially if large or multiple, should undergo colonoscopy to excise the lesion or lesions and search for additional neoplasms. The decision to perform colonoscopy for patients with polyps smaller than 1 cm in diameter must be individualized and depends on the patient's age, comorbidities, and past or family history of colorectal neoplasia. Complete colonoscopy should be done at the time of every initial polypectomy to detect and resect all synchronous adenomas. Additional colonoscopic examinations may be required after resection of a large sessile adenoma, if there are multiple adenomas, if the quality of the colonic preparation was suboptimal, or if the colonoscopist is not reasonably confident that all adenomas have been found and resected.

MANAGEMENT OF SMALL POLYPS

Small polyps (<1 cm and either sessile or pedunculated) can be resected by a number of different techniques, both with and without electrocautery. However, the monopolar hot biopsy forceps has limitations and risks, including bleeding and perforation, that need to be carefully considered. Considering that a small adenoma is a dysplastic lesion, resection of any small polyp is justified. Currently, there is no evidence that small, distally located hyperplastic polyps carry an increased risk for colorectal cancer. Thus, a traditional hyperplastic polyp found during flexible sigmoidoscopy is not, by itself, an indication for colonoscopy. However, there is accumulating evidence that certain variants of hyperplastic-appearing or serrated polyps may indeed be a precursor to colorectal cancer. For example, traditional serrated adenomas have recently been linked to the development of sporadic microsatellite unstable adenocarcinomas. Hyperplastic-appearing polyps at risk for such progression are usually large, sessile, and found proximally in the colon. These have been called atypical hyperplastic polyps, sessile serrated polyps, or sessile serrated adenomas, among other terms (see Chapter 19 for details).

Thus, an evolving consensus among gastroenterologists is that large proximally located, hyperplastic-appearing serrated polyps be managed in the same way as adenomas.[39,40] Data also conflict as to whether small distal adenomas predict the presence of proximal, clinically significant adenomas. Recent studies seem to indicate that there is no increased risk of proximal adenomas or neoplasia in patients with small distal adenomas found on flexible sigmoidoscopy.[41,42] However, it has become standard care that any adenoma found on sigmoidoscopy is an indication for colonoscopy.

MANAGEMENT OF LARGE PEDUNCULATED POLYPS

Endoscopic resection of large polyps can be challenging because of the risks of hemorrhage, perforation, and incomplete resection. Most endoscopists resect large pedunculated polyps using a hot snare. However, in certain large centers, endoscopic mucosal resection has been shown to be successfully used for large pedunculated polyps with flat broad stalks.[43]

Large pedunculated polyps (>1 cm in diameter) resected in one piece should be examined by the pathologist for adequacy of resection. The guidelines for polyp specimen processing were discussed in Chapter 1. Piecemeal resection of large pedunculated polyps impedes, but does not preclude, pathologic assessment of adequacy of resection. However, in this instance, the pathologist depends on the endoscopist to deliver a readily available stalk.

MANAGEMENT OF LARGE SESSILE POLYPS

The prevalence of large sessile polyps is approximately 0.8% to 5.2% in patients undergoing colonoscopy. Malignancy is found in 5% to 22% of these polyps. These polyps tend to recur locally after resection, and one recent study quoted

a rate as high as 46%.[44] This same study found that the recurrence rate could be reduced to 3.8% with repeated endoscopic procedures and the use of argon plasma coagulation. Another recent study found that the use of endoscopic mucosal resection for resection of large sessile polyps led to a cure rate at 1-year surveillance of 100% if the polyp was removed intact, and 96% if the polyp was removed piecemeal.[45]

Assessment of the adequacy of excision of a large sessile polyp (>2 cm) is problematic and depends on both the endoscopist's assessment of whether a residual lesion is present and the pathologist's ability to identify resection margins with confidence. This includes the issue of whether a large sessile polyp is resected intact or piecemeal. Hence, the endoscopist may tattoo the polypectomy site with India ink after endoscopic resection to facilitate visualization during a subsequent endoscopic procedure.

A patient who has undergone colonoscopic excision of a large sessile polyp in piecemeal fashion should undergo follow-up colonoscopy in 2 to 6 months to verify complete removal. If residual polyp tissue is present, it should be resected, and the completeness of this resection should be documented within another 2- to 6-month interval. Once complete removal has been established, subsequent surveillance needs to be individualized on the basis of the endoscopist's judgment. If complete resection is not possible after two or three procedures, the patient should be considered for surgical resection.[46]

Postpolypectomy Surveillance

Because a large number of patients with adenomas are being identified by colonoscopy, the burden placed on medical resources (i.e., the timely availability of colonoscopy) is increasing dramatically.[47] Thus, the U.S. Multi-Society Task Force on Colorectal Cancer and the American Cancer Society recently revised the recommendations for surveillance colonoscopy in patients after polypectomy. The new guidelines, which emphasize stratification of patients into high- and low-risk groups (Table 2-2), are based on the assumption that the initial screening colonoscopy was of optimal quality. A high-quality procedure is defined as one that reaches the cecum, has an excellent colonic preparation, and has a withdrawal time from the cecum to the anus of at least 6 minutes.[46]

After an initial colonoscopy has been performed with complete polypectomy, patients deemed to be at low risk of developing metachronous advanced adenomas should have a follow-up colonoscopy performed in 5 to 10 years. The exact length of follow-up in these patients is determined by clinician judgment and patient comfort. Low-risk patients include those with only one to two small (<1 cm) tubular adenomas with only low-grade dysplasia. Patients at high risk for developing advanced adenomas should undergo repeat colonoscopy in 3 years (Table 2-3). This includes patients with 3 to 10 adenomas, any adenoma larger than 1 cm, or any adenoma with villous or high-grade dysplasia. If the follow-up colonoscopy is normal or shows only one or two small tubular adenomas with low-grade dysplasia, the interval for the next surveillance colonoscopy can be extended to 5 years. Family history and proximal location may also predict metachronous, advanced adenomas. Currently, the data are insufficient to include these two variables as possible risk factors, and thus they were not included in the formulation of the Multi-Society Task Force guidelines.[48,49] However, family history of colon cancer in a first-degree relative does increase the risk of colorectal cancer. Thus, clinicians need to individualize follow-up in these cases. It should also be noted that interobserver variability with regard to diagnosis of villous components and high-grade dysplasia in an adenoma is high.[50] Thus, reproducible histologic criteria must be devel-

TABLE 2-2 Risk Factors for Development of Metachronous Advanced Adenomas

High Risk	Low Risk
• 3 to 10 adenomas • Any adenoma greater than 1 cm • Adenoma with villous features • High-grade dysplasia	• No adenomatous polyps • 1 to 2 small (<1 cm) tubular adenomas with low-grade dysplasia

TABLE 2-3 Guidelines for Postpolypectomy Surveillance after Initial Colonoscopy

Low-risk patients	Follow-up colonoscopy in 5 to 10 yr. Precise timing should be based on clinical judgment, patient comfort, and family history.
High-risk patients	Follow-up colonoscopy in 3 yr, provided that piecemeal polypectomy was not performed and the adenomas are completely removed. If follow-up endoscopy is normal or reveals only 1 to 2 small tubular adenomas with low-grade dysplasia, the interval for subsequent examination should be 5 yr.
Small hyperplastic rectal polyps	Repeat colonoscopy in 10 yr, as in average risk guidelines. (exception: patients with hyperplastic polyposis syndrome)

From Winawer SJ, Zauber AG, Fletcher RH, et al: Guidelines for colonoscopy surveillance after polypectomy: A consensus update by the US Multi-Society Task Force on Colorectal Cancer and the American Cancer Society. CA Cancer J Clin 56:153-159; quiz 184-185, 2006.

oped by pathologists so that future prospective outcome studies can accurately predict the fate of patients with "advanced" adenomas.

Management of Malignant Polyps

A malignant polyp is defined as an adenomatous polyp with cancer invading the submucosa; favorable and unfavorable histologic features are reviewed in Table 2-4. Guidelines from the American College of Gastroenterology for the management of malignant polyps are reviewed in Table 2-5.[36]

No further treatment is indicated after colonoscopic resection of a malignant polyp if the endoscopic and pathologic criteria listed in Table 2-4 are fulfilled. Patients with a malignant pedunculated polyp with favorable criteria may be observed in the same way as patients with a history of advanced colonic adenomas. Patients with a malignant sessile polyp that shows favorable prognostic criteria should have follow-up colonoscopy within 3 to 6 months to check for residual neoplastic tissue at the polypectomy site. After one negative follow-up examination, the clinician may revert to a standard surveillance regimen.

TABLE 2-4 Malignant Colonic Polyps: Favorable and Unfavorable Features

Favorable	Unfavorable
Cancer is well differentiated to moderately differentiated (grade I or II)	Cancer is poorly differentiated (grade III)
Absence of lymphovascular invasion	Lymphovascular invasion is present
Carcinoma is ≥2 mm from deep margin	Cancer is <2 mm from deep margin

TABLE 2-5 Malignant Colonic Polyps: Management

Findings	Management
Pedunculated polyp with favorable histology	No change in surveillance regimen
Sessile polyp with favorable histology	Follow-up colonoscopy in 3 to 6 mo; if no evidence of residual adenoma or cancer on follow-up, return to regular surveillance.
Pedunculated or sessile polyp; at least one unfavorable histologic feature	Consider surgical resection.

From Bond JH: Polyp guideline: Diagnosis, treatment, and surveillance for patients with colorectal polyps. Practice Parameters Committee of the American College of Gastroenterology. Am J Gastroenterol 95:3053-3063, 2000.

When a patient's malignant polyp has poor ("unfavorable") prognostic features, the relative risk of surgical resection should be weighed against the risk of death from metastatic carcinoma. If a malignant polyp is located in a part of the lower rectum that may require an abdominal-perineal resection, local excision, rather than standard cancer resection, may be justified. In brief, the risk of local recurrence or lymph node metastasis from an invasive carcinoma in a colonoscopically resected malignant adenomatous polyp is considered less than the risk of death from colonic surgery if the following criteria are fulfilled:

- The polyp is considered to be completely excised by the endoscopist and is submitted in toto for pathologic examination.
- In the pathology laboratory, the polyp is fixed and sectioned so that it is possible for the pathologist to accurately determine the depth of invasion, grade of differentiation, and completeness of the excision of the carcinoma.
- The cancer is not poorly differentiated (grade III).
- There is no evidence of vascular or lymphatic involvement.
- The margin of excision is not involved. Invasion of the stalk of a pedunculated polyp in itself is not an unfavorable prognostic finding as long as the cancer does not extend within 2 mm of the deep margin of stalk resection.

A recent study[51] that evaluated the outcome of endoscopic polypectomy of malignant polyps versus surgery based on histologic characteristics found that in those with "favorable" characteristics, endoscopic polypectomy alone seemed to be sufficient.

Colonoscopic Surveillance after Colon Cancer Resection

Patients who have undergone resection for colon cancer should be entered into a surveillance program to detect early recurrence of the initial primary cancer and to detect metachronous colorectal neoplasms. Only patients with stage I, II, or III colon or rectal cancers should be candidates for surveillance colonoscopy. Numerous studies have found that 2% to 7% of patients with colorectal cancer have one or more synchronous cancers in the colon and rectum at the time of initial diagnosis.[52] It has also been shown that in surveillance groups after cancer resection there is an annual incidence for metachronous cancers of 0.35% per year.[52]

On the basis of the available data, patients should undergo a high-quality perioperative clearing by colonoscopy in nonobstructive tumors, and by CT colography or double-contrast barium enema in obstructing tumors. A

TABLE 2-6 Colonoscopy Recommendations for Surveillance after Cancer Resection

1. Patients with colon and rectal cancer should undergo high-quality perioperative clearing. In the case of nonobstructing tumors, this can be done by preoperative colonoscopy. In the case of obstructing colon cancers, computed tomography colonography with intravenous contrast or double-contrast barium enema can be used to detect neoplasms in the proximal colon. In these cases, a colonoscopy to clear the colon of synchronous disease should be considered 3 to 6 mo after the resection if no unresectable metastases are found during surgery. Alternatively, colonoscopy can be performed intraoperatively.
2. Patients undergoing curative resection for colon or rectal cancer should undergo a colonoscopy 1 yr after the resection (or 1 yr after a colonoscopy performed to clear the colon of synchronous disease). This colonoscopy at 1 yr is in addition to the perioperative colonoscopy for synchronous tumors.
3. If the examination performed at 1 yr is normal, then the interval before the next subsequent examination should be 3 yr. If that colonoscopy is normal, then the interval before the next subsequent examination should be 5 yr.
4. After the examination at 1 yr, the intervals before subsequent examinations may be shortened if there is evidence of hereditary nonpolyposis colorectal cancer or if adenoma findings warrant earlier colonoscopy.
5. Periodic examination of the rectum to identify local recurrence, usually performed at 3- to 6-mo intervals for the first 2 or 3 yr, may be considered after low anterior resection of rectal cancer. The technique used is typically rigid proctoscopy, flexible proctoscopy, or rectal endoscopic ultrasound. These examinations are independent of the colonoscopic examinations for detection of metachronous disease.

subsequent colonoscopy should be performed within 3 to 6 months or intraoperatively in patients with obstructing tumors. Surveillance endoscopy should be performed in all patients 1 year after resection because of the high yield of detecting early metachronous cancers. If the first surveillance colonoscopy is negative, the next examination needs to be done at a 3-year interval. If that procedure is also normal, then the subsequent colonoscopy should be done at 5-year intervals. The Multi-Society Task Force recommendations for surveillance in patients after colorectal cancer resection are reviewed in Table 2-6.

TABLE 2-7 Quality Improvement Targets in Colonoscopy

Improvement	Goal
Percentage of adenomas with villous elements	<10%
Reports using the terms *carcinoma in situ* or *intramucosal adenocarcinoma*	None
Designation of the degree of dysplasia in adenomas as low grade or high grade	100%
Use of the terms *mild, moderate*, or *severe* to describe dysplasia and adenomas	None
Adequate characterization of malignant polyps (resection line "margin," degree of differentiation, presence or absence of vascular [or lymphatic] invasion)	100%

From Rex DK, Bond JH, Winawer S, et al: Quality in the technical performance of colonoscopy and the continuous quality improvement process for colonoscopy: Recommendations of the U.S. Multi-Society Task Force on Colorectal Cancer. Am J Gastroenterol 97:1296-1308, 2002.

Interaction of GI Endoscopists and Pathologists

An American College of Gastroenterology review on quality improvement in colonoscopy stressed the great importance of the interaction between the pathologist and GI endoscopist in the management of patients.[53] The quality improvement targets identified to improve the care provided to patients undergoing colonoscopy and polypectomy are indicated in Table 2-7.

REFERENCES

References, with PubMed access, are available in the online edition through Expert Consult.

CHAPTER 3

Diagnostic Cytology of the GI Tract

HELEN H. WANG

The popularity of GI cytology for the diagnosis of infection and malignancy has waxed and waned over the past few decades. The ability to distinguish between high-grade dysplasia or carcinoma in situ and invasive carcinoma in biopsy specimens and the more prevalent expertise of surgical pathology cause some to consider cytology an unnecessary duplication of GI mucosal biopsies.[1,2] However, the combined use of endoscopy, ultrasound guidance, and fine-needle aspiration has expanded the horizons of GI cytology.[3]

SPECIMEN TYPES

Types of GI tract specimens commonly received in the cytology laboratory include endoscopic brushings and ultrasound-guided endoscopic fine-needle aspirations. Endoscopic fine-needle aspirations have enabled endoscopists to reach farther than they can with biopsy forceps to sample mural lesions, including lesions adjacent to the GI tract. The nonendoscopic specimens obtained with either the balloon- or mesh-type samplers have been evaluated in the research setting to ascertain their usefulness in the surveillance of populations at high risk for esophageal carcinoma.[4-6]

SPECIMEN PREPARATIONS

Direct smears can be made from materials collected on the endoscopic brush, in the needle, or on the balloon and mesh samplers; these can then be either fixed immediately in 95% ethanol and stained with the Papanicolaou method or left to air-dry and stained with Diff-Quik (Dade-Behring, Inc., Deerfield, IL) or Wright-Giemsa stain. Alternatively, the material can be rinsed into a medium such as CytoLyt (Cytyc Corporation, Marlborough, MA) or 50% ethanol. The specimen can then be processed by a concentration method, such as either ThinPrep Processor (Cytyc Corporation, Marlborough, MA) or cytospin, to make slides that are then stained with the Papanicolaou method.

VALUE AND ACCURACY OF SPECIMENS

Cytology specimens have some advantages over specimens obtained by endoscopic biopsy. The brush can sample a wider area and the fine needle can reach deeper lesions than can be reached by biopsy forceps. Also, both the brush and the fine needle are less invasive than biopsy forceps and less likely to cause bleeding. In addition, cytology has shorter turnaround time than histology. Direct smears can be ready for review within minutes with no compromise of the quality of the preparation (unlike frozen sections of biopsy specimens, which compromise the quality of the final or permanent preparation). However, as mentioned, cytology is limited in its ability to distinguish between high-grade dysplasia or carcinoma in situ and invasive carcinoma.

In spite of the potential duplication of cytology and biopsy, the literature has consistently shown that the highest diagnostic yield is obtained with the combined use of these specimens.[7-9] The yield of cytology is significantly higher when the brushing is performed before rather than after the biopsy.[10]

Normal Morphology

ESOPHAGUS

Intermediate-type squamous cells with abundant cytoplasm and vesicular nuclei are seen in the normal esophagus (Fig. 3-1). Superficial-type squamous cells with abundant cytoplasm and small pyknotic nuclei can also be seen in small numbers. Single cells and clusters of ciliated columnar cells from the respiratory tract with no clinical significance may be seen rarely.

STOMACH

Gastric surface foveolar cells can shed as single cells or in sheets. When in sheets, the columnar cells with abundant cytoplasm, regularly spaced nuclei, and open chromatin arrange in a honeycomb or palisaded pattern (Fig. 3-2), depending on the orientation. When they are shed as single cells, they often lose their cytoplasm to become naked nuclei. In endoscopic fine-needle aspiration specimens, the sheets of foveolar cells can mimic cells from a mucinous neoplasm, and the single naked nuclei, because of their small monomorphic appearance, can mimic cells from a pancreatic endocrine tumor.

SMALL INTESTINE

The lining cells of the small intestine can be easily distinguished from gastric foveolar cells by the presence of goblet

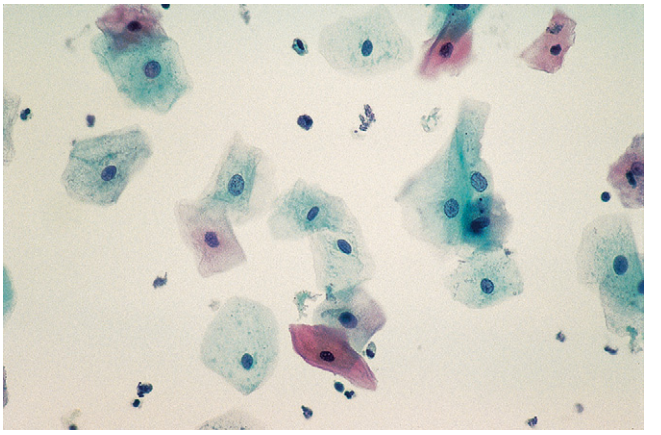

FIGURE 3-1 Brushing specimen from a normal esophagus composed predominantly of intermediate squamous cells. Scattered inflammatory cells are also noted in this field (Papanicolaou).

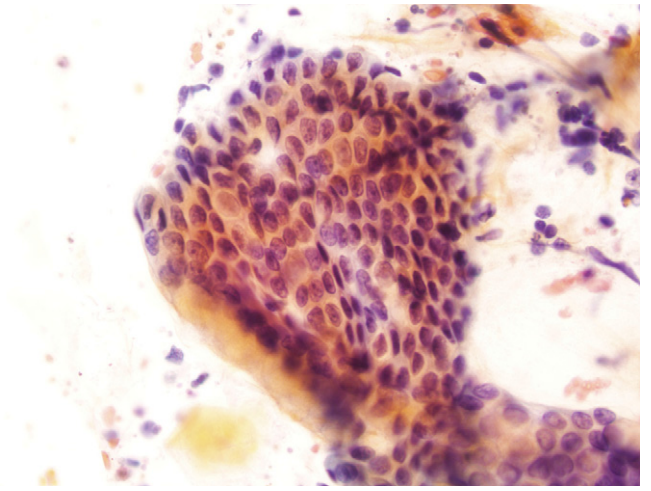

FIGURE 3-2 A sheet of benign gastric foveolar cells in a slightly distorted honeycomb pattern with evident columnar cells in palisading arrangement at the periphery is seen in this gastric brushing specimen. The presence of small nucleoli in some of the cells may indicate reactive change (Papanicolaou).

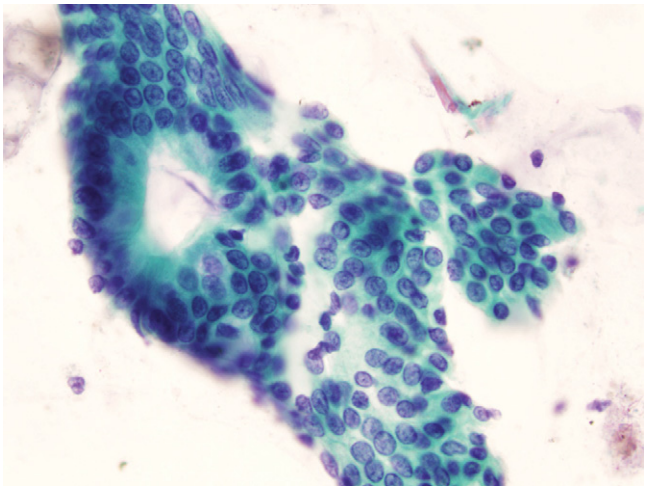

FIGURE 3-4 A sheet of normal colonic columnar epithelial cells is present in this colonic brushing specimen. A gland opening is seen in the left half of the field (Papanicolaou).

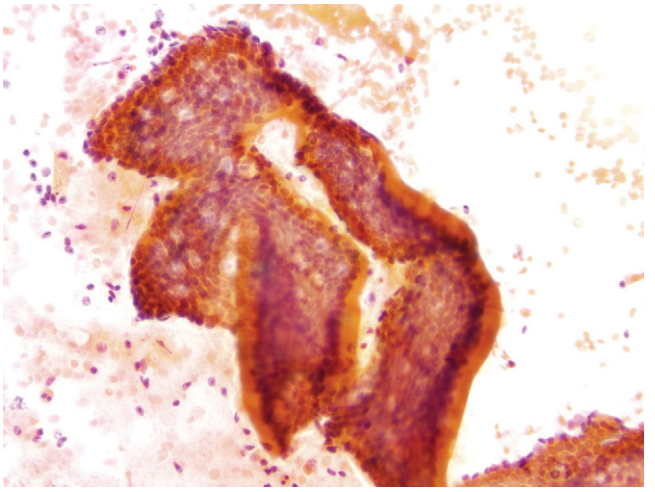

FIGURE 3-3 A complex sheet of small intestinal–type epithelium is seen in this duodenal brushing specimen. It has a Swiss-cheese appearance, with the "holes" representing either goblet cells or gland openings of the crypts (Papanicolaou).

cells. On low magnification, the specimen typically has a Swiss cheese appearance, with the "holes" representing either goblet cells or gland openings of the crypts (Fig. 3-3). On high magnification, the absorptive cells have either finely granular or vacuolated cytoplasm, and the goblet cells have single large mucin vacuoles and crescent-shaped nuclei with rounded contours. The striated border of the absorptive cells may be seen at the periphery of the sheets.

LARGE INTESTINE

Normal epithelium is characterized on cytology by sheets or strips of tall columnar cells with abundant cytoplasm and basal nuclei. Partial or complete openings of the colonic crypts may be seen (Fig. 3-4).

Infections

Most infectious agents that affect human hosts can infect the GI tract. Some infectious agents have a predilection for the GI tract. The more common ones are discussed in this section.

CANDIDA

Candida almost exclusively involves the esophageal portion of the GI tract and can occur in both immunocompetent and immunocompromised patients. Brushings are in fact more sensitive than biopsy specimens in the detection of esophageal candidiasis.[7] Contamination by oral *candida* is usually not a problem because the brush is contained within a sheath when it is passed into and out of the endoscope and is expelled from the sheath only to sample the lesion. The organisms appear as pink to purple pseudohyphae and yeast forms on Papanicolaou stain (Fig. 3-5). Reactive squamous cells as well as inflammatory cells are often noted in the background.

HERPES SIMPLEX VIRUS

Herpes simplex virus infection can theoretically affect epithelial cells anywhere along the GI tract, but it is most commonly seen in the esophagus. Multinucleation, nuclear molding, ground-glass chromatin, and eosinophilic intranuclear inclusions are the characteristic features of infected cells (Fig. 3-6).

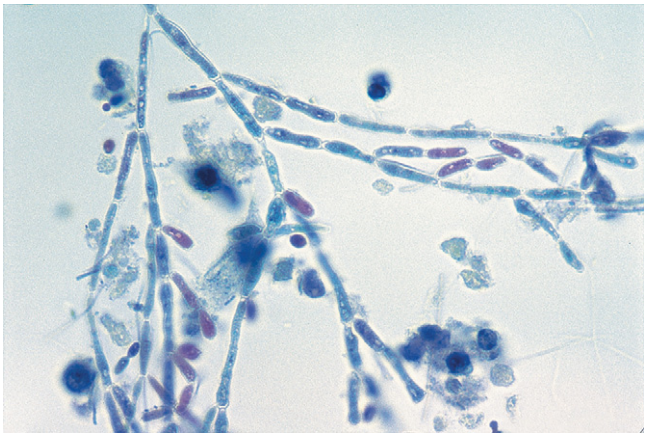

FIGURE 3-5 Pseudohyphae and yeast forms from *Candida* species are seen in this esophageal brushing specimen. Inflammatory cells and debris are in the background (Papanicolaou).

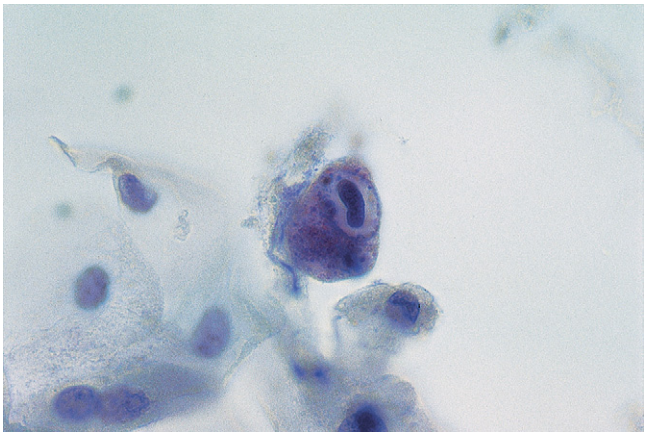

FIGURE 3-7 Both intranuclear and intracytoplasmic inclusions are seen in this cytomegalovirus-infected cell from an esophageal brushing. The intranuclear inclusion is a large amphophilic to basophilic body surrounded by a halo, and the intracytoplasmic inclusion is characterized by small, granular, basophilic to amphophilic bodies (Papanicolaou).

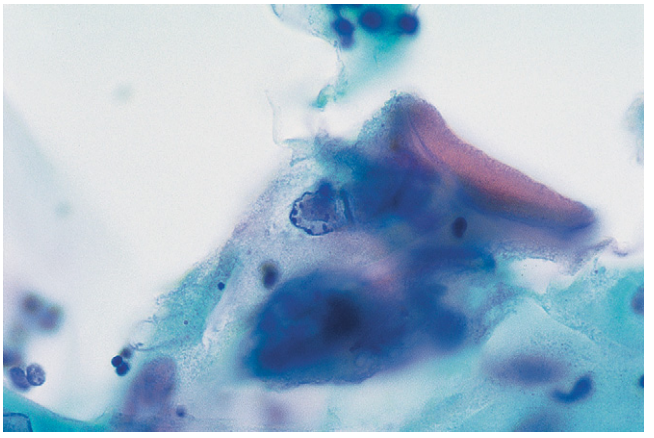

FIGURE 3-6 A Cowdry type B inclusion characterized by an eosinophilic intranuclear body surrounded by a halo is seen in the center of the field, from an esophageal brushing of herpetic esophagitis (Papanicolaou).

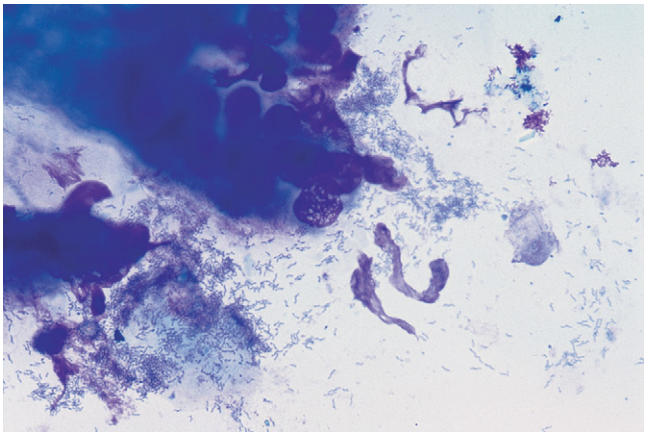

FIGURE 3-8 Numerous S-shaped organisms consistent with *Helicobacter pylori* are present in the mucus adjacent to a sheet of epithelial cells on a gastric brushing specimen (Diff-Quik).

CYTOMEGALOVIRUS

Cytomegalovirus infection affects epithelial, stromal, and endothelial cells along the GI tract and is characterized by large cells with a single large basophilic intranuclear inclusion with a perinuclear halo (Fig. 3-7). Intracytoplasmic textured inclusions can occasionally be seen in the affected cells.

HELICOBACTER PYLORI

Helicobacter pylori infection occurs exclusively in the stomach and perhaps is the most common infection of the GI tract. These organisms can be demonstrated either on imprint smears of gastric biopsies or on brush cytology specimens.[11] Imprint and brushing cytology specimens are comparable in sensitivity (88%) and specificity (61%) with histologic examination of sections stained with hematoxylin and eosin and modified Giemsa.[11] The benefits of imprint and brushing cytology are the rapid results, high specificity, and low cost. However, the efficacy of cytologic detection of these organisms depends on the extent of colonization by the organism. When present in a large quantity, they are evident even at low magnification, but they can be difficult to identify when present in small numbers. On Papanicolaou stain, *H. pylori* organisms appear as faintly basophilic, S-shaped rods admixed with mucus in the vicinity of glandular cell clusters (Fig. 3-8). Special stains, such as a triple stain, combining silver, hematoxylin and eosin, and alcian blue at pH 2.5, can enhance their detection by cytology.[12]

GIARDIA

Giardia affects the duodenum of both immunocompetent and immunocompromised hosts. Brush cytology is a useful method for detecting *Giardia* because the organisms are on the luminal surfaces of the intestinal epithelial cells. They are flat, gray, pear shaped, and binucleate, with four pairs of flagella (Fig. 3-9).[13]

ATYPICAL MYCOBACTERIA

Because atypical mycobacteria accumulate within macrophages in the lamina propria, very rigorous brushing is required for the infected macrophages to be included in the cytology sample. The presence of isolated foamy histiocytes on the smear should raise the level of suspicion of an atypical mycobacterial infection (Fig. 3-10). In general, the organisms are present in large numbers. On Diff-Quik-stained smears, the mycobacteria form numerous rod-shaped negative images, either within the histiocytes or in the background (Fig. 3-11).[14] Special stains for acid-fast bacilli are necessary to confirm the diagnosis.

CRYPTOSPORIDIA

Cryptosporidia can involve any glandular epithelium of the GI tract in HIV-infected patients and can be detected by examination of stool and cytology specimens.[15] Cryptosporidia are 2- to 5-μm round basophilic bodies on the luminal surfaces of the epithelial cells. Therefore, they are seen only when the plane of focus is shifted to the surfaces of the cells where the organisms reside (Fig. 3-12). When in doubt, confirmatory Gomori's methenamine-silver stain can be applied.

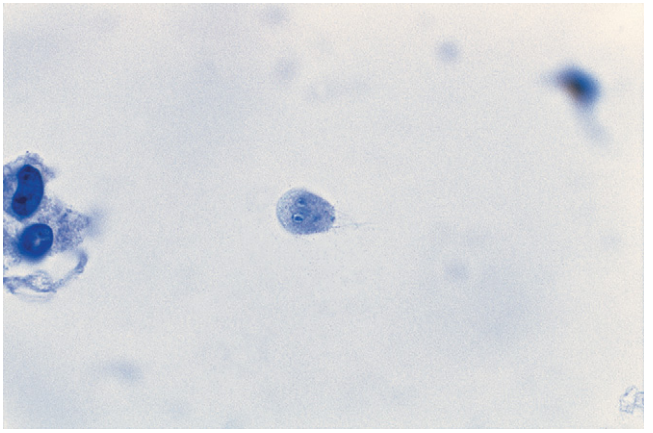

FIGURE 3-9 A pear-shaped, gray, binucleate *Giardia* organism is seen in the center of the field, from a duodenal brushing specimen (Papanicolaou).

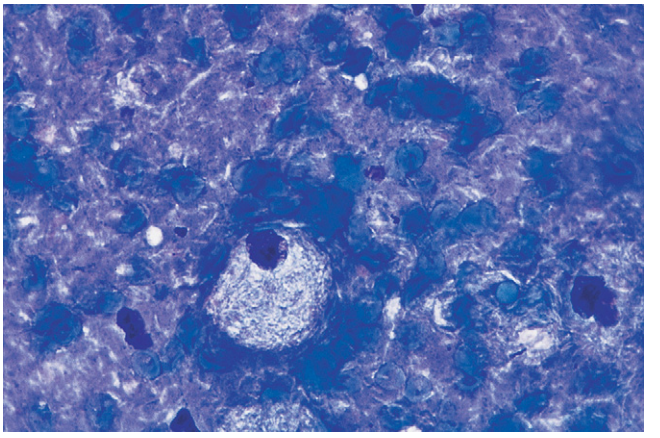

FIGURE 3-11 Numerous negative images of rod-shaped organisms are seen within and outside the histiocyte in the center of the field (from the same case as in Figure 3-7) (Diff-Quik).

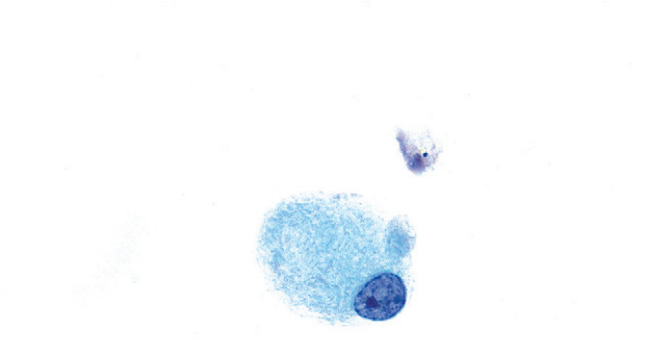

FIGURE 3-10 A histiocyte with abundant granular cytoplasm is present in this duodenal brushing specimen from an HIV-infected man. On special stain, the cell is shown to be filled with acid-fast bacilli, consistent with atypical mycobacteria (Papanicolaou).

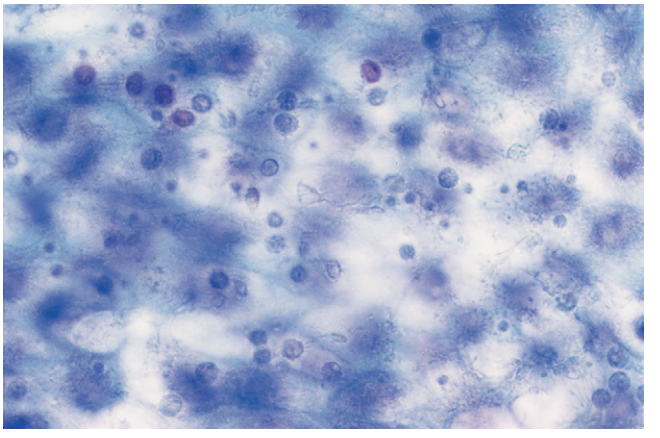

FIGURE 3-12 Many 2- to 5-μm-diameter, round, basophilic bodies are seen on the surface of this sheet of gastric epithelial cells on a brushing specimen (Papanicolaou).

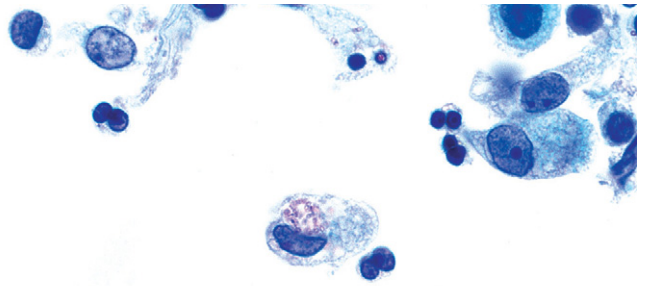

FIGURE 3-13 Several 1- to 3-µm-diameter eosinophilic rods are in the cytoplasm of the cell in the center of this duodenal brushing specimen. They are typically found in the supranuclear portion of the cytoplasm (Papanicolaou).

MICROSPORIDIA

Microsporidia can also be detected on cytologic specimens, such as stool, nasal secretions, duodenal aspirates, and bile, as well as on brushing specimens from the duodenum and biliary tract.[16-18] On Papanicolaou stain, they appear in aggregates as brightly eosinophilic, rod-shaped or ovoid organisms, measuring 1 to 3 µm in diameter (Fig. 3-13). They are present in epithelial cells as well as in inflammatory cells. When in the epithelial cells, they are in the supranuclear portion of the cytoplasm and therefore they (like cryptosporidia) are seen at a slightly different plane of focus from that of the epithelial nuclei.

Inflammatory, Reactive, or Metaplastic Changes

NONSPECIFIC CHANGES

Any injury to the mucosa can evoke a nonspecific inflammatory or reactive epithelial change. When the injury is sufficient to result in ulceration, the change (i.e., the epithelial repair) can become so extreme that it may mimic a malignancy. It is often difficult to determine whether the reparative epithelium is of glandular or squamous origin. Although epithelial repair is characterized by prominent eosinophilic nucleoli, they are usually neither huge nor numerous (i.e., more than three or four) (Fig. 3-14). The atypical stromal cells or their stripped nuclei from granulation tissue can also be quite alarming (Fig. 3-15). In spite of striking nuclear enlargement of such cells, hyperchromasia is absent. Instead, they have fine, homogeneous chromatin and a thin, smooth nuclear membrane.

Both cellular arrangements and the features of individual cells are useful in distinguishing between severe reactive and neoplastic changes. Cells with reactive or reparative changes are usually arranged in flat sheets without three-dimensionality or prominent cell dyshesion. In contrast, dyshesion, presented either as "feathering" (dissociation of cells) at the periphery of cell clusters or as the dispersion of numerous isolated cells, is usually evident with neoplasms, as is three-dimensionality. In addition, the enlarged nuclei in reactive or reparative changes usually have uniform size and a similar number of small, prominent nucleoli. These again are in contrast to the variation in nuclear and nucleolar size and shape as well as the

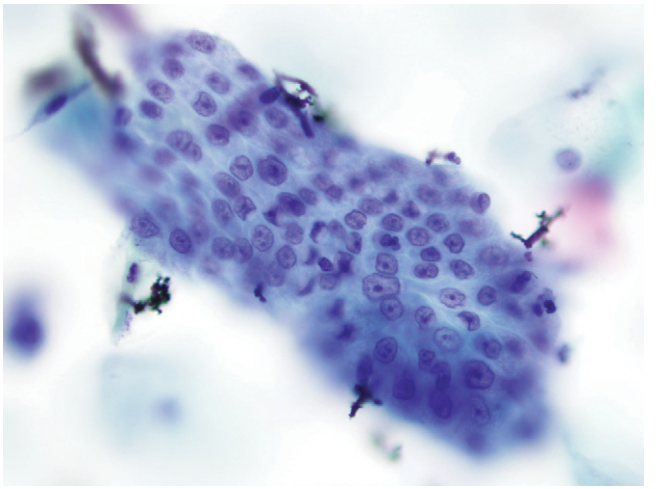

FIGURE 3-14 A sheet of reactive epithelial cells is seen in this esophageal brushing specimen. The cells have sharp cellular borders and are variably enlarged with prominent nucleoli. The nuclear membranes in some cells appear wavy but without sharp angles or indentations. A few inflammatory cells are superimposed on or infiltrating this sheet. It is difficult to be certain whether these cells are squamous or glandular (Papanicolaou). (Courtesy of Dr. Mark Roth of the National Cancer Institute, Rockville, MD.)

FIGURE 3-15 A single, atypical, ovoid to spindle-shaped cell with enlarged nuclei and prominent nucleoli is seen in a gastric brushing specimen from a patient with resection-proven benign gastric ulcer with abundant granulation tissue at the ulcer bed (Papanicolaou).

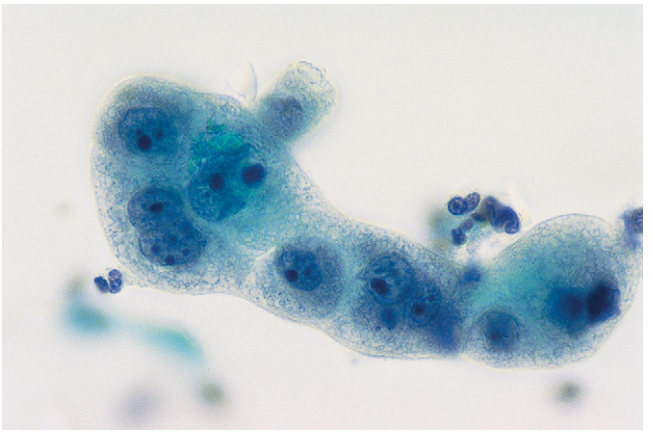

FIGURE 3-16 A group of proportionally enlarged epithelial cells showing prominent nucleoli and finely vacuolated cytoplasm is seen on this esophageal brushing specimen from a patient with previous radiation therapy for squamous cell carcinoma (Papanicolaou).

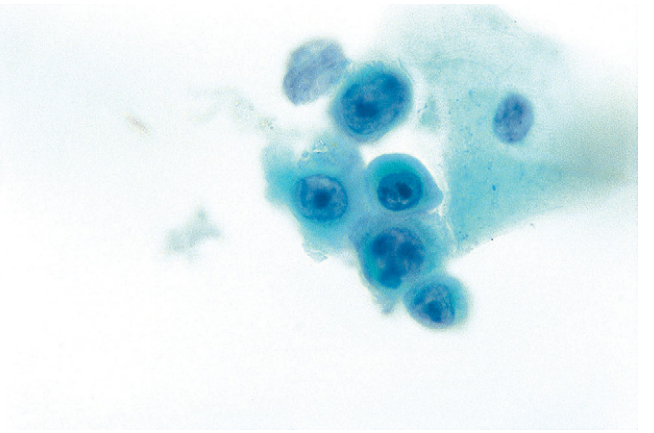

FIGURE 3-17 A loose group of parabasal-sized squamous cells with dense cytoplasm and prominent nucleoli can be seen in this esophageal brushing specimen from a patient known to have pemphigus vulgaris (Papanicolaou).

chromatin pattern in the neoplastic lesions. Specific types of reactive cells may also be seen, such as those with radiation-induced changes (Fig. 3-16). As in other organs, the cells are proportionally enlarged, with metachromatic cytoplasm and nuclear or cytoplasmic vacuoles.

PEMPHIGUS

Rarely, pemphigus vulgaris, an autoimmune disease of the skin and mucous membrane that attacks the intercellular junctions and causes a suprabasilar bleb or blister as well as acantholysis, may affect the esophagus. Numerous acantholytic cells are usually present. The characteristic cells are round to polygonal, uniform, parabasal-sized isolated cells.[19,20] The cytoplasm is dense and may have perinuclear eosinophilic staining or a clear halo. The cells appear atypical because of the high nucleus-to-cytoplasm ratio, the enlarged nuclei, and the prominent, multiple, even irregular nucleoli (Fig. 3-17). A bar- or bullet-shaped nucleolus is characteristic.[21] However, the cells have smooth nuclear membranes and pale, fine, and even chromatin. Normal mitotic figures can be seen. These atypical cells resemble those in repair except for the increased number of single cells.

BARRETT'S EPITHELIUM

Cytology is not the optimal tool for the diagnosis of Barrett's epithelium. When glandular epithelial cells are seen in a cytology specimen, it is difficult to be certain whether they represent cells from the gastric side of the esophagogastric junction or metaplastic glandular cells from the esophagus. It has also been shown that cytology is neither sensitive nor specific for the detection of goblet cells,[22,23] a hallmark of Barrett's epithelium, in part because of the absence of a blue hue of acid mucin with the Papanicolaou stain. However, a long segment of Barrett's

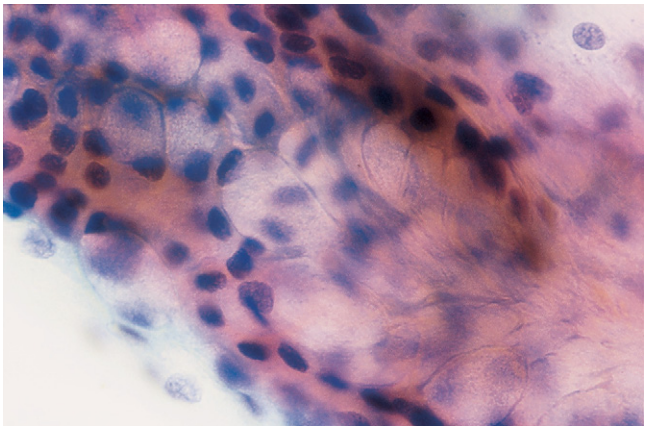

FIGURE 3-18 A sheet of glandular cells, some with large vacuoles expanding the cytoplasm and crescent-shaped nuclei, is seen on a brushing specimen from the esophagogastric junction, consistent with Barrett's esophagus (Papanicolaou).

epithelium is more readily appreciated by cytology because of the reduced probability of sampling error.[22] Its appearance is similar to that of the lining epithelium of the small intestine, with a Swiss cheese pattern at low magnification and goblet cells with single, large cytoplasmic vacuoles on high magnification (Fig. 3-18). The honeycomb arrangement of the glandular cells in Barrett's epithelium usually tends to be slightly more irregular than that of normal small intestinal epithelium.

Neoplastic Lesions

SQUAMOUS DYSPLASIA OR CARCINOMA

Squamous dysplastic cells of the esophagus have morphology similar to that of the dysplastic cells on cervicovaginal Pap smears (Box 3-1).[24] The cellular features of squamous

BOX 3-1 Squamous Dysplasia (Figs. 3-19 and 3-20)

- Some but not all of the malignant features to varying degrees, such as increased nucleus-to-cytoplasm ratio, nuclear enlargement, hyperchromasia, irregular nuclear membrane, and aberrant chromatin pattern
- Fewer atypical cells than carcinoma
- Absent tumor diathesis

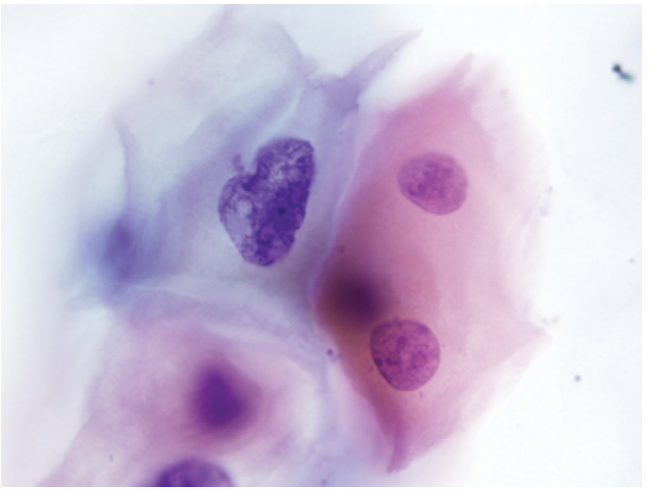

FIGURE 3-19 A dysplastic squamous cell is surrounded by a few reactive-appearing squamous cells. The dysplastic cell shows mild hyperchromasia, nuclear membrane irregularity, and chromatin aberration, but it still has a fair amount of cytoplasm. Therefore, it is considered low-grade (Papanicolaou). (Courtesy of Dr. Mark Roth of the National Cancer Institute, Rockville, MD.)

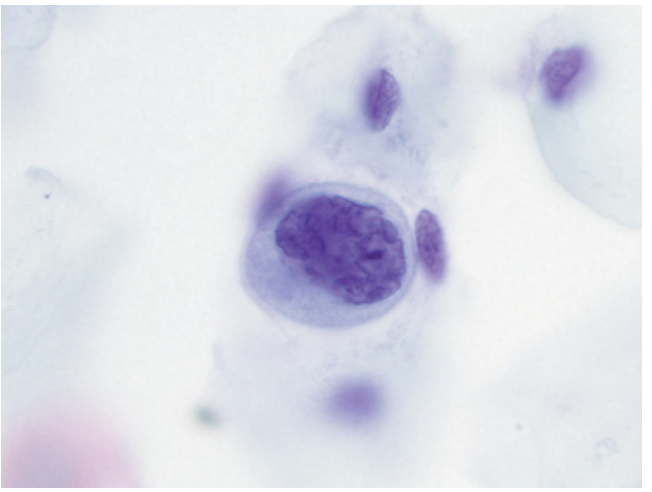

FIGURE 3-20 Compared to the dysplastic cell in Figure 3-19, this dysplastic squamous cell has more pronounced nuclear membrane irregularity and a much higher nucleus-to-cytoplasm ratio, and is, therefore, considered high-grade (Papanicolaou). (Courtesy of Dr. Mark Roth of the National Cancer Institute, Rockville, MD.)

BOX 3-2 Well-Differentiated Squamous Cell Carcinoma (Fig. 3-21)

- Predominantly isolated cells with sharp cytoplasmic borders and variable cell shapes, such as round, oval, or spindle shaped
- Hyperchromatic or pyknotic nuclei with obscured chromatin and irregular, angulated nuclear contours
- Keratinized cytoplasm
- Prominent necrosis or tumor diathesis and keratinaceous debris in the background

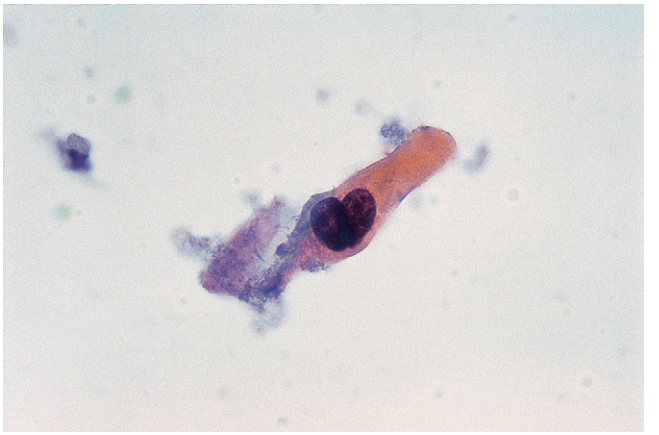

FIGURE 3-21 A keratinized squamous cell with a hyperchromatic nucleus characteristic of well-differentiated squamous cell carcinoma is present in this esophageal brushing specimen (Papanicolaou).

cell carcinoma vary with the degree of differentiation (Boxes 3-2 and 3-3).

GLANDULAR DYSPLASIA OR CARCINOMA

Glandular dysplasia and carcinoma in the esophagus usually arise in the setting of Barrett's epithelium. The precursor lesions of adenocarcinoma in the stomach and in the intestine can present as either polypoid or flat dysplastic lesions. Adenomas of the stomach and dysplasia of the esophagus or stomach are similar in cytologic appearance. Although the few studies on this topic were based on very small numbers of cases[22,23,25,26] and were insufficient to provide definitive conclusions on the usefulness of cytologic surveillance,[27] the preliminary results appear promising. Low-grade dysplasia may be difficult to distinguish from artifactual crowding, whereas high-grade dysplasia may be confused with either severe reparative change or invasive carcinoma (Boxes 3-4, 3-5, and 3-6).

The amount and characteristics of the cytoplasm of the tumor cells depend on the degree of differentiation. Appearance varies from abundant vacuolated or granular cytoplasm to scant dense cytoplasm that is difficult to distinguish from that of a poorly differentiated squamous cell carcinoma.

BOX 3-3 Moderately and Poorly Differentiated Squamous Cell Carcinoma (Fig. 3-22)

- Less striking keratinization of the cytoplasm
- Tumor cells in crowded, haphazardly arranged cell clusters with indistinct cell borders
- Vesicular chromatin with prominent nucleoli

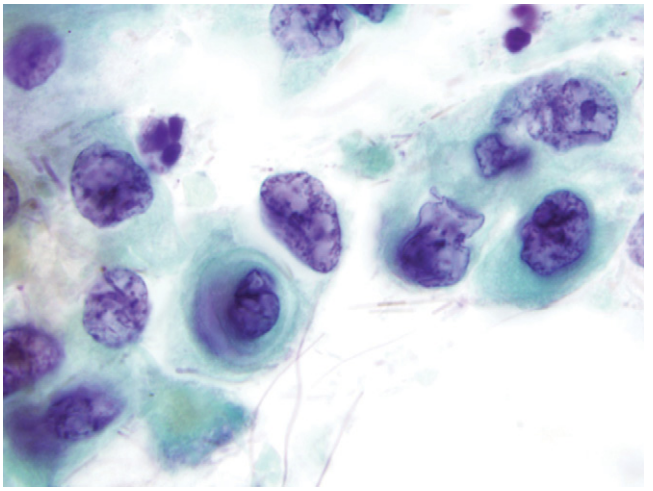

FIGURE 3-22 In contrast to the cells seen in Figure 3-21, tumor cells from a poorly differentiated squamous cell carcinoma have vesicular chromatin and occasional prominent nucleoli. The single-cell pattern, dense basophilic cytoplasm, and endoplasmic and ectoplasmic demarcation in a cell close to the center of the field suggest squamous differentiation (Papanicolaou).

BOX 3-4 Low-Grade Glandular Dysplasia (Fig. 3-23)

- Architectural abnormality (e.g., stratification manifested as crowding and overlapping on cytology)
- Elongated nuclei with increased nucleus-to-cytoplasm ratio
- Mild hyperchromasia and absent or inconspicuous nucleoli
- Minimal or negligible dyshesion

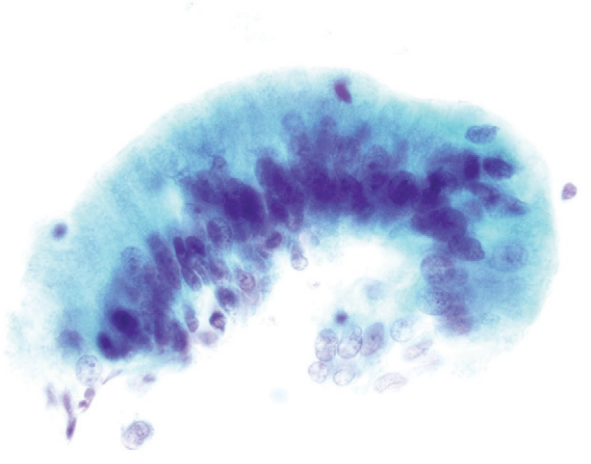

FIGURE 3-23 A strip of stratified columnar cells with slightly enlarged and elongated nuclei is seen in an esophageal brushing specimen from a patient with biopsy-proven low-grade dysplasia in Barrett's esophagus (Papanicolaou).

BOX 3-5 High-Grade Glandular Dysplasia (Fig. 3-24)

- Both architectural and cellular abnormalities
- Atypical cells in haphazardly arranged sheets and clusters, or singly as a result of dyshesion
- Cellular abnormalities similar to those seen in invasive adenocarcinoma but less pronounced

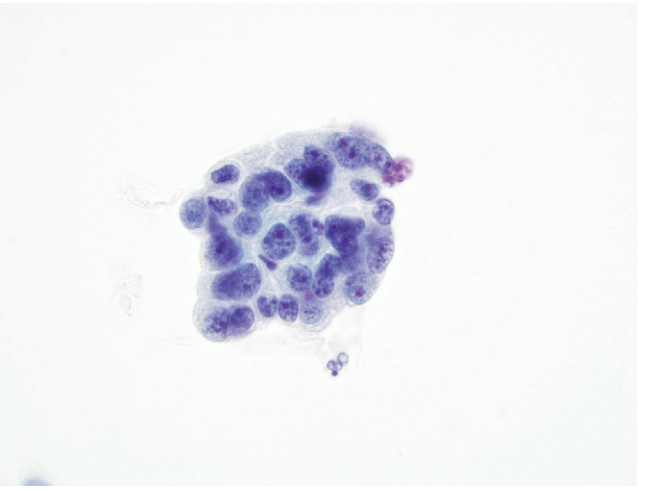

FIGURE 3-24 A sheet of haphazardly arranged and overlapped atypical cells with granular cytoplasm in a clean background is seen in an esophageal brushing specimen from a patient with biopsy-proven high-grade dysplasia in Barrett's esophagus. The nuclei show chromatin aberration and occasional nucleoli, but the cells do not appear to be malignant (Papanicolaou).

Signet ring cell carcinoma, a type of adenocarcinoma that occurs most commonly in the stomach, is worthy of special consideration because it can be difficult to detect on both cytologic and histologic preparations. Because the malignant cells infiltrate predominantly the lamina propria, they are often not included in the brush cytology sample unless mucosal ulceration is present. The reactive or reparative epithelial changes associated with an ulcer can distract the attention of the pathologist from the real lesion. In addition, the numerous inflammatory cells from the ulcer can obscure the scattered, isolated tumor cells (Box 3-7).

Even when detected, some signet ring cells have such bland nuclei that they can be mistaken for histiocytes, which have intracytoplasmic phagocytized material and a very low nucleus-to-cytoplasm ratio. A high degree of suspicion is the best safeguard against failure to detect a signet ring cell carcinoma by cytology. When in doubt, immunocytochemical studies can be applied to the cytologic material to determine whether the phenotype of the cells of interest is epithelial or histiocytic. Carcinoma cells should be positive for epithelial markers, such as keratin and epithelial membrane antigen, whereas histiocytes express CD-68 as detected by the KP-1 antibody.