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CHAPTER 23

Large Intestine (Colon)

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NORMAL LARGE INTESTINE

Normal large bowel gross anatomy and microscopic anatomy[1-3] are outlined here. The large bowel extends from the ileocecal valve to the anus and measures 120 cm to 150 cm in adults. It can be clinically useful to divide the large bowel into regions. The cecum, the most proximal saccular part of the large bowel, lies inferior to a horizontal line defined by the ileocecal valve. The cecum is completely invested by peritoneum and contains the opening of the vermiform appendix. The right colon, 15 cm to 20 cm in length, extends to the hepatic flexure. The right colon lacks mesentery and lies mostly in the retroperitoneum except for its anterior and right lateral serosa. The transverse colon averages 30 cm to 60 cm in length, runs from the hepatic flexure to the splenic flexure, and has a mesentery. The descending colon begins at the splenic flexure, becomes retroperitoneal, and extends for 20 cm to 25 cm. At the distal portion of the descending colon, the large bowel once again acquires a mesentery to become the sigmoid colon, which measures approximately 40 cm in length. The sigmoid colon arbitrarily becomes the rectum at approximately the level of the third sacral vertebra. The rectum, measuring 10 cm to 15 cm in length, ends at the anal canal. The upper one third of the rectum is covered by peritoneum; the lower two thirds lies in the retroperitoneum surrounded by the fatty mesorectum.

Beneath the mesothelium-covered serosa lies a subserosal layer of fibroadipose tissue. The muscularis externa of the large bowel is composed of an inner circular layer and an outer longitudinally running layer of smooth muscle that condenses into three longitudinally running taeniae coli, the mesocolic taenia and two antimesenteric taeniae. The taeniae unite at the base of the vermiform appendix. They flare at the rectum and incorporate into its external muscular layer. The inner and outer layers of muscularis externa are separated by the myenteric plexus of Auerbach. Appendages of subserosal fat typically hang from the large bowel to form the epiploic appendices.

Extending luminally from the muscularis externa lie the fibroadipose tissue, blood vessels, lymphatics, and nerves of the submucosa. The submucosa contains Meissner's plexus, which is usually found closely juxtaposed to the muscularis mucosae. The inner surface of the large bowel is characterized by horizontally oriented folds (plicae semilunares) and fine innominate grooves of the mucosa.

The proximal colon to the splenic flexure derives its blood supply from the superior mesenteric artery through the ileocolic, right colic, and middle colic branches. The remainder of the colon is supplied by the left colic and sigmoid branches of the inferior mesenteric artery. The inferior mesenteric artery and iliac vessels provide blood to the rectum. Veins accompany the arteries and share their names. The large bowel venous drainage enters the portal circulation except for the distal rectum, which drains into the systemic circulation through the middle and inferior rectal veins. In portal hypertension, this area can serve as a portal-systemic shunt and can be a site of varices. The lymph node drainage is divided into those lymph nodes close to the bowel wall (e.g., pericolic, perirectal) and those that follow the blood vessels (e.g., mesenteric).

The vagus nerves supply stimulatory nervous activity to the right colon and proximal transverse colon. The remainder of the large bowel is supplied by pelvic postganglionic parasympathetic nerves. The inhibitory nervous activity is derived from the superior and inferior mesenteric plexuses.

The large bowel mucosa is composed of a single-cell layer of colorectal epithelium covering the lumen and lining the crypts, the supporting lamina propria and a small smooth muscle band referred to as the *muscularis mucosae*. The normal colorectal luminal surface of the mucosa is straight; the glands are made up of tubules (crypts) that are tightly packed, parallel, nonbranching, and closely approximating the muscularis mucosae (Fig. 23-1). The appearance of the colonic tubules is similar to rows of test tubes placed in a rack. Goblet cells interspersed between colorectal absorptive cells line the colonic tubules. Scattered neuroendocrine cells can be observed usually near the base of the crypt and contain basally oriented eosinophilic cytoplasmic granules. The lamina propria contains a modest amount of mixed inflammatory cells including plasma cells, lymphocytes, eosinophils, mast cells, and macrophages. Intraepithelial lymphocytes are present normally but usually are fewer than 6 per 100 colorectal epithelial cells. The muscularis mucosae is arranged into two layers (an inner circular and outer longitudinally running layer) and is usually thin and regular. The submucosa is typically devoid of inflammatory cells. Scattered mucosal and submucosal lymphoid follicles are normally encountered, especially in younger individuals. In areas of mucosal lymphoid follicles, the mucosal architecture may be distorted and the muscularis mucosae can be incomplete. Flattened epithelial cells known as *M cells* overlie the mucosal lymphoid aggregates. The epithelium of the M-cell zone typically contains numerous intraepithelial lymphocytes.[1-3] Paneth cells with their basal nuclei and luminal cytoplasmic refractile red granules are seen in the base of colonic crypts but are considered normal only in the cecum and proximal right colon.[2,3]

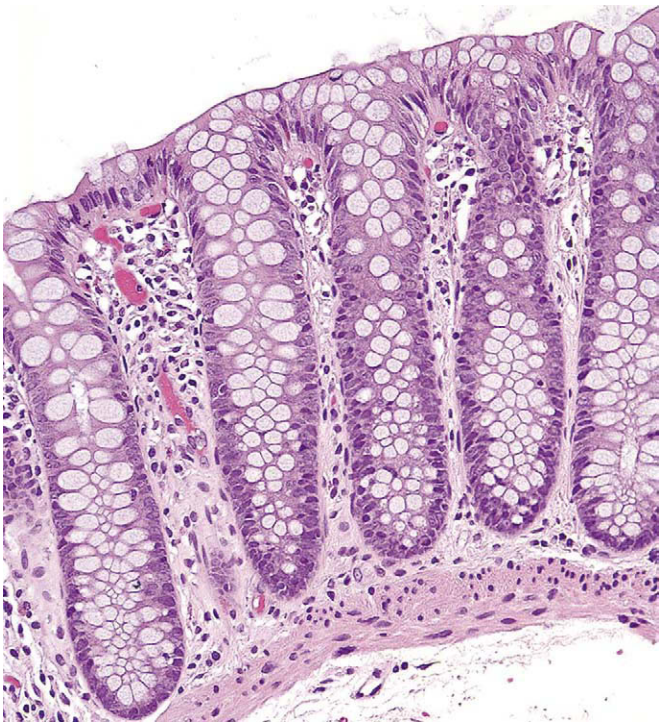

Figure 23-1 ■ Normal colonic mucosa. The luminal surface is straight, and the colonic tubules are tightly packed, parallel, nonbranching, and closely approximating the muscularis mucosae.

Mucosal biopsy interpretation can be hampered by changes associated with bowel preparation and with the trauma of the biopsy procedure itself. Changes ascribed to bowel preparation include decreased intraepithelial mucin, increased numbers of mitotic figures, surface apoptosis with karyorrhectic debris in the superficial lamina propria, and small numbers of neutrophils and eosinophils in surface or crypt epithelium.[2-7] Edema and recent hemorrhage into tissues not associated with other degenerative or inflammatory changes most likely represent biopsy-related trauma.

Muciphages (foamy macrophages containing faintly periodic acid–Schiff [PAS]-positive material) are often present in the lamina propria of the large bowel, especially the rectum, where they most likely represent a nonspecific response to mucosal injury (i.e., trauma).[8,9] Muciphages should be distinguished from xanthelasma/xanthomatous polyp, which can also occur in the large intestine (Fig. 23-2).

LARGE BOWEL TUMORS

Common Adenomas and Malignant Polyps

An *adenoma,* defined as a benign intraepithelial neoplasm composed of epithelial cells exhibiting cytologic dysplasia, is considered the precursor lesion of most colorectal carcinomas.[1,10-12] Dysplasia is characterized by decreased intraepithelial mucin, epithelial nuclear enlargement with hyperchromasia, nuclear stratification, and increased numbers of mitotic figures. Large bowel adenomas are highly prevalent in Western societies. The frequency of these tumors markedly increases after age 40 years and reaches a peak at age 70 years. Adenomas are usually asymptomatic but large ones may bleed.

Adenomas usually produce a raised endoscopically or grossly detectable abnormality, generally a protrusion or polyp that can often be further subclassified as sessile or pedunculated. Some adenomas appear flat; some may cause mucosal depressions. Adenomas occur singly or can be

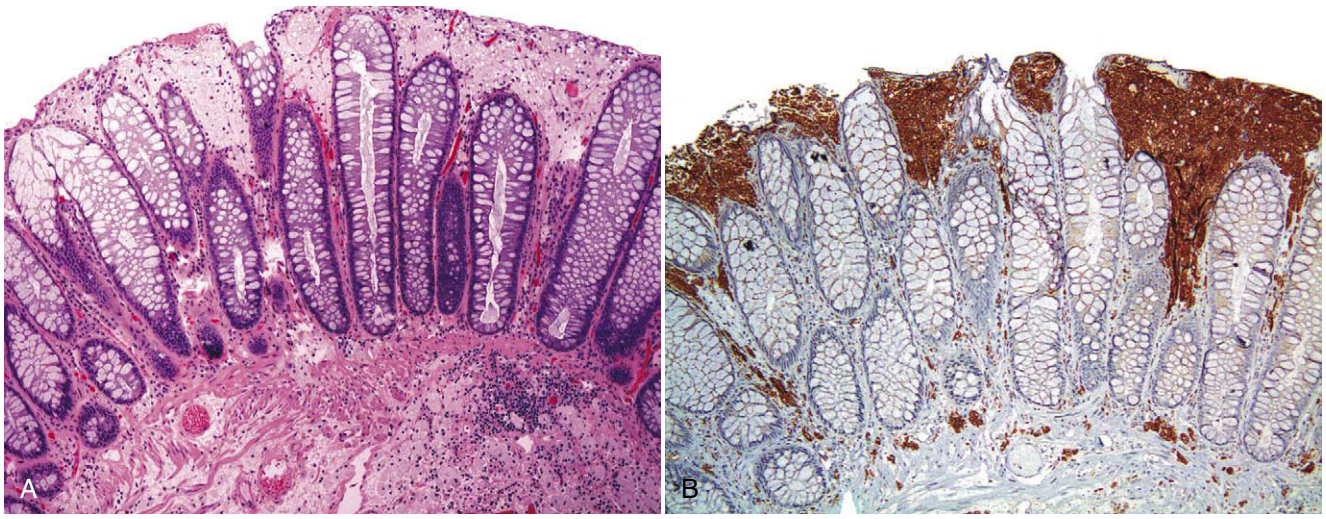

Figure 23-2 ■ **A,** Large bowel xanthelasma/xanthomatous polyp with foamy macrophages infiltrating the superficial lamina propria and submucosa. **B,** Large bowel xanthoma/xanthomatous polyp. The histiocytes are highlighted with a CD68 immunostain.

multiple. Multiple (≥10) adenomas may indicate a genetic syndrome such as familial adenomatous polyposis (FAP), attenuated FAP, or MYH-associated polyposis syndrome.[13] Most adenomas are small, measuring less than 10 mm.

Adenomas should be classified histologically based on the pattern of growth as tubular, villous, or tubulovillous following the World Health Organization (WHO) guidelines.[1,14] Adenomas in which simple tubules make up more than 80% of the area are classified as *tubular*. Adenomas with greater than 80% of their area showing a villiform configuration are called *villous adenomas* (Fig. 23-3); all others should be reported as *tubulovillous adenomas*.[1]

Once discovered, adenomas are characteristically removed by endoscopy or surgery because they are an important precursor lesion to colorectal carcinoma. Therefore, it is not surprising that occasionally a resected polyp thought to be a benign adenoma may contain an area of carcinoma.

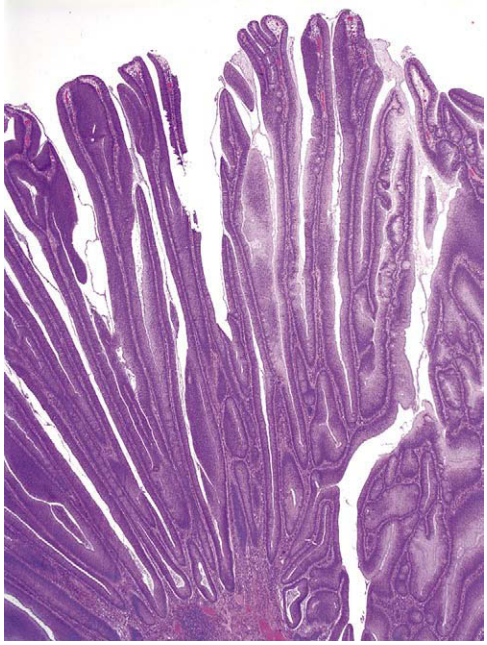

Figure 23-3 ■ Colorectal villous adenoma.

Nomenclature

OVERVIEW

The various nomenclatures applied to colorectal adenomas, dysplasia, and malignant polyps can be confusing. Unfortunately, no unified accepted guidelines exist.[10-12,14] Most surgical pathologists use variations of the 1989 WHO terminology.[11] In this system, the terms *dysplasia, adenocarcinoma in situ, intramucosal adenocarcinoma,* and *invasive adenocarcinoma* are accepted. Each has a precise meaning when applied to colorectal polyps and appropriate patient care requires that the endoscopist, surgeon, and surgical pathologist understand the significance of each of these terms.

All adenomas demonstrate at least low-grade epithelial dysplasia. Without dysplasia, an adenoma cannot be recognized and distinguished from normal colonic mucosa. *Low-grade dysplasia* is characterized by a slight decrease in the amount of intracellular mucin, mild nuclear enlargement with hyperchromasia, some nuclear stratification, and an increased number of mitotic figures (Fig. 23-4). Increasing degrees of dysplasia (low-grade to high-grade) show progressive loss of intracellular mucin, progressive increase in nuclear size with stratification, and a loss of nuclear polarity. *Adenocarcinoma in situ* describes the next step in the dysplasia-carcinoma sequence. Here, the atypical glands assume a complex cribriform or back-to-back gland configuration but the basement membrane remains intact (Fig. 23-5). Some experts consider adenocarcinoma in situ as part of the spectrum of high-grade glandular dysplasia and report both under the same term.[12] When carcinoma cells infiltrate into the lamina propria or muscularis mucosae only, terms such as *high-grade glandular dysplasia* and *adenocarcinoma in situ* are technically no longer applicable because both require an intact basement membrane. There-

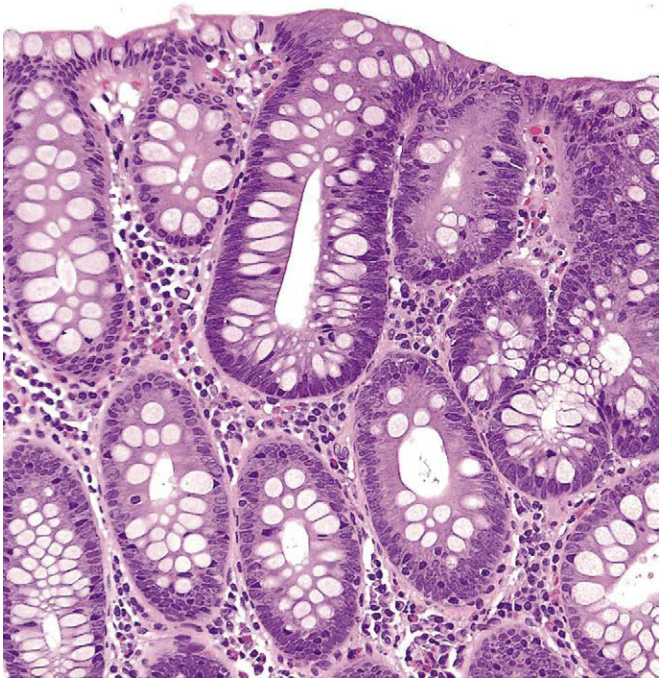

Figure 23-4 ■ Tubular adenoma showing low-grade glandular dysplasia. Evident are decreased intracellular mucin, nuclear enlargement with hyperchromasia, and nuclear stratification.

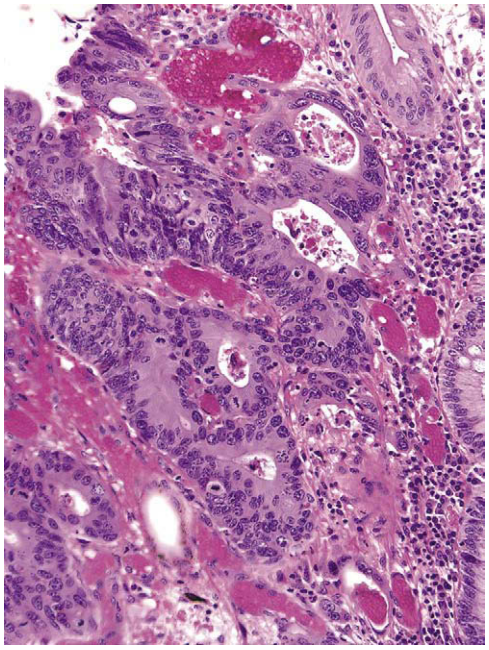

Figure 23-6 ■ High-grade glandular dysplasia (intramucosal adenocarcinoma) arising in a tubular adenoma. Individual and small groups of adenocarcinoma cells have infiltrated beyond the basement membrane into the lamina propria.

fore, the term *intramucosal adenocarcinoma* is more accurate (Fig. 23-6).[1,11] Finally, when carcinoma cells have invaded the submucosa (or beyond) the lesion is labeled *invasive adenocarcinoma*. Invasion is invariably associated with an infiltrative pattern to neoplastic glands associated with tumor desmoplasia (Fig. 23-7). This tumor desmoplasia is extremely helpful in recognizing invasion of at least the submucosa, especially in small biopsy specimens.

The nomenclature controversy principally centers on the observation that in the colon and rectum, infiltrating carcinoma cells do not become clinically significant (i.e., able to metastasize) until they have invaded the submucosa.[1,12,15,16]

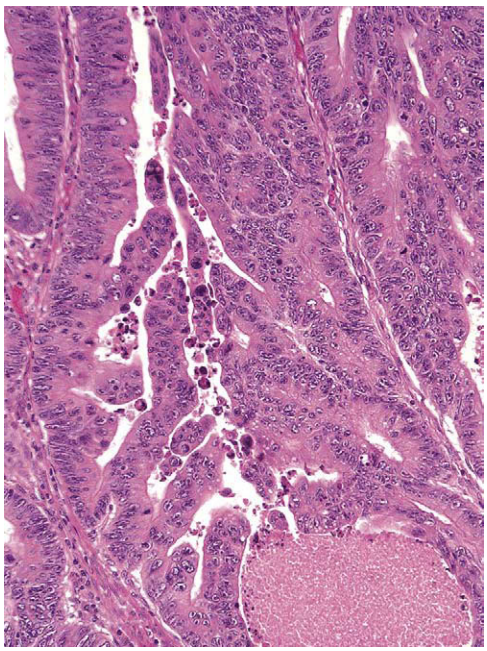

Figure 23-5 ■ Portion of a tubulovillous adenoma with high-grade glandular dysplasia (high-grade dysplasia and adenocarcinoma in situ). Areas of full-thickness nuclear stratification are visible, as well as a region showing complex gland-in-gland configuration with papillation and individual cell necrosis. The basement membrane, however, remains intact.

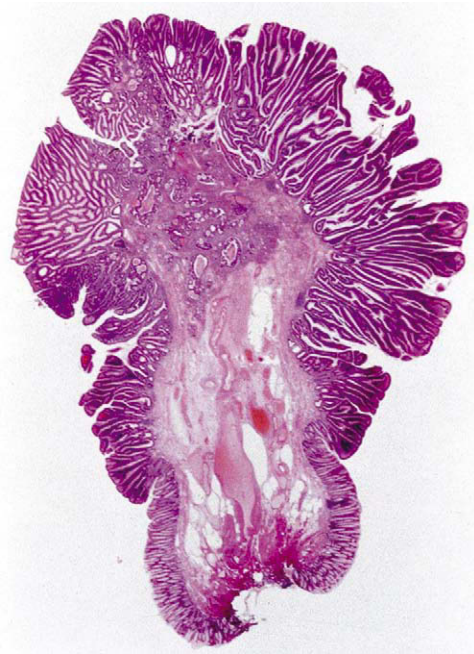

Figure 23-7 ■ Invasive well-differentiated adenocarcinoma arising in a tubulovillous adenoma. A focal breakdown in pattern with infiltration of adenocarcinoma cells into the submucosa is evident. The invasive focus is associated with tumor desmoplasia and chronic inflammation.

Only polyps containing invasive adenocarcinoma require a decision for additional treatment on the part of the clinician. Adenoma, adenocarcinoma in situ, and even intramucosal adenocarcinoma lack metastatic capability and are considered adequately treated by polypectomy alone.[1,11,13,14,16] As a result, some pathologists advocate modification of the nomenclature to account for clinical behavior and promulgate use of the term *high-grade glandular dysplasia* to encompass high-grade dysplasia, adenocarcinoma in situ, and even intramucosal adenocarcinoma.[10,14] Although the 1989 WHO guidelines accepted and defined two (low-grade, high-grade) or three (mild, moderate, severe) grades of dysplasia, adenocarcinoma in situ, and intramucosal adenocarcinoma, the authors of those guidelines recommended a similar behavior-based modification for intramucosal carcinoma and stated that "… intramucosal adenocarcinoma of the colon has not been shown to metastasize, and for this reason 'carcinoma in situ' is more appropriate."[11]

The 2000 version of the WHO classification added little clarification and introduced new and even more confusing terms.[14] The authors stated that the defining feature of colorectal adenocarcinoma is invasion through the muscularis mucosae into the submucosa. However, once defined, worrisome lesions not fulfilling this criterion become difficult to describe. For example, the 2000 WHO classification defines adenocarcinoma in situ and intramucosal adenocarcinoma as lesions with morphologic characteristics of "adenocarcinoma" confined to the epithelium or that "invade" the lamina propria alone and lack invasion through the muscularis mucosae. The WHO goes on to state that these lesions have virtually no risk of metastasis. According to the WHO, the term "… high-grade intraepithelial neoplasia is more appropriate than adenocarcinoma in situ and … intramucosal neoplasia is more appropriate than intramucosal adenocarcinoma." In the 2000 version, the WHO believes that use of these terms will help avoid overtreatment.[14]

The problems with this classification are many. The inaccurate use of the term *invasion* to describe lesions that are not by definition invasive carcinoma is confusing. The lesser lesion of high-grade intraepithelial neoplasia sounds worse than the term used to describe intramucosal adenocarcinoma (*intramucosal neoplasia*). Furthermore, all adenomas, strictly speaking, are intraepithelial neoplasia. An effort to achieve consensus (largely between Eastern [Japanese] and Western pathologists)[17-20] resulted in the Vienna classification of gastrointestinal (GI) neoplasia,[20] presented in Table 23-1.

Problems with the Vienna system include the following: (1) inaccurate use of the word *invasion*; (2) category 4 "noninvasive" high-grade neoplasia including potentially dangerous lesions (e.g., suspicious for invasive adenocarcinoma); and (3) category 5 "invasive neoplasms" including intramucosal adenocarcinoma, which is widely accepted to be clinically benign in the colon and rectum. It is unlikely that this system of categories without clinical correlation will ever gain widespread acceptance.

A PRAGMATIC VIEW

As modified from the 1989 WHO classification, low-grade dysplasia, high-grade dysplasia, adenocarcinoma in situ, and intramucosal adenocarcinoma exist and can be recognized by pathologists.[1,11] This nomenclature remains attractive because it can be applied throughout the GI tract. If one chooses to diagnose high-grade dysplasia, adenocarcinoma in situ, and intramucosal adenocarcinoma in colorectal biopsy specimens, specific mention in the report that these lesions lack metastatic potential is helpful to clinicians.

Because infiltrating carcinoma cells in a colorectal polyp do not become clinically significant (i.e., able to metastasize) until they have invaded the submucosa,[1,14-16,21-48] only a polyp containing invasive adenocarcinoma (invasion of at least the submucosa) should be considered malignant. Only invasive adenocarcinoma requires a decision regarding additional treatment. Therefore, the presence or absence of invasive adenocarcinoma should be specifically mentioned in the pathology report. To comply with the American College of Gastroenterology (ACG), the U.S. Multi-Society Task Force on Colorectal Cancer, and the American Cancer Society guidelines,[13,28,49] a villous component (villous or tubulovillous adenoma) and high-grade dysplasia should be reported because these features require more frequent surveillance. Carcinoma in situ and intramucosal adenocarcinoma can be reported parenthetically as high-grade dysplasia. Most mistakes that pathologists make in reporting colorectal adenomas, dysplasia, and malignant polyps occur in three major categories: (1) the pathology report is not clear (nonspecific or noncommittal terms are used or the presence or absence of invasive adenocarcinoma is not clearly stated); (2) mispositioned glands (pseudocarcinomatous invasion) are misinterpreted as invasive adenocarcinoma; and (3) the margin of excision is either not identified or not discussed.

TABLE 23-1
Vienna Classification of Gastrointestinal Neoplasia

Category	Definition
1	Negative for neoplasia/dysplasia
2	Indefinite for neoplasia/dysplasia
3	Noninvasive low-grade neoplasia (low-grade adenoma/dysplasia)
4	Noninvasive high-grade neoplasia • High-grade adenoma/dysplasia • Noninvasive carcinoma (carcinoma in situ) • Suspicious for invasive carcinoma
5	Invasive neoplasia • Intramucosal carcinoma • Submucosal carcinoma or beyond

Malignant Polyps

DIFFERENTIAL DIAGNOSIS

A common problem concerns differentiating invasive carcinoma complicating a colorectal adenoma from pseudocarcinomatous invasion (pseudoinvasion). *Pseudoinvasion* describes a situation in which neoplastic glands of the adenoma are mispositioned, presumably by trauma, into or beneath the muscularis mucosae.[50-58] Pseudoinvasion is relatively common, reported in 3% to 10% of resected colorectal polyps.[50,52,53] Distinguishing this epithelial mis-

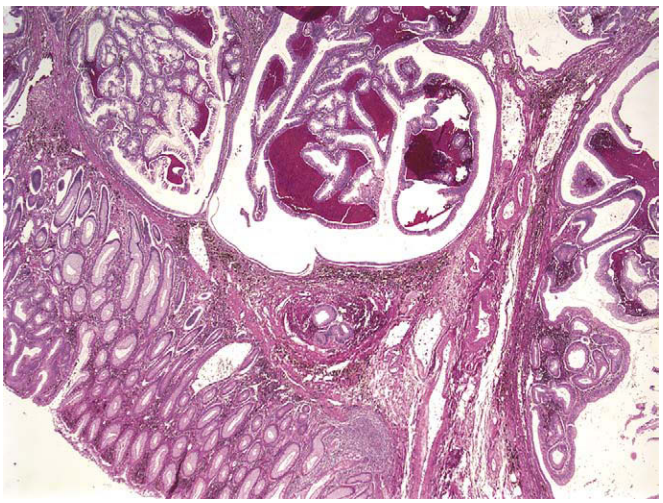

Figure 23-8 ■ Portion of a tubulovillous adenoma showing pseudocarcinomatous invasion. The mispositioned glands have a rounded external contour, lack an infiltrative pattern, lack tumor desmoplasia, and show the presence of surrounding lamina propria. Hemorrhage and hemosiderin deposits in nearby connective tissue are also present.

placement from invasive adenocarcinoma can be difficult. Some reported series of "malignant polyps" have included and even illustrated polyps with pseudoinvasion as examples of invasive adenocarcinoma associated with adenoma.[51] Histologic features favoring pseudoinvasion include the lack of an infiltrative pattern, the lack of tumor desmoplasia, the presence of lamina propria around mispositioned glands, the lack of increased atypia in mispositioned epithelium as compared with the surface epithelium of the adenoma, and the presence of hemorrhage or hemosiderin deposits in nearby connective tissue (Fig. 23-8).

Occasionally, the misplaced glands of pseudoinvasion can become cystic, can rupture, and can be associated with dissection of mucus into the connective tissues of the polyp. In this case, the distinction between mucinous adenocarcinoma and misplaced glands can be extremely difficult.[50-59] Table 23-2 illustrates histologic features that can aid in this differential diagnosis. Examination of additional sections can help in difficult cases because almost all mucinous adenocarcinomas contain at least small foci of typical non-mucinous-type adenocarcinoma.

PATIENT MANAGEMENT

A rational decision concerning management of a patient with an endoscopically removed malignant colorectal polyp (one containing invasive adenocarcinoma) requires weighing the chances of finding residual or metastatic cancer with a follow-up surgical excision (whom do I help?) against the risk of surgical mortality and morbidity (whom do I hurt?). Some investigators have advocated surgical resection for all patients.[60] Currently, however, almost all surgeons and gastroenterologists embrace a more conservative approach and use certain gross and histologic features as indications for follow-up colectomy.[1,58] These features include sessile growth,[16,21] residual villous adenoma, a short stalk (<3 mm),[22] stalk invasion,[23] level 4 invasion,[16,21] lymphatic or vascular permeation,[44] lack of a residual adjacent adenoma (so-called polypoid carcinoma), poor differentiation,[24,25,42,43] and invasive carcinoma at or near a margin of resection.[24,25,42]

We and others[24,25,29,42] believe that two features identify patients likely to avoid an adverse outcome defined as residual or metastatic adenocarcinoma in a subsequent colectomy specimen or during clinical follow-up. Patients with *favorable histology* (defined as well- or moderately differentiated adenocarcinoma with a 2-mm tumor-free margin of resection in the polypectomy specimen) experienced no adverse outcome and are considered adequately treated by polypectomy alone. Similar, although not identical, therapeutic recommendations have been adopted by the ACG.[27,28] These guidelines consider colonoscopic polypectomy definitive treatment for a patient with a malignant polyp if the following criteria are fulfilled: (1) the polyp is considered completely excised at endoscopy, (2) the specimen is properly processed by the pathology laboratory, (3) the cancer is not poorly differentiated, (4) no histologic evidence of vascular or lymphatic involvement exists, and (5) the resection margin is not involved by carcinoma.

Lymphatic or venous invasion, proposed as an indication for follow-up colectomy, remains controversial.[16,22,26,34,35,39,44,60] Only a few malignant polyps with these features have been reported and almost all have had positive margins, contained poorly differentiated invasive carcinoma, or both. We think that lymphatic or venous invasion is not a reliable criterion because the distinction from retraction artifact is frequently difficult. Cooper and colleagues[44] encountered significant interobserver variation in assessing this feature. Furthermore, no guidelines exist that establish the extent to which a pathologist must go to diagnose lymphatic or venous invasion (e.g., number of sections or use of immunostains). Although patients can be stratified into high-risk and low-risk groups based on margin status and grade of invasive adenocarcinoma,[42] and lymphatic or

TABLE 23-2

Differential Features Between Dissecting Mucus of Pseudocarcinomatous Invasion and Invasive Mucinous Adenocarcinoma

Feature	Pseudoinvasion	Invasive Mucinous Adenocarcinoma
Shape of mucous pools	Rounded	Irregular, infiltrating
Location of epithelium	Periphery of pool	Floating in pool
Configuration of epithelium	Single, often discontinuous layer, basal polarity of nuclei	Cellular piling up, complex glandular proliferation, gland-in-gland configuration
Cytologic features	Dysplasia similar to surface adenoma	Atypia pronounced
Tumor desmoplasia	Absent	Usually present
Hemorrhage and hemosiderin deposition	Usually present	Usually absent
Supporting lamina propria	Sometimes present	Absent

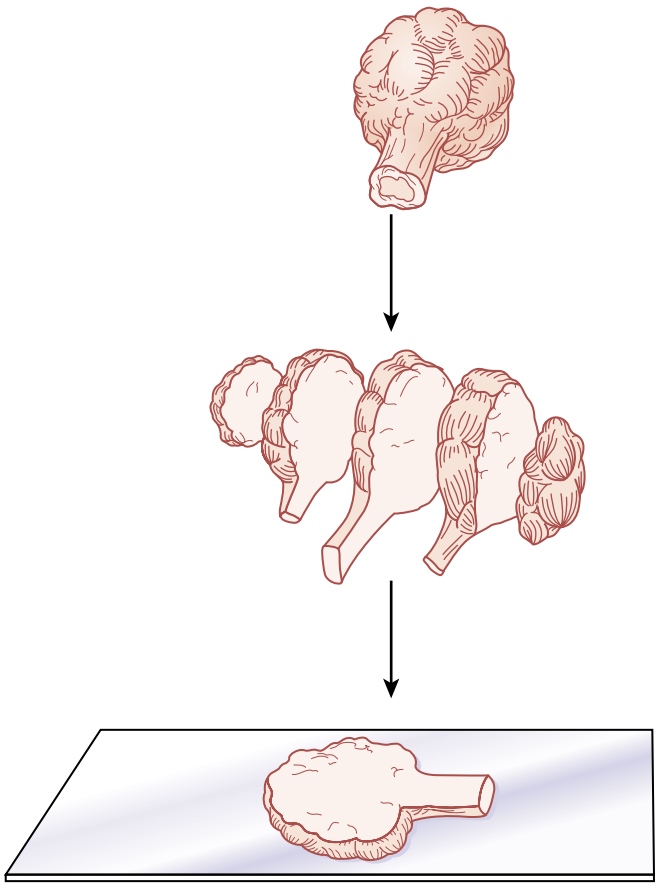

Figure 23-9 ■ Pedunculated polyps should be trimmed on either side of the stalk. A section of the polyp with stalk and margin can be embedded in one block to maintain the correct anatomic relationships. The remainder of the polyp should be submitted in additional blocks.

venous invasion is used by the ACG[28] and in deference to these guidelines, the presence or absence of angiolymphatic invasion should be reported.

As a guide for therapy, the major studies of endoscopic polypectomy for malignant polyps[21-48] have shown that the chance of finding residual or metastatic cancer in a subsequent colon resection specimen or during follow-up in the "favorable histology" group is less than 1%. Weighing these odds against the published operative mortality rates for colectomy that range between 2% and 8%,[38-40] it seems that subsequent major surgical resection should be avoided in the "favorable histology" subgroup.[25,42]

If a decision for subsequent colorectal resection is made, a cancer operation is recommended rather than a more limited procedure because cancer was the indication for surgery. Residual carcinoma in a follow-up resection specimen can be expected in only 10% of cases. These cases of residual or metastatic carcinoma that are discovered within this subset of pT1 lesions are overrepresented by cases containing poorly differentiated carcinoma.

Common Adenomas and Malignant Polyps: Specimen Handling and Reporting

Evaluation of the resection line is critical to proper patient management; therefore, correct handling of the polypectomy specimen is of utmost importance.[24,25,30,42] The entire polyp should be immediately placed into fixative. Following adequate fixation, a polyp with a stalk should be trimmed on either side of the stalk as illustrated in Figure 23-9. The section of the polyp with stalk and margin can be embedded in a block, to maintain the correct anatomic relationship. The remainder of the polyp should be submitted in separate blocks. For polyps without stalks (sessile growths or those in which the stalk has retracted), look for the effect of cautery on the gross specimen. This will appear as a lighter-colored area or a defect on the external surface of the polyp. Carefully trim on either side of this defect (Fig. 23-10) and place this tissue in a block. Again, the remaining tissue should be submitted in separate blocks. Routine examination of a minimum of three step-sections stained with hematoxylin-eosin (H&E) from each block is recommended.

In the pathology report, the presence or absence of invasive carcinoma must clearly be stated. With malignant polyps, the grade of carcinoma must be noted, the resection line must be identified and assessed, and the status of that resection line must be clearly stated in the pathology report. A distance measurement of carcinoma-free margin should be included in the report. In deference to the ACG, the presence or absence of angiolymphatic invasion should be investigated and reported.[28]

The treating physician must individualize the decision for follow-up colorectal excision by weighing the patient's

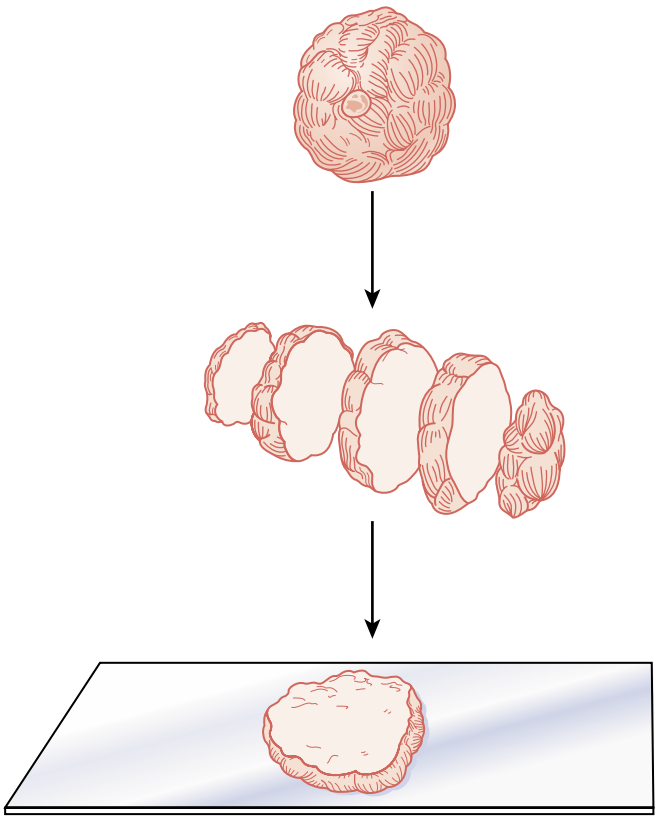

Figure 23-10 ■ Polyps without stalks should be trimmed on either side of the electrocautery margin of excision. This margin should appear as a lighter or darker area or defect on the external surface of the polyp. The section with margins should be submitted in one block with the remainder of the polyp placed in additional blocks.

wishes against the estimated cancer recurrence risk and the predicted operative morbidity and mortality.[40] Advances in laparoscopic resection of the colon and rectum could drastically reduce the morbidity and mortality of operative resection that now constitutes the major contraindication for surgery. These newer surgical techniques may require reassessment of the current management recommendations for malignant colorectal polyps.[61]

Colorectal Adenocarcinoma

Genetic Considerations, Microsatellite Instability, and Lynch's Syndrome

More than 150,000 new cases of colorectal carcinoma occur in the United States each year and account for approximately 52,000 deaths annually. The peak incidence occurs between the ages of 60 and 79 years; fewer than 20% of cancers occur in patients less than 50 years of age. Risk factors for carcinoma include diets rich in animal fat, sedentary lifestyle, and coexisting inflammatory bowel disease (IBD).

At least five separate but overlapping molecular pathways to colorectal cancer may exist.[62] Approximately 80% of colorectal carcinomas occur sporadically, whereas 20% appear to have a genetic basis.[1,63] The genetic group includes the 3% of cases related to Lynch's syndrome (hereditary nonpolyposis colon cancer syndrome [HNPCC]) and the 1% associated with FAP and its variants. The other 16% of cases show strong familial clustering but a specific genetic cause has yet to be found. Colorectal carcinoma can also be viewed another way. Approximately 85% of colorectal cancers are thought to originate through the chromosomal instability pathway. These tumors typically demonstrate DNA aneuploidy and have abnormalities of chromosomes 5, 17, and 18 and contain mutational changes in *APC* gene, K-*ras* proto-oncogene, *DCC* tumor suppressor gene, and *p53* tumor suppressor gene.[64] FAP colorectal carcinomas arise through this pathway. Approximately 15% of colorectal carcinoma appears to arise in the so-called mutator phenotype. These cancers tend to be DNA diploid and are associated with microsatellite instability (MSI). The cancers related to Lynch's syndrome are associated with the mutator phenotype.

DNA integrity is essential for normal cell function. DNA insults can result from the direct effects of chemicals or radiation and are usually corrected through the excision repair system. DNA replication errors are of two types: (1) simple mispairing of nucleotides, the most common type; and (2) "slipping" errors, in which genes may contain too many or too few copies of repeat short DNA nucleotide sequences known as *microsatellites*. Normally, these errors are recognized, the cell cycle is arrested, and the mismatched segment is corrected. For those errors not immediately corrected by DNA polymerase, the mismatch repair (MMR) system acts as a backup for additional proofreading of DNA. Failure to repair mismatches allows the error (mutation) to persist and to become the template for subsequent DNA replication.[65] The known MMR genes and their relative frequency in Lynch's syndrome are presented in Table 23-3.

TABLE 23-3
Mismatch Repair Gene and Frequencies in Lynch's Syndrome

Gene	Frequency (%)	Location
hMLH1	49	3p21
hMSH2	45	2p15
hPMS2	4	7p22
hPMS1	1	2p32
hMSH6	1	2p15
hMSH3	0	5q11-13

MSI is best viewed as an epiphenomenon found in colorectal tumor DNA but not in non-neoplastic tissues. It indicates that extensive mutation exists in the nonencoding repetitive DNA sequences that are particularly prone to replication error, the microsatellites. The majority of MSI is linked to somatic inactivation of *hMLH1* through hypermethylation inactivation of the promotor region, but it can also be detected in persons with germline MMR gene mutations, the definition of Lynch's syndrome.[65] MSI is detected in 15% of colorectal cancers overall and is present in more than 95% of the cancers found in patients with Lynch's syndrome.

Because patients with Lynch's syndrome have a germline mutation of an MMR gene, they are at increased lifetime risk for colorectal (≈80%) and other cancers.[63,66] These cancers develop at significantly younger ages (e.g., average age for colorectal carcinoma ≤44 years).[66] Other tumors related to Lynch's syndrome include cancers of the endometrium, ovary, stomach, biliary tract, urinary tract, kidney, central nervous system, small bowel, and skin.[66]

Patients and families with Lynch's syndrome can sometimes be identified by taking a careful patient and family medical history, can be suggested from the pathologic findings of excised tumors, and can be detected by direct evaluation of the MMR system. Pathologic features of colorectal cancer that suggest MSI/Lynch's syndrome include right-sided location, synchronous or metachronous large bowel cancers, large and bulky polypoid tumors with circumscribed pushing margins, tumors showing prominent lymphoid infiltrate, and cancers of poor differentiation (medullary or undifferentiated carcinoma) or mucinous and signet ring cell histologic pattern (Figs. 23-11 and 23-12).[1,63,67]

The diagnosis of Lynch's syndrome is evolving. Originally, the Amsterdam criteria were used to identify HNPCC clinically including patients with Lynch's syndrome.[68] The original Amsterdam criteria included (1) three or more relatives with colorectal cancer with at least one first-degree relative, (2) colorectal carcinoma in two generations, and (3) one or more colorectal carcinomas occurring in a person less than 50 years of age. To increase the sensitivity, the Amsterdam criteria were modified (Amsterdam II criteria) to include (1) three or more relatives with any carcinoma related to Lynch's syndrome, (2) colorectal carcinoma in two generations, and (3) and one or more carcinomas related to Lynch's syndrome in a person younger than 50 years of age.[69] Detecting Lynch's syndrome based on the Amsterdam criteria alone poses many problems. Patient histories are less useful now than in the past because of

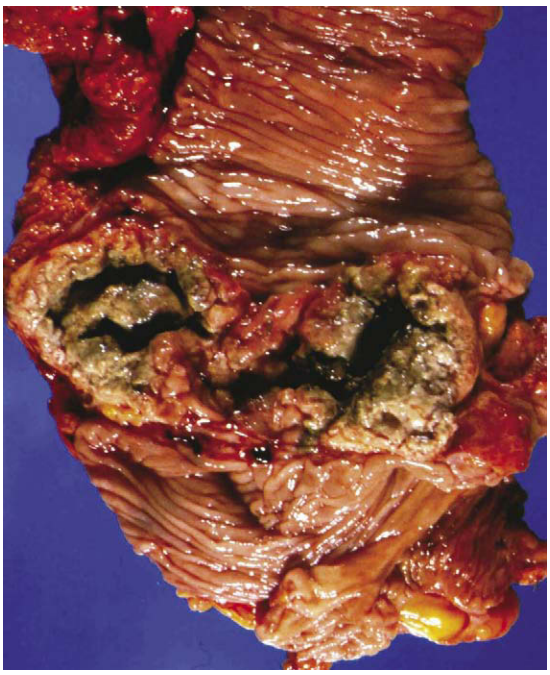

Figure 23-11 ■ Sporadic microsatellite instability–high (MSI-H) colorectal adenocarcinoma involving the cecum. The tumor is large and bulky with areas of necrosis.

smaller family sizes. Excision of colorectal adenomas interrupts the adenoma-carcinoma sequence. Patients in whom the family history is unknown or incomplete limit the utility of these criteria. Physician history taking is often not thorough. More importantly, depending on the cohort, up to 33% of persons having a germline mutation of an MMR gene have negative Amsterdam criteria and only 60% of Amsterdam criteria–positive kindred have a detectable mutation.[69-76] This Amsterdam criteria–positive/gene mutation–negative kindred is often referred to as having *familial colorectal cancer syndrome type X*.

Special testing (MSI testing by polymerase chain reaction [PCR] or immunohistochemical stains) now augments the clinical criteria. Controversy over the use of MSI analysis led to the development of the Bethesda guidelines for testing colorectal tumors for MSI. The latest iteration, the revised Bethesda guidelines,[72] requires than just one of the following criteria be met: (1) colorectal cancer before age 50 years, (2) synchronous or metachronous colorectal or other tumor related to Lynch's syndrome regardless of the patient's age, (3) colorectal cancer with MSI-high pathology (MSI-H) in a patient less than 60 years old, (4) person with colorectal cancer and a first-degree relative with colorectal adenoma or carcinoma or other Lynch's syndrome–related tumor (cancer <50 years; adenoma <40 years), and (5) colorectal cancer with two or more relatives with colorectal or other Lynch's syndrome–related tumor regardless of age.

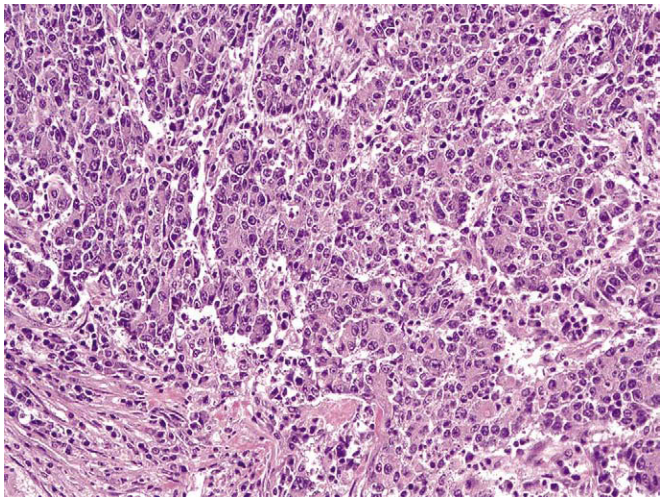

Figure 23-12 ■ Sporadic microsatellite instability–high (MSI-H) colorectal medullary carcinoma composed of uniform polygonal cells arranged in a nesting pattern with no gland formation.

The American Gastroenterological Association position states that genetic testing should be performed on (1) families meeting Amsterdam criteria, (2) any affected person meeting the modified Bethesda guidelines, and (3) any first-degree relative of those with known mutations of MMR genes.[63] These guidelines suggest that after pretest genetic counseling and written informed consent, immunohistochemical analysis for MMR gene products or MSI testing by PCR be performed on tumor tissue. The international guidelines for evaluation of MSI by PCR recommend use of consensus markers: BAT25, BAT26, D5S346, D2S123, and D17S250. If two or more markers are abnormal, the carcinoma is considered MSI-H. If one marker is abnormal, the tumor is classified as MSI-low (MSI-L). If no markers are abnormal, the cancer is referred to as MSI-stable (MSS). Laboratories using more than five loci modify this classification with 30% to 40% or more abnormal defined as MSI-H, less than 30% to 40% as MSI-L, and none abnormal as MSS. Immunohistochemistry can be used to detect MSI. Almost all MSI-H cancers can be identified if the antibody panel includes MLH1, MSH2, PMS2, and MSH6 (Figs. 23-13 and 23-14).[73,76] Immunohistochemical analysis and MSI analysis by PCR have specific advantages and limitations. PCR requires a molecular laboratory and usually requires normal tissue for comparison. Immunohistochemistry is more widely available but can be limited by poor tissue fixation or poor technique rendering interpretation difficult. Immunohistochemistry may be superior because the findings can direct gene sequencing and MSI is not always seen in Lynch's syndrome kindred with MSH6 germline mutation.[66] Patients with MSI-H cancer should undergo additional genetic testing including gene sequencing. MSS and MSI-L tumors require no further testing.[63] Additional genetic evaluation may be considered if the clinical history is compelling.

The clinical significance of identifying Lynch's syndrome is that affected individuals and at-risk persons are recognized and can be screened and treated with correct surgical procedures. Subtotal colectomy is usually recommended to treat colon cancer related to Lynch's syndrome because of the high likelihood of synchronous or metachronous cancers. Partial colectomy with colonoscopy every 1 to 2 years is a reasonable alternative.[66] Furthermore, clinicians can institute proper screening such as colonoscopy at a young age (beginning at age 25 or 5 years younger than the youngest cancer history in the family), periodic endometrial sampling (every 1 to 2 years starting at age 25 years), pelvic ultrasound, CA125 serum testing, and urine cytology

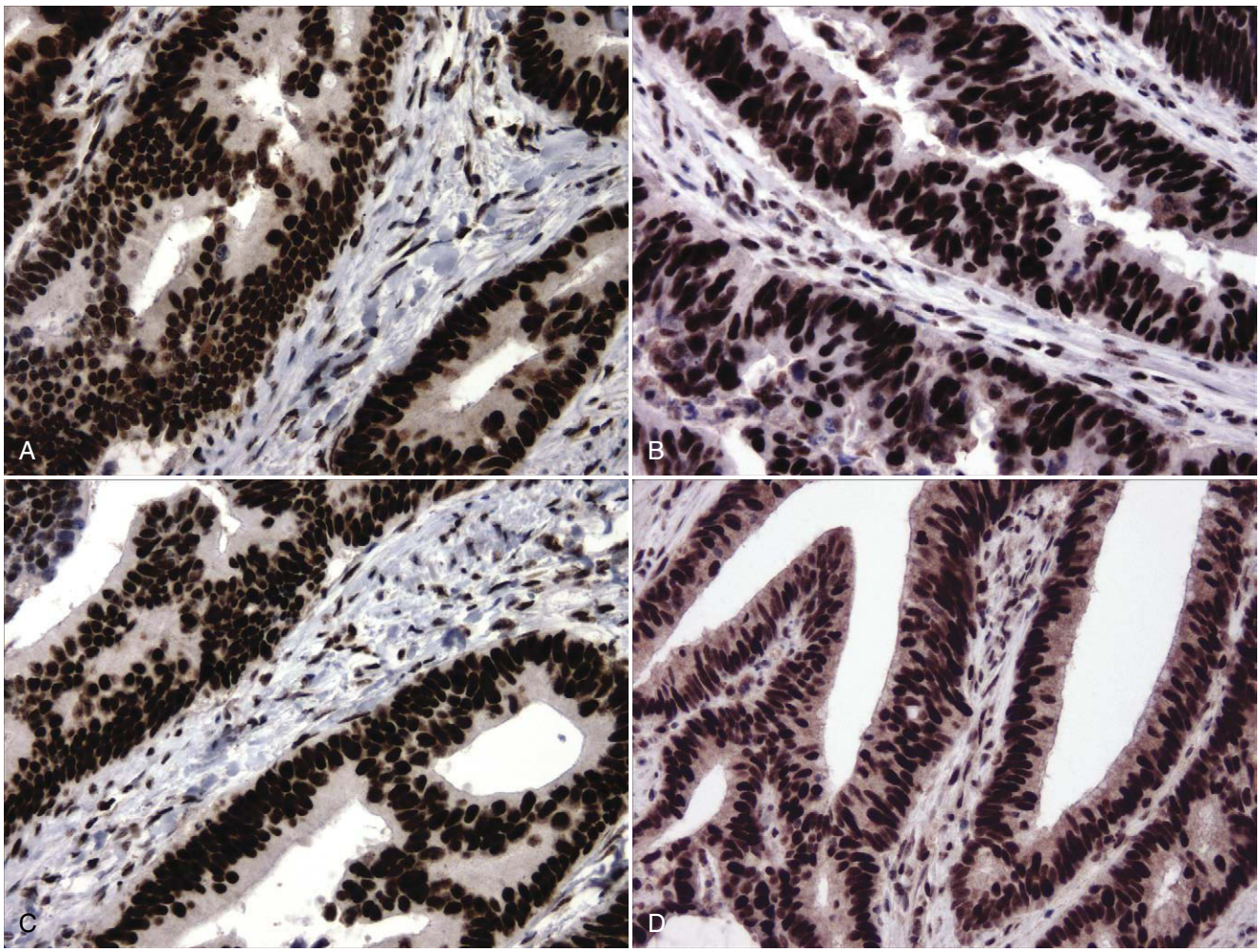

Figure 23-13 ■ Immunohistochemical stains for mismatch repair gene proteins from a sporadic colorectal carcinoma not related to Lynch's syndrome that shows normal expression of *MLH1* (**A**), *MSH2* (**B**), *PMS2* (**C**), *and MSH6* (**D**).

or molecular testing for urinary tract carcinoma. Many experts screen all resected colorectal cancers for MSI initially by PCR. Immunohistochemical analysis is a useful alternative and some prefer this as the initial test because an abnormality in protein expression correlates almost invariably with MSI-H by PCR. In cases showing normal MMR proteins or equivocal staining by immunohistochemical analysis, MSI testing by PCR should be done in clinically suspicious cases to exclude a germline mutation that can yield an antigenic protein that is biologically inactive.

MSI testing in sporadic colorectal carcinoma is a subject of considerable contemporary interest and debate. Much like their counterparts in patients with Lynch's syndrome, sporadic MSI-H carcinomas have a predilection for the right colon, mucinous histologic features, and a prominent lymphoid infiltrate.[77] Strong arguments exist for routine testing for MSI in all resected colorectal carcinomas including the lower mortality rate independent of tumor stage.[78] Sporadic MSI-H cancer can also be associated with an increased rate of metachronous tumors with subsequent clinical implications for cancer surgery, surveillance, and follow-up. MSI status may also have implications for chemotherapy. Improved survival is reported in patients with MSS and MSI-L stage II and stage III cancers who are treated with fluorouracil-based regimens.[79,80] Finally, routine MSI testing could increase the detection of Lynch's syndrome because 44% of probands were more than 50 years old and up to 22% of patients with Lynch's syndrome did not fulfill Amsterdam or Bethesda guidelines.[76]

COLORECTAL SERRATED POLYPS AND THE SERRATED PATHWAY TO COLORECTAL CANCER

Colorectal Hyperplastic Polyps and Hyperplastic (Serrated) Polyposis Syndrome

Hyperplastic polyps are the most common benign polyps of the large intestine.[1,81] These polyps are usually small (<5 mm), sessile, and are often about the same color as the surrounding colonic mucosa. Histologically, evenly distributed absorptive and goblet cells line crypts that are elongate and dilated (Fig. 23-15). Inhibition of normal apoptosis is thought to be the underlying mechanism for polyp formation and because more epithelial cells are present per unit area than normal, the cells must pseudostratify, thus imparting a serrated or micropapillary appearance. Characteristically, the basement membrane under the surface epithelium is thickened and hyalinized. Regenerative epithelial changes, mitotic figures, and active inflammation can be quite prom-

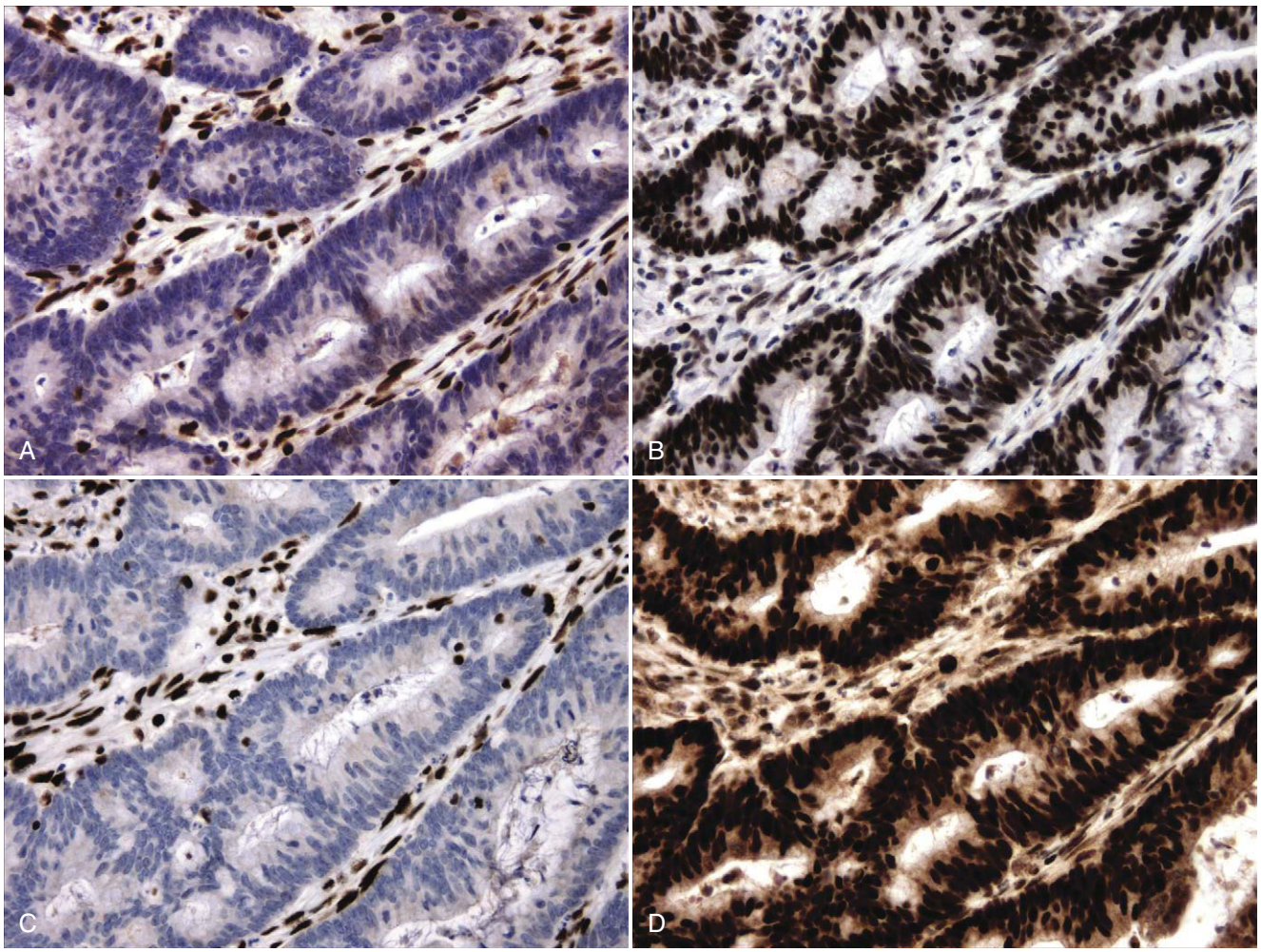

Figure 23-14 ■ Immunohistochemical analysis of a colorectal adenocarcinoma from a patient with Lynch's syndrome who has a germline mutation of *hMLH1*. Note the loss of expression of *MLH1* (**A**) and *PMS2* (**C**) in comparison with the intact expression of *MSH2* (**B**) and *MSH6* (**D**).

inent at the crypt bases. This regenerative area can occasionally cause diagnostic confusion with dysplasia and carcinoma, especially in a variant referred to as *inverted hyperplastic polyp*.[82,83] In this inverted variety, the regenerative epithelium of the crypt base is misplaced into or beneath the muscularis mucosae. Most examples of inverted hyperplastic polyp are now probably best classified as *sessile serrated polyp* (see later) and are easily recognized if one is cognizant of its existence and also notes the overall architectural and cytologic similarity to hyperplastic polyp/sessile serrated polyp. The entity is distinguished from invasive adenocarcinoma by the lack of infiltration and tumor desmoplasia.

The differential diagnosis between hyperplastic polyp and tubular adenoma can be difficult, especially in a diminutive polyp that has been treated by hot biopsy (so-called thermal polyp). Useful features in the differential diagnosis are found in Table 23-4.

When the choice between hyperplastic polyp and tubular adenoma is difficult, as long as an adenoma diagnosis is not going to result in surgical resection (e.g., right colonic adenoma incompletely excised), we err on the side of adenoma to ensure that the patient will receive more frequent surveillance. Mixtures of hyperplastic polyp, sessile serrated polyp, and adenoma occur.[84,85] Mixed polyps and serrated adenomas are considered in more detail later.

Hyperplastic (Serrated) Polyposis Syndrome. Rare examples of patients with colons carpeted by hyperplastic-like polyps (hyperplastic polyposis) have been described (Fig. 23-16). The WHO defines *hyperplastic polyposis* as (1) 5 or more hyperplastic polyps proximal to the sigmoid colon of which 2 are larger than 1 cm, (2) any number of hyperplastic polyps proximal to the sigmoid colon if the person has a first-degree relative with hyperplastic polyposis, and (3) more than 30 hyperplastic polyps of any size and any

TABLE 23-4
Hyperplastic Polyp versus Tubular Adenoma

Feature	Hyperplastic Polyp	Tubular Adenoma
Regenerative zone	Basal	Surface
Dysplasia	No	Yes
Apoptosis	Usually no	Yes
Hyalinized basement membrane	Yes	No

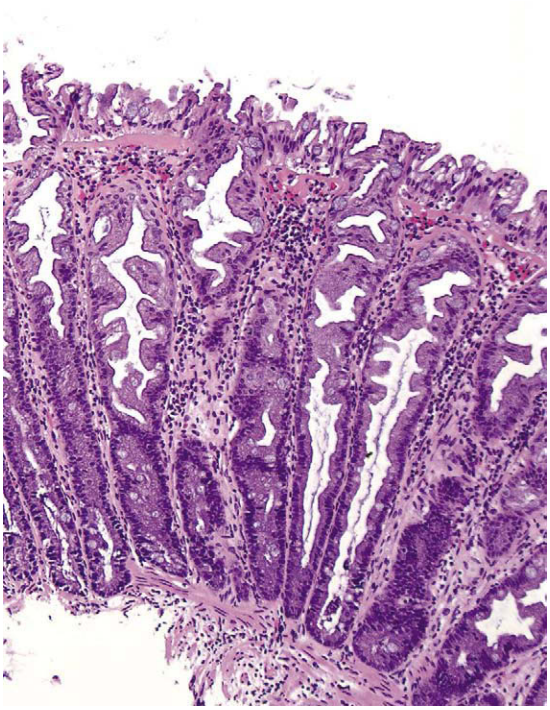

Figure 23-15 ■ Rectal hyperplastic polyp showing elongated crypts with dilatation, evenly distributed absorptive and goblet cells, and a thickened surface basement membrane.

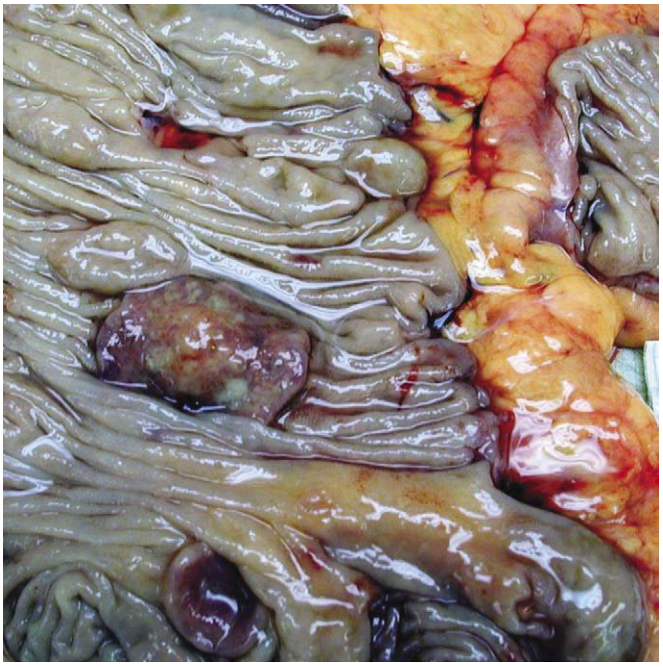

Figure 23-17 ■ Two synchronous invasive colorectal adenocarcinomas arising in association with hyperplastic (serrated) polyposis syndrome. The background mucosa shows the typical gross appearance of hyperplastic polyps as well as some larger sessile polyps and prominent folds. *(Courtesy of James Taylor, MD, Tulsa, Okla.)*

location.[86] The form with 30 or more small hyperplastic polyps without sessile serrated polyp morphology (see later) has been called *type 2 hyperplastic polyposis* and probably does not predispose to adenocarcinoma.[87] Type 1, associated with large (>1 cm) polyps with sessile serrated polyp morphology, is associated with MSI-H cancers (Fig. 23-17) in which methylation-induced loss of expression of *hMLH1* occurs.[87,88] Indeed, hyperplastic polyposis may be a marker for the *mutator phenotype*. *MYH* mutation should be considered when multiple adenomas coexist with hyperplastic polyposis.[88a] Colectomy specimens in hyperplastic polyposis typically show a spectrum of serrated polyps with typical hyperplastic polyps, traditionally defined serrated adenomas (see later), and unusual hyperplastic polyps (sessile serrated polyps; see later). *Serrated polyposis* may be a better name for this syndrome. Patients with hyperplastic polyposis are prone to colorectal carcinoma with a reported prevalence of up to 50%. Once the condition has been diagnosed, careful consideration should be given to the clinical follow-up and prophylactic colectomy may be indicated.[89] Some patients have shown evidence of inheritance presumably caused by a genetic predisposition to hypermethylation. The type and order of methylated genes vary and may account for MSS, MSI-L, and MSI-H cancers. When several cancers in hyperplastic polyposis syndrome families are MSI-H, the distinction from Lynch's syndrome can be difficult. Features that favor hyperplastic polyposis include (1) background serrated adenomas and sessile serrated polyps, (2) the presence of some MSS or MSI-L cancers in the kindred, (3) older age at onset of cancer, (4) limited numbers of affected family members, (5) methylation of *hMLH1*, and (6) failure to detect germline mutation of MMR genes.

Figure 23-16 ■ Hyperplastic (serrated) polyposis syndrome showing numerous small mucosal polyps as well as some larger sessile polyps, plaques, and prominent mucosal folds.

Serrated Polyps and Colorectal Adenocarcinoma

Several lines of evidence link "hyperplastic polyps" with colorectal carcinoma. Investigators have reported individual cases and small series of carcinoma complicating hyperplastic polyps.[90-98] The association between colorectal cancer and hyperplastic polyposis has already been noted. The rate of coexisting hyperplastic polyps, but not adenomas, is high in patients with MSI-H carcinoma.[90] A large series of MSI-H colorectal carcinomas predated by biopsy-proved hyperplastic polyps at the same site has been reported.[95]

TABLE 23-5
Methylation/Mutations in Serrated Polyp Family

Gene	HP (%)	SSP (%)	Mixed (%)
MINT 1	23	30	100
MINT 2	32	70	100
MINT 31	23	70	100
hMLH 1	0	13	70
MGMT	36	57	60
KRAS (mutation)	18	13	0
BRAF (mutation)	19	75	89

HP, hyperplastic polyp; mixed, mixed polyps and serrated adenomas; SSP, sessile serrated polyp.

Molecular events involved in the serrated polyp family are now recognized. Methylation-induced inactivation of MMR genes occurs in both hyperplastic polyps and carcinoma. As shown in Table 23-5, methylation inactivation of genes and certain gene mutations (especially *BRAF*) appear to be involved in the serrated pathway to carcinoma.[99,100] These molecular events have been verified.[101-106]

Hyperplastic polyps associated with carcinoma have been unusually large and right-sided lesions. They have been reported using numerous synonyms, including giant hyperplastic polyp, sessile serrated adenoma, sessile serrated polyp, inverted hyperplastic polyp, and polyp with epithelial serrated proliferation.

It is becoming clear that several different pathologic entities have been called *hyperplastic polyps* in the past. This serrated polyp family includes conventional hyperplastic polyp, mixed hyperplastic/sessile serrated polyp/adenoma (Fig. 23-18), serrated adenoma (epithelial dysplasia defined, usually pedunculated and left sided, having eosinophilic cytoplasm and showing gastric foveolar change and often referred to as the traditionally defined serrated adenoma) (Fig. 23-19), and hyperplastic-like polyps with unusual features that have been referred to as sessile serrated polyps or sessile serrated adenomas.[84,91,93-96] Sessile serrated polyps appear related to serrated adenomas and mixed polyps and could be the specific precursor lesion to sporadic MSI-H carcinoma. Transitions from sessile serrated polyps to areas of dysplasia and carcinoma with loss of hMLH1 protein expression have been described (Fig. 23-20).[97,98]

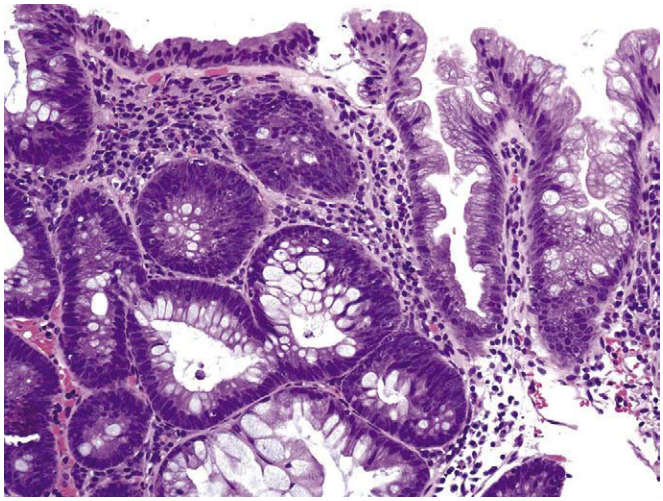

Figure 23-18 ■ Mixed sessile serrated polyp and conventional tubular adenoma.

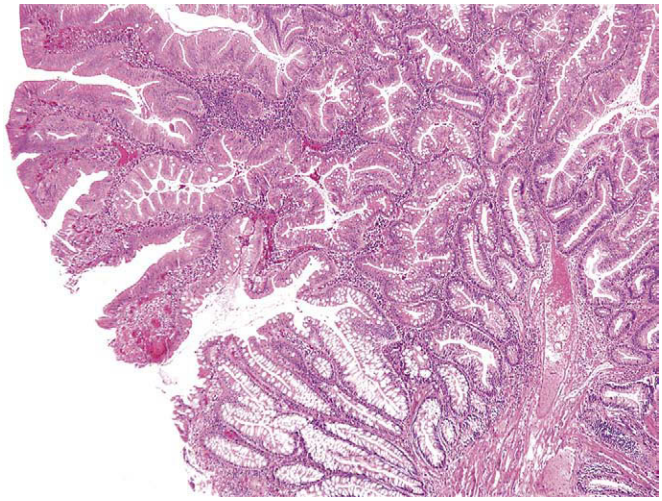

Figure 23-19 ■ Traditionally defined serrated adenoma. These polyps are typically pedunculated and left sided. The mucosal fronds show prominent serration and are made up of cells containing eosinophilic cytoplasm and nuclei exhibiting dysplasia.

Sessile serrated polyps as the name implies are sessile, large (frequently ≥1 cm), right sided, and often show poor endoscopic circumscription. Numerous cytologic and architectural abnormalities have been reported in sessile serrated polyps, especially those associated with carcinoma.[92,95,97,98] The abnormal proliferation or dysmaturation features include persisting nuclear atypia with large nuclei and nucleoli high (upper third) in the crypts, high (upper third of the crypt) mitotic figures, and irregular distribution of dystrophic goblet cells. Architectural abnormalities include basal crypt dilatation, horizontally oriented crypts, crypt branching, an increased epithelial-to-stromal ratio (>50%), inverted crypts, prominent serration, increased surface villosity or papillations, and the lack of a surface basement membrane thickening typical of conventional hyperplastic polyps. Some authors suggest that a diagnosis of sessile serrated polyp requires the presence of at least four of the architectural and abnormal proliferation features mentioned earlier (Figs. 23-21 and 23-22).[102]

Once recognized, the sessile serrated polyp creates a patient management dilemma. Calling them "sessile serrated adenomas" may not be an appropriate default. First and foremost, these lesions do not show the cytologic dysplasia that should be definitional for adenoma. Sessile serrated adenoma is often confused by gastroenterologists and surgeons with serrated adenoma or villous adenoma. It is unknown whether colonic resection (which is typically done for incompletely excised adenomas) should be recommended for sessile serrated polyps that are incompletely excised at endoscopy. Furthermore, endoscopic follow-up for serrated adenoma would typically be in 3 years (if the clinician considers serrated adenoma or sessile serrated adenoma a variant villous adenoma) or in 5 years. In a cohort of 91 patients with sessile serrated polyps preceding MSI-H carcinomas, 19 predated the carcinomas by less than 3 years.[95] We think that these lesions should be diagnosed as sessile serrated polyps and that they should be treated by

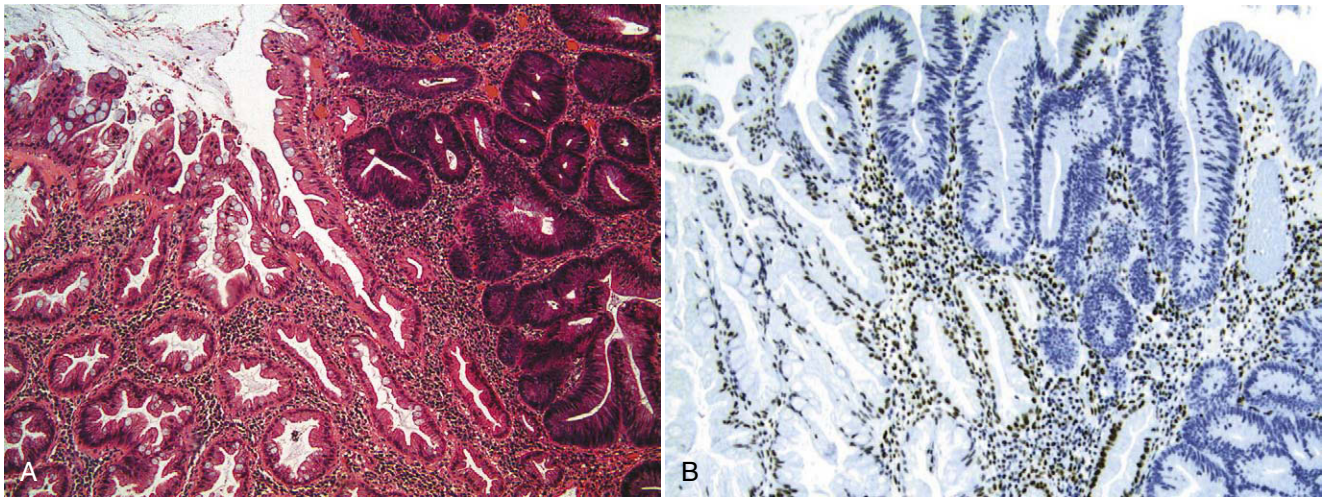

Figure 23-20 ■ **A,** Mixed sessile serrated polyp *(left)* and conventional tubular adenoma *(right)*. **B,** The area of dysplasia in this example demonstrates loss of nuclear *hMLH1* expression by immunohistochemistry.

complete endoscopic excision if possible. Until more is known, a shorter surveillance interval (e.g., 1 to 2 years) rather than resection seems prudent for these types of polyps that are incompletely excised or associated with additional, endoscopically similar polyps that have remained unsampled.[93-96]

Pathologic Evaluation of Colorectal Carcinoma

CLINICAL FEATURES AND GROSS OR ENDOSCOPIC PATHOLOGY

Colorectal carcinoma occurs more often in men (male-to-female ratio, 3:2), with a median age of 62 years.[1] Most patients present with rectal bleeding, anemia, change in bowel habits, bowel obstruction, or less often perforation.[1] Patients with right-sided colon carcinoma are more likely to present with anemia and fatigue, whereas left-sided carcinoma is more likely to produce melena, constipation, and change in bowel habits. Approximately half of all large bowel carcinomas occur in the rectum, 25% occur in the sigmoid colon, and the rest are evenly distributed throughout the remainder of the colon.[1] That said, with increased use of colonoscopy with removal of adenomas, clinicians have seen a right-sided migration of carcinomas since the late 1970s.

Carcinomas of the right colon tend to produce large, exophytic tumors (see Fig. 23-11). Carcinomas of the descending colon are more likely to be stenotic and produce the so-called "napkin ring" tumor. Carcinomas anywhere can be fungating, ulcerated, or necrotic masses; the most common macroscopic appearance is an ulcer with raised,

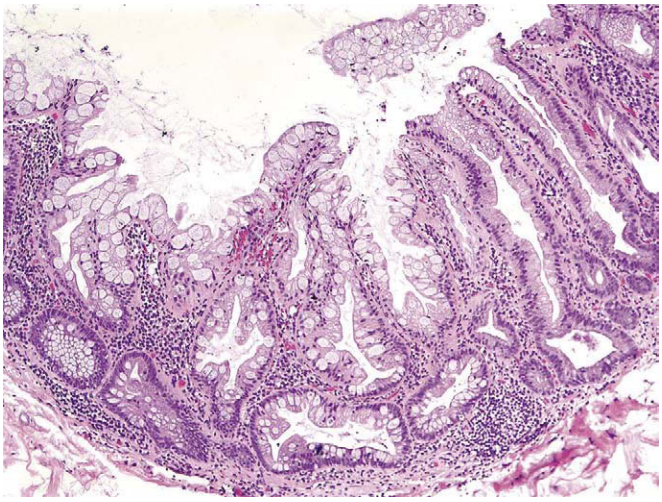

Figure 23-21 ■ Architectural abnormalities in sessile serrated polyps includes basal crypt dilatation, horizontally oriented crypts, branching crypts, and an increased epithelial-to-stromal ratio. This example of sessile serrated polyp also shows an abnormal distribution of goblet cells, some of which show dystrophic features.

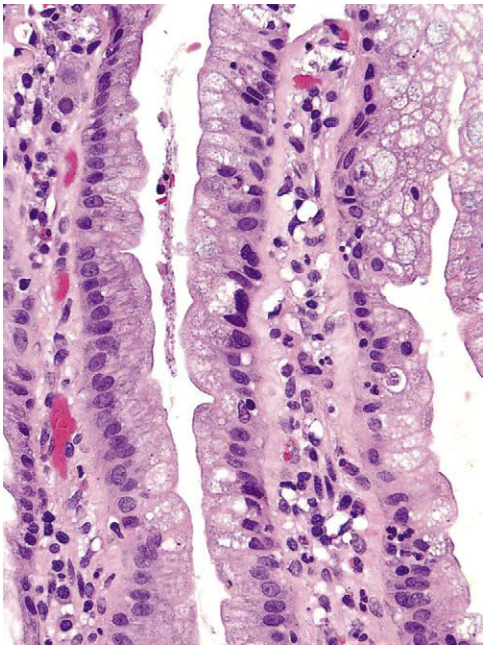

Figure 23-22 ■ High-magnification view of the upper third of a crypt from a sessile serrated polyp showing persistence of larger nuclei with nucleoli.

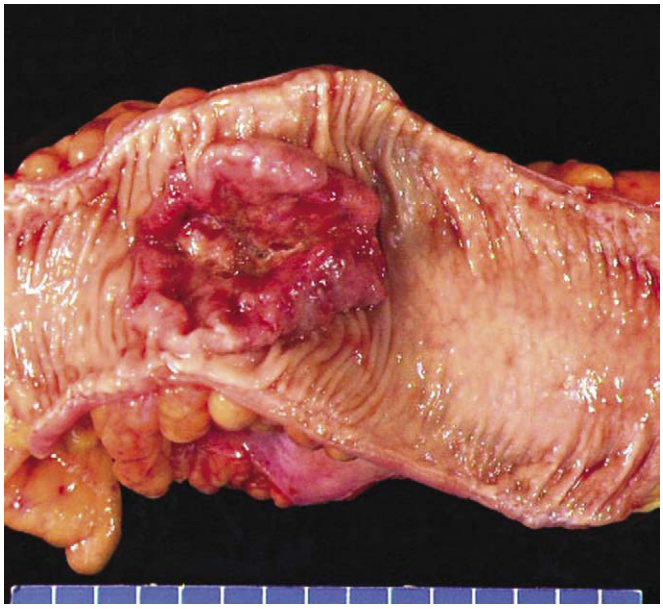

Figure 23-23 ■ Sigmoid colon adenocarcinoma showing an ulcerated mass with raised, indurated edges.

indurated edges (Fig. 23-23). MSI-H colorectal carcinomas, whether sporadic or associated with Lynch's syndrome, tend to be right sided, multiple, large, and bulky (see Fig. 23-11).

TYPING, GRADING, AND STAGING

Histologic typing, grading, and pathologic staging provide prognostic information and are used to guide management of patients with colorectal carcinoma. Obviously, the surgical pathologists' skill, knowledge, and enthusiasm determine the assessment of these prognostic variables. Carcinomas should be classified and graded following the guidelines of the WHO.[1,14] Staging should follow American Joint Commission on Cancer and International Union Against Cancer (tumor, node, metastasis [TNM] system) guidelines.[1] Reporting is facilitated by use of the College of American Pathologists (CAP) cancer protocols, which are available at their website (www.cap.org).

The following features adversely affect prognosis: advanced stage, extensive local spread, lymph node involvement, aggressive histologic type, high histologic grade, extramural venous invasion, and free mesothelial surface invasion.[1,67,107-109] Although useful information is gleaned through these classic grading and staging exercises, the process is not without problems and controversy. No general agreement exists on staging or grading and all current schemes have shortcomings.[109-111] Using current systems, most fall into a moderate-stage, moderate-grade category in which the probability of survival is roughly 50/50.

The CAP considered and commented on the multitude of reputed prognostic factors in a consensus statement[67] and concluded that certain factors have been definitively proved to be of prognostic import, including local extent of tumor (pT), regional lymph node metastases (pN), blood or lymphatic vessel invasion, and residual tumor following surgery with curative intent. Other factors that have repeatedly been shown to be of prognostic importance include tumor grade, radial margin status, and residual tumor in specimens following neoadjuvant therapy.[67] The CAP recommends that these additional features should also be included in pathology reports. Although customarily included in pathology reports, parameters such as tumor size and gross configuration have been well studied and are of no prognostic significance.[67] That still leaves an incredibly large group of factors that may be considered prognostic but have not yet been sufficiently studied.

This discussion focuses on controversial areas in classic staging and grading including methods of lymph node dissection and assessment of histologic grade and type. Additionally, the role of flow cytometric analysis, markers of proliferative activity, and other ancillary testing will be examined.

Lymph Node Dissection

The single most important factor related to patient prognosis is the presence or absence of lymph node metastases. No doubt exists that searching for lymph nodes in a resection specimen is tedious. The lymph node yield per case is directly proportional to the dissector's enthusiasm and skill. As a general rule, a standard resection specimen for carcinoma of the sigmoid colon or rectum should contain 10 to 25 lymph nodes, although we all have had cases in which the dissector found far fewer. Minimum numbers of lymph nodes harvested is increasingly considered a measure of quality.[112,113] Therefore, the routine use of clearance techniques for lymph node dissection has been debated. Certainly, clearance techniques have advantages. One is likely to find more lymph nodes in a specimen and the lymph node yield will no longer depend solely on the dissector's ability and enthusiasm. However, the clearance process is time consuming and it may delay reporting.[114,115] Clearing is relatively expensive because of the large volumes of clearing agents used and the prolonged technologists' or pathologists' time. Common clearing agents are often flammable and toxic.

Cawthorn and colleagues[114] showed that clearance techniques increase the yield of lymph nodes per specimen when compared with routine dissection. However, the proportion of stage 1, 2, and 3 cases did not change. The number of positive lymph nodes found was similar between cleared and noncleared groups. This finding was later confirmed.[113] Clearance techniques are considered unnecessary for routine cases.[67,116]

Additional controversy is added by consideration of nontraditional methods of lymph node examination such as the following: immunohistochemical analysis for carcinoembryonic antigen (CEA), cytokeratins, and epithelial membrane antigen; PCR testing looking for tumor DNA or RNA; and sentinel lymph node examination. The biologic significance of these nontraditional methods lacks validation,[67,117-121] and "positive" nodes found by these techniques may have no effect on prognosis.[122] Currently, the CAP recommends that all grossly identified lymph nodes be sectioned (without multiple levels) in a routine fashion.[67,121] Pathologists should find as many lymph nodes as possible and should recognize that the rules of representative sampling and probability apply.[112] As a general rule, 12 negative lymph nodes usually correlate with true pN0 status.[112,121,123,124] Extramural tumor nodules of any size with smooth con-

tours are counted as replaced regional lymph nodes.[111] Sentinel lymph node examination does not accurately predict either conventionally defined nodal metastasis or micrometastasis and is not considered useful in the study of patients with colorectal carcinoma.[125]

Histologic Grading

Pathologists admit that grading is more art than science. Grading is subjective and prone to interobserver and intraobserver variation. One multicenter trial noted 3% well-differentiated adenocarcinomas from one institution, whereas another hospital reported 97% well-differentiated cases.[111] Marked heterogeneity exists within a given tumor. Some observers grade on the average, whereas others assign a grade corresponding to the least-differentiated area. Many grading systems are used for colorectal carcinoma.[111,126-132] All employ slightly different criteria that are poorly defined. Some use three grades and others four. Some exclude mucinous carcinoma altogether and others include it as grade IV or grade III. Criteria for mucinous carcinoma are hardly ever defined.

We follow the guidelines of Dukes and Bussey[132] and use a three-grade system.[1] Well-differentiated adenocarcinoma (grade I), which should account for 10% to 20% of cases, shows tubular differentiation; the nuclear polarity is easily discerned, and nuclei are generally uniform in size (Fig. 23-24). Approximately 70% of adenocarcinomas are moderately differentiated (grade II) exhibiting a more complex and irregular tubular pattern, and the polarity of nuclei is lost or is only barely discernible (Fig. 23-25). The remaining poorly differentiated adenocarcinomas (grade III) consist of highly irregular glands or may show an absence of glandular architecture. Nuclear polarity is lost (Fig. 23-26). When variability exists within a given tumor, the grade is determined by the worst area no matter how small. Mucinous carcinoma and signet ring cell carcinoma are considered poorly differentiated or grade III.[133]

Jass and colleagues[111] investigated grading using a Cox regression analysis model in 447 resection specimens. The only grading parameters associated with prognosis were the amount of tubule configuration, the pattern of growth (expanding versus infiltrative), and the degree of lymphocytic infiltration. When stage-related parameters were added into the Cox regression model, only three factors emerged as significant: (1) lymph node involvement, (2) local spread (i.e., the components of stage), and (3) the amount of lymphocytic infiltration in the neoplasm (i.e., a reflection of MSI status). This study provided the scientific verification of the original observation by Dukes and Bussey[132] that grade was subservient to stage in prognosis and re-emphasizes the need for careful specimen dissection and examination to determine the amount of local spread and lymph node status.

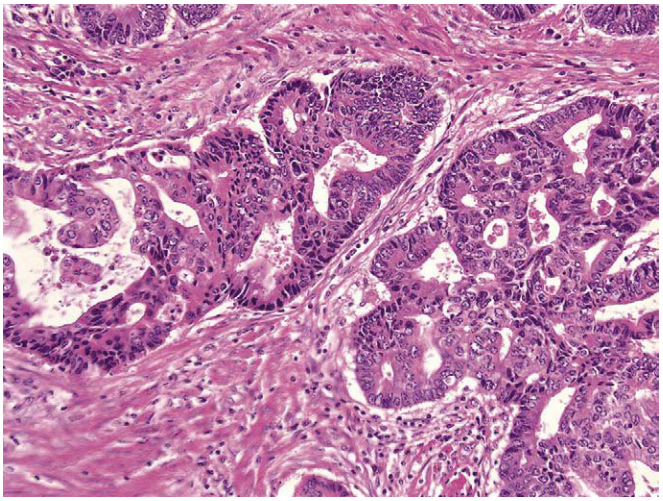

Figure 23-25 ■ Invasive moderately differentiated adenocarcinoma exhibiting a complex and irregular tubular pattern with some loss of nuclear polarity.

Histologic Type

Many clinicians believe that mucinous carcinoma and signet ring cell carcinoma are associated with significantly worse prognosis than nonmucinous adenocarcinoma. Unfortu-

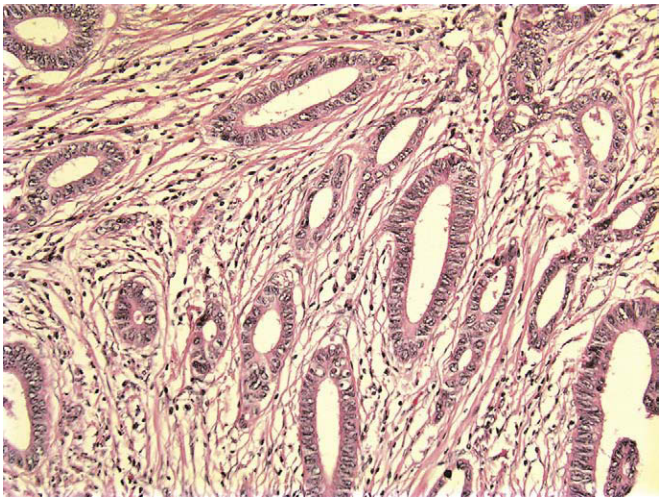

Figure 23-24 ■ Invasive well-differentiated adenocarcinoma showing easily discernible tubule formation and basally oriented nuclei that are relatively uniform in size.

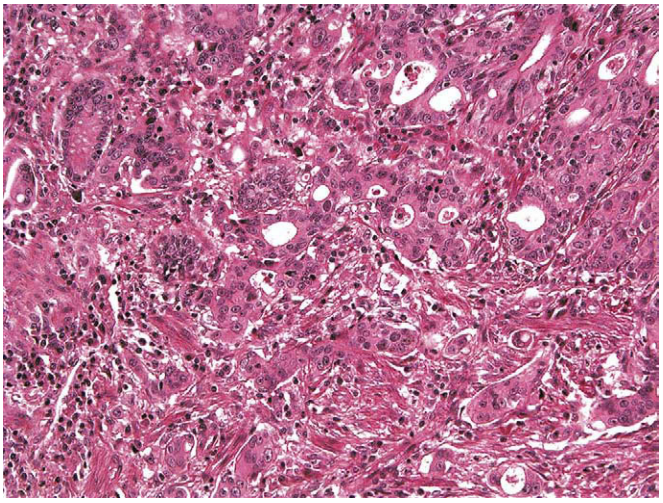

Figure 23-26 ■ Invasive poorly differentiated adenocarcinoma consisting of carcinoma cells arranged in highly irregular glands and showing areas without glandular architecture. The nuclear polarity is lost.

nately, the definitions of mucinous and signet ring cell carcinoma vary.[1,67,134-138] Work by Sasaki and colleagues[137] and Umpleby and associates[138] verified that mucinous and signet ring cell carcinomas are associated with a worse prognosis, but these tumors manifest at high stage and are associated with extensive local spread.

Sasaki and colleagues[137] scrutinized a large cohort of mucinous, signet ring cell, and nonmucinous carcinomas using a Cox multiple regression model. According to this study, the only significant adverse prognosis–related independent variables were the presence of lymph node metastases and the extent of local spread (i.e., the components of stage), along with an infiltrative growth pattern and minimal lymphocytic infiltration. Sasaki and colleagues[137] and Umpleby and associates[138] concluded that mucinous carcinoma (>75% to 80% by volume) and signet ring cell carcinoma (>50% cells with signet ring morphology) (Fig. 23-27) are more aggressive. These histologic features were not, however, significantly associated with poor prognosis when they were controlled for stage.

Flow Cytometry

Flow cytometry for examination of DNA content in human tumors involves cells or isolated nuclei stained in suspension with a fluorescent dye that binds stoichiometrically with double-stranded DNA. These stained cells or nuclei are then passed one by one through an excitor light source (laser). The amount of fluorescence produced by the bound dye is detectable by a photoelectric cell, and the information is stored electronically. With this technique, thousands of measurements can be made in seconds and displayed on a histogram. The position of peaks on the x-axis is proportional to the amount of DNA per cell, and the height of the peaks on the y-axis is proportional to the number of cells demonstrating a particular DNA content. Using this method, diploid cell populations can be distinguished from nondiploid (including DNA aneuploid) cell populations.

Studies of paraffin-embedded and fresh colorectal carcinoma specimens have demonstrated an inconsistent association between DNA aneuploidy and survival.[134,139] In at least one of these studies,[139] stage was retained as a strong independent variable associated with prognosis after multiple regression analysis. Other investigators showed no independent association between DNA aneuploidy and prognosis in a large group of patients with colorectal carcinoma, with stage as the only independent variable associated with prognosis.[140]

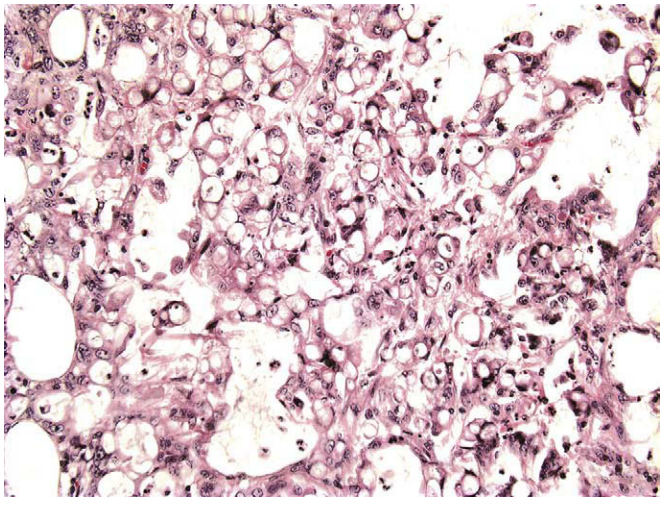

Figure 23-27 ■ Invasive signet cell adenocarcinoma of large bowel.

DNA content analysis by flow cytometry is of no proved clinical value.[67] The technology and methods lack standardization, and the results among groups generally are not comparable. Most published studies have employed paraffin-embedded material. This may not be optimal because DNA fragments and partial nuclei tend to stick together, thus leading to increased yields of pseudoaneuploid histograms.[133] The proportion of cases showing aneuploid peaks is lower when fresh intact cells are used. In terms of interpretation, control histograms are easy to read but tumor histograms are less clean and interpretations are subject to interobserver variation. In a cohort of 165 patients with colorectal carcinoma prospectively studied, results of flow cytometric analysis showed no correlation between DNA aneuploidy and any standard staging or grading parameter and had no independent association with prognosis.[133,141] The CAP believes that DNA analysis has not been adequately studied for determination of prognostic value and the data are insufficient to recommend a specific technologic method.[67]

Various proliferation markers have been studied in colorectal carcinoma. For example, a cohort of 122 patients with colorectal carcinoma were studied using an antibody that recognizes Ki-67, a nuclear antigen expressed in all phases of the cell cycle except G_0.[108] No correlation was found between Ki-67 scores and stage, grade, or prognosis. Stage, growth pattern, and lymphocytic infiltration were the only factors independently associated with prognosis. The CAP believes that data are insufficient to recommend inclusion of proliferation indices in pathology reports for prognostic information.[67]

Early Nonpolypoid Colorectal Carcinoma

Early invasive colorectal carcinoma (pT1-invasive carcinoma limited to the submucosa) warrants special mention given the advent of endoscopic techniques allowing gastroenterologists and surgeons to resect some carcinomas locally either surgically or through the endoscope (e.g., endoscopic mucosal resection [EMR]). Because lymph node status is the strongest prognostic factor in colorectal carcinoma, the question asked, particularly by surgeons, is whether local excision or EMR is enough or should definitive surgical resection be performed for pT1 lesions. The issue is further complicated by the low rate of lymph node metastases in pT1 colorectal carcinoma, estimated at 3% to 17%.[132,142-145] This dilemma prompted evaluation of histologic parameters and molecular markers that correlate with positive lymph node status in excised pT1 colorectal carcinoma.

Features that consistently correlate with positive lymph node status in pT1 colorectal carcinoma include angiolymphatic invasion, poor differentiation, tumor budding (Fig. 23-28), and SM3 invasion (invasion of the deepest third of the submucosa).[144-148] Although various immunostains and molecular markers have not been significantly associated with lymph node status,[144] gene expression profiling could improve the prediction of patients likely to have positive lymph nodes and could improve outcomes.[149]

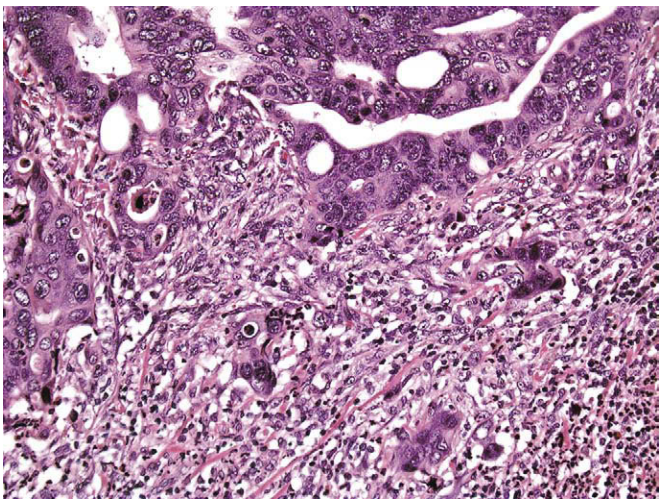

Figure 23-28 ■ Tumor budding can be seen at the advancing edge of an invasive adenocarcinoma. The phenomenon is usually defined as the presence of small clusters or individual "undifferentiated" carcinoma cells at the invasive margin. These areas would correlate with poor differentiation in some grading schemes.

Treatment-Related Ancillary Testing

Cetuximab is a chimeric monoclonal antibody that binds to epidermal growth factor receptor (EGFr). It has clinical significant activity when given alone or in combination with irinotecan in patients with advanced irinotecan-refractory colorectal carcinoma.[150-152] Approximately 85% of colorectal cancers express EGFr on immunohistochemical analysis but that expression does not correlate with gene amplification.[153] Immunohistochemical analysis for EGFr is sometimes used as a selection criterion for cetuximab.[154] The threshold for positive staining results has been extraordinarily low (1+ staining in >1% of cancer cells) and neither the proportion of positive tumor cells nor the intensity of staining has correlated with clinical response. Some patients who tested negative for EGFr responded to cetuximab and many patients who tested positive did not. Consequently, the National Comprehensive Cancer Network guidelines for colorectal cancer management recommend against using EGFr expression based on immunohistochemical results to select patients for cetuximab therapy.[151,155] Patients with colorectal cancer bearing mutated K-*ras* do not benefit from cetuximab.[155a]

Bevacizumab is a monoclonal antibody directed against vascular endothelial growth factor (VEGF), which is critical in the regulation of angiogenesis. This monoclonal antibody added to fluorouracil-based chemotherapy regimens resulted in significant improvement in patients with advanced colorectal carcinoma.[156,157] VEGF is expressed in approximately 50% of colorectal carcinomas.[157] Neither microvessel density determination, which is prone to significant methodologic variation,[158] nor VEGF determinations by immunohistochemical analysis were considered a selection criterion.

Before 2000, fluorouracil, a thymidylate synthase inhibitor, was the only effective treatment for advanced colorectal cancer and because leucovorin (folinic acid) enhances the effect by stabilizing the bond between fluorouracil and thymidylate synthase, both agents are often given together.[152,159,160] Other cytotoxic drugs such as irinotecan, an inhibitor of topoisomerase I, and oxaliplatin, which distorts DNA by cross-linking into adducts, are now approved for treatment for advanced colorectal carcinoma.[152,159,160]

Irinotecan has efficacy as a first-line treatment for advanced colorectal cancer but lacks efficacy as adjunct therapy. Irinotecan is hydrolyzed into an active metabolite (SN-38) by hepatic carboxyl esterase. SN-38 is converted into an inactive form by uridine diphosphate glucuronosyltransferase isoform 1A1 (UGT1A1). In patients with polymorphisms of UGT1A1, the toxicities of irinotecan (diarrhea, nausea, vomiting, myelosuppression, alopecia) are more severe. Although results indicate that UGT1A1*28 polymorphisms have some relevance to toxicity, especially hematologic toxicity with the first cycle of chemotherapy,[161] determination of the polymorphism seems to have marginal clinical implications. The observed toxicities can be managed clinically, other UGT1A enzymes may play a role as well,[162] and data do not support dose reduction based on a molecular test.

Cisplatin and its analogues (oxaliplatin) are particularly toxic and molecular markers to identify patients likely to respond have been investigated. Oxaliplatin adducts are repaired by the nucleotide excision repair complex. ERCC1 (excision repair cross-complementation group 1) is 1 of 16 genes that encode proteins of this complex.[163] Polymorphisms that reduce levels of ERCC1 correlate with clinical sensitivity to oxaliplatin[163,164] and could be used for patient selection.

Histologic Variants of Colorectal Carcinoma

MEDULLARY (UNDIFFERENTIATED) CARCINOMA

The medullary variant of colorectal carcinoma occurs predominantly in women and usually occurs in the cecum and right colon.[1,14] Histologically, it is composed of uniform polygonal cells arranged in a nesting or trabecular pattern with minimal gland formation. Immunohistochemistry is often employed to rule out neuroendocrine carcinoma or melanoma. Other characteristic features of medullary carcinoma include a prominent lymphoid component that can either be peritumoral, often described as Crohn's disease–like, or intratumoral with tumor-infiltrating lymphocytes (more than five per high-power field; see Figs. 23-11 and 23-12).[165] Medullary carcinoma is seen with increased frequency in MSI-H colorectal carcinoma whether sporadic or in association with Lynch's syndrome.

ADENOSQUAMOUS AND SQUAMOUS CARCINOMA

Adenosquamous carcinoma, defined by having a malignant glandular and squamous component, occurs rarely as a primary carcinoma in the colon and rectum (Fig. 23-29). The possibility of metastasis must always be considered. Adjacent adenoma can help to confirm a primary tumor. Adenosquamous carcinoma has been described in patients with ulcerative colitis (UC), FAP, schistosomiasis, and endometriosis. Occasionally, squamous differentiation can be found in adenomas (Fig. 23-30). Pure squamous colorectal carcinoma outside of the anal canal is extremely rare. The possible diagnosis of metastasis must be excluded. Squamous carcinoma has been reported in fistulas, in association with radiation, and in patients with IBD, tuberculosis, and schistosomiasis.[1,14,166]

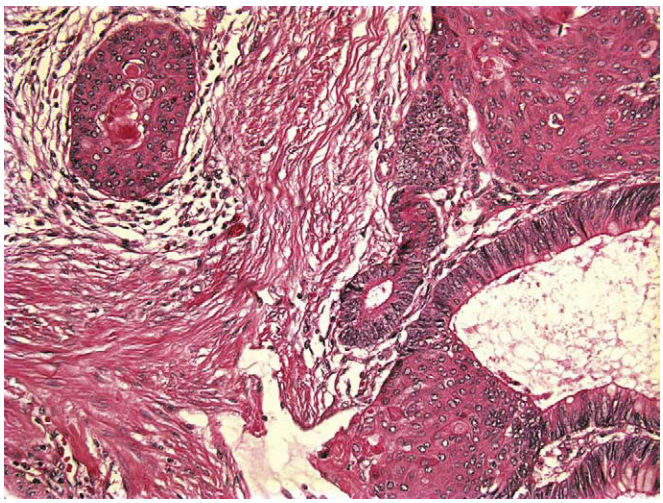

Figure 23-29 ■ Invasive well-differentiated adenosquamous carcinoma of the large bowel demonstrating a malignant glandular and squamous component.

MICROGLANDULAR GOBLET CELL ADENOCARCINOMA (SO-CALLED GOBLET CELL CARCINOID)

Occasional case reports of microglandular goblet cell adenocarcinoma (goblet cell carcinoid) identical to that seen in the vermiform appendix have been described in the large bowel. These tumors are composed of trabeculae and nests of well-differentiated adenocarcinoma cells showing differentiation toward goblet cells. Scattered or no endocrine differentiation is characteristically seen by immunohistochemical analysis for chromogranin and synaptophysin. Although cytologically bland, these carcinomas are often aggressive in the colon and rectum.[1]

CARCINOSARCOMA

Carcinosarcoma is often referred to as *spindle cell carcinoma* or *metaplastic carcinoma* and can occur rarely in the large bowel. Frequently, a high-grade squamous or glandular component is detected. The mesenchymal component can be undifferentiated or can show striated or smooth muscle differentiation or areas of cartilage or bone. These tumors are associated with a poor prognosis.[1,167,168]

GIANT CELL CARCINOMA AND CHORIOCARCINOMA

Giant cell carcinoma and choriocarcinoma can occur purely or as focal components of an otherwise typical high-grade adenocarcinoma or carcinosarcoma. In choriocarcinoma, the giant cells express beta human chorionic gonadotropin (HCG). Carcinomas with giant cells that fail to stain for beta HCG are referred to as *giant cell carcinomas*.[1,169,170]

Endocrine Tumors of Large Bowel

Endocrine tumors involving the colon and rectum can be classified into three types based on morphology: (1) carcinoid tumor (well-differentiated neuroendocrine tumor), (2) intermediate-grade neuroendocrine carcinoma, and (3) high-grade neuroendocrine carcinoma, which can be further subdivided into small cell and large cell types.[1,14] Right-sided endocrine tumors are usually large, whereas rectal endocrine tumors manifest as small polyps, most being solitary and less than 1.0 cm in greatest cross dimension.

Rectal carcinoids are quite common. They most often exhibit hindgut patterns of growth with trabeculae, small acini, and tubular structures that may contain luminal mucin and that must not be confused with goblet cell carcinoid (microglandular goblet cell adenocarcinoma) (Fig. 23-31). Mitoses are rare. The cytoplasm of the carcinoid tumor cells may be clear or eosinophilic and can sometimes appear granular. Nuclei are regular and ovoid and contain granular chromatin. Neuroendocrine differentiation can be proved with immunohistochemical analysis for chromogranin and synaptophysin. Hormonally inactive carcinoids that are less than 2.0 cm in greatest cross dimension without

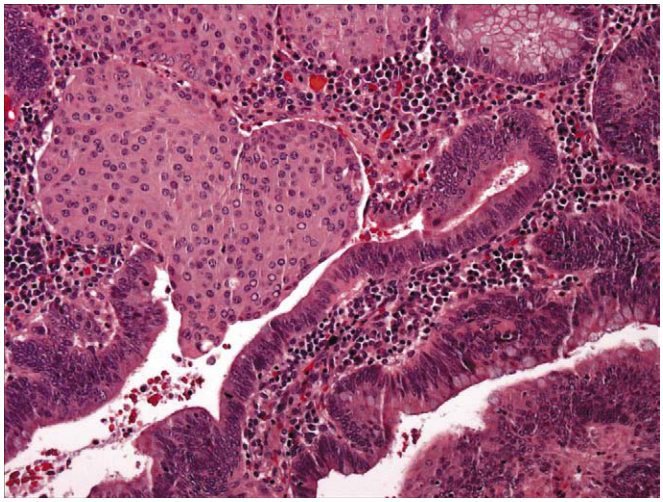

Figure 23-30 ■ An area of otherwise typical conventional tubular adenoma containing an area showing squamous differentiation.

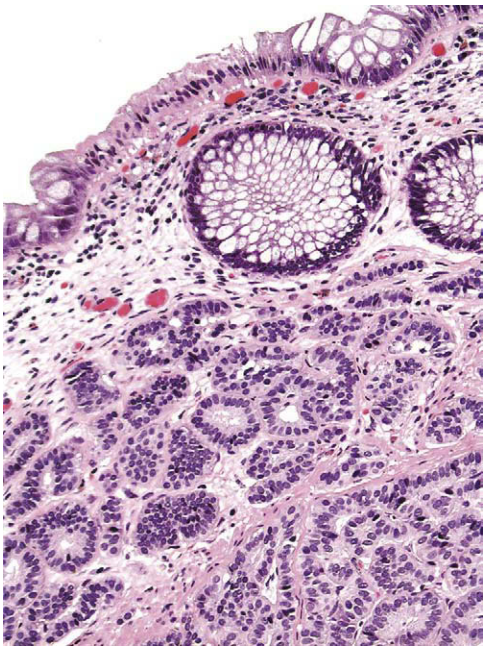

Figure 23-31 ■ Rectal carcinoid showing trabeculae, small acini, and tubular structures.

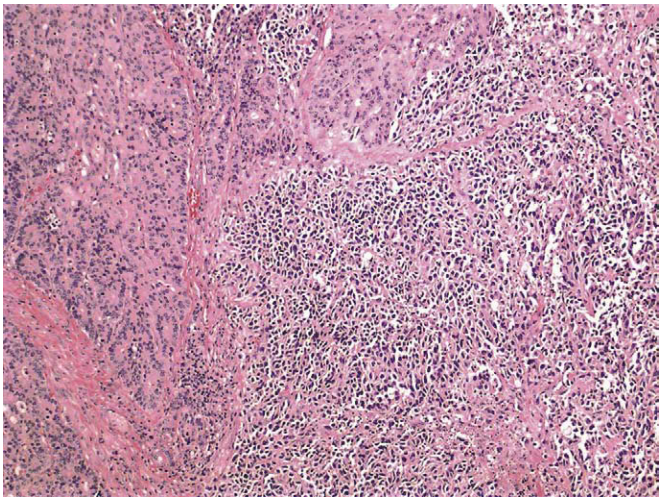

Figure 23-32 ■ Transition from intermediate-grade neuroendocrine carcinoma *(left)* to high-grade neuroendocrine carcinoma of small cell type *(right)*.

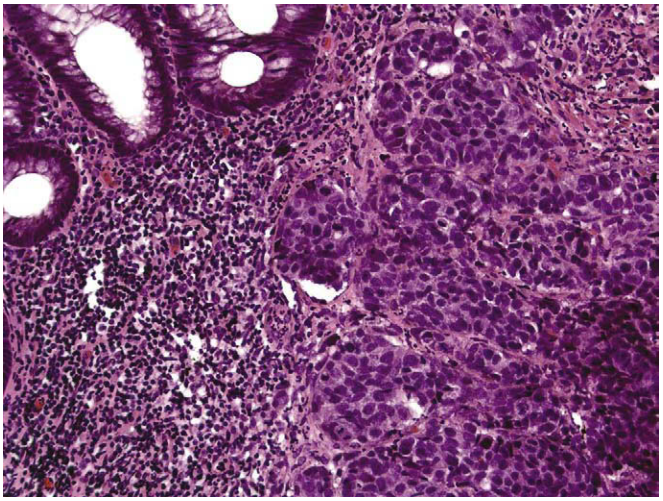

Figure 23-34 ■ Large cell neuroendocrine carcinoma showing an "endocrinoid" growth pattern to large round cells containing nuclei with coarse chromatin and occasional nucleoli and numerous mitotic figures.

angiolymphatic invasion act in a clinically benign fashion.[1,171]

Intermediate-grade neuroendocrine carcinoma acts more aggressively and is often characterized by angiolymphatic invasion, more frequent mitotic figures, nuclear pleomorphism with open nuclear chromatin, increased apoptotic bodies, and areas of necrosis (Fig. 23-32).[1] Transitions from low-grade to intermediate-grade and high-grade neuroendocrine carcinoma can be observed in rare cases.

High-grade neuroendocrine carcinoma is important to recognize because of its particularly poor prognosis and because of chemotherapeutic considerations.[1,172] The small cell variant is composed of sheets of densely packed small to intermediate-size cells with dark hyperchromatic nuclei, inconspicuous nucleoli, frequent mitoses, and very little cytoplasm with molding (Fig. 23-33). Foci of squamous and glandular differentiation can be seen in high-grade neuroendocrine carcinoma. Large cell neuroendocrine carcinoma shows an endocrinoid growth pattern but contains larger cells that are round or polygonal and contain more abundant cytoplasm. The nuclei show a coarse chromatin pattern and in contrast to small cell carcinoma are often nucleolated (Fig. 23-34). Large cell carcinoma and small cell carcinoma of the colon and rectum have a poor prognosis.

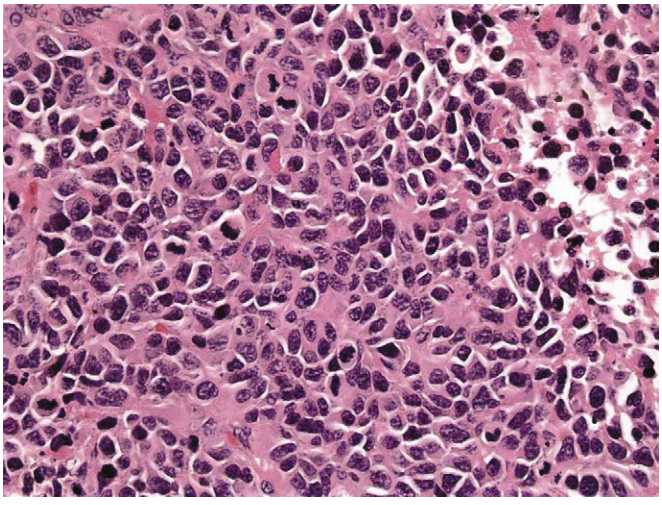

Figure 23-33 ■ Small cell carcinoma is composed of sheets of densely packed cells of small to intermediate size with dark hyperchromatic nuclei, inconspicuous nucleoli, numerous mitotic figures, and scant cytoplasm.

Lymphoproliferative Disorders of the Large Bowel

Virtually any subtype of lymphoma or leukemia can involve the colon and rectum. The reader is directed to the section covering the hematolymphoid system for more detailed discussions of these entities. Use of the WHO classification for tumors of the hematopoietic and lymphoid tissues is recommended.[173] This discussion focuses on the most common lymphoproliferative disorders affecting the colon and rectum.

Approximately one half of extranodal lymphomas involve the GI tract. Diffuse large B-cell lymphoma makes up the majority of these cases and is usually easily identified by the surgical pathologist as malignant.[174] B-cell lineage should be confirmed with CD20 immunostaining. An immunohistochemical panel to rule out undifferentiated carcinoma, melanoma, and high-grade neuroendocrine carcinoma is helpful in practice. Differentiation of germinal center type (better prognosis) from nongerminal center type of diffuse large B-cell lymphoma should be made using immunostains for CD10, bcl-6, and MUM-1.[175]

Burkitt's lymphoma and Burkitt-like lymphoma can involve the colon and rectum.[1,173,174] These lymphomas are composed of relatively uniform medium-sized cells with coarse chromatin and prominent nucleoli. B-cell lineage should be confirmed with CD20 immunostain and, as described earlier, other high-grade neoplasms should be excluded. Most investigators recommend the workup of Burkitt's and Burkitt-like lymphoma with MIB-1 immuno-

staining, which should highlight at least 90% of cells.[174] Burkitt's lymphoma cells also characteristically stain positive for CD10 and bcl-6.

Lymphoid hyperplasia must be distinguished from follicular lymphoma involving the colon and rectum. This is especially true in the setting of low rectal or anorectal lymphoid hyperplasia (so-called anorectal tonsil) and in defunctioned bowel seen in the setting of primary IBD. Localized lymphoid hyperplasia of the anorectal area can manifest with bleeding, prolapse, or anorectal discomfort. The endoscopic appearance can vary from a sessile polyp, which can measure up to 5.0 cm in greatest dimension, to mere thickening of the mucosa resembling cobblestoning. Histologically, one sees lymphoid hyperplasia with germinal center formation and scattered interfollicular collections of pale-staining histiocytes.[1] Distinction from follicular lymphoma can usually be made with standard H&E-stained sections but immunostaining for bcl-2, which is overexpressed in follicular lymphoma because of the t(14;18) translocation, can be an extremely helpful adjunct. Positive bcl-2 staining is seen in neoplastic follicles but not in reactive germinal centers.[174] Up to 40% of cases of multiple lymphomatous polyposis are caused by follicular lymphoma (Fig. 23-35).[176]

Mantle cell lymphoma usually manifests with widespread lymphadenopathy and frequent bone marrow involvement. Overt GI tract involvement occurs in 10% to 20% of patients and clinically occult disease can affect up to 80% of patients.[177] Colonic involvement can manifest as a mass, a polyp, diffuse mucosal thickening, or multiple lymphomatous polyposis.[1] Approximately one third of patients with lymphomatous polyposis have mantle cell lymphoma.[176] The histologic pattern of mantle cell lymphoma typically shows mucosa and submucosal infiltrates by small atypical lymphocytes surrounding germinal centers with effacement. The lymphoma cells express the B-cell marker CD20 and often coexpress CD5. The t(11;14) translocation causes overexpression of cyclin D-1, which is now considered defining.[173,174]

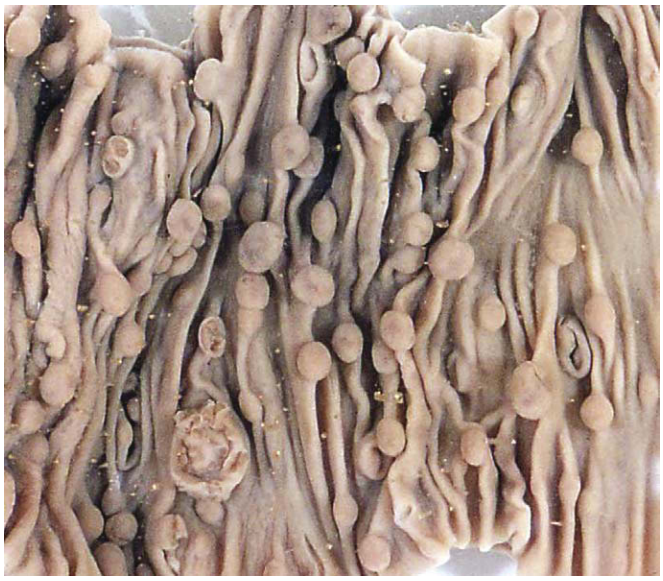

Figure 23-35 ■ Multiple lymphomatous polyposis showing spherical mucosally covered polyps situated on a small pedicle. Larger lymphomatous polyps can be centrally ulcerated.

Extranodal marginal zone B-cell lymphoma of the mucosa-associated lymphoid tissue (MALT) type can involve the colon and rectum and is responsible for up to 25% of cases manifesting as multiple lymphomatous polyposis.[1,176] Similar to its appearance in the stomach, colorectal marginal zone B-cell lymphoma of MALT type creates destructive lymphoepithelial lesions and produces an expansive proliferation of marginal zone lymphocytes. An appropriate immunohistochemical profile includes positive staining for pan B-cell markers and negative staining for CD3, CD5, CD10, CD31, and cyclin D-1. Gene rearrangement studies by PCR can be helpful in difficult cases.[1,173,174]

Mesenchymal Tumors of the Colon and Rectum, Excluding Vascular Lesions

Mesenchymal tumors involving the colon and rectum are unusual and include GI stromal tumors (GISTs), true smooth muscle tumors, neural tumors, inflammatory fibroid polyp, fatty tumors, fibrohistiocytic tumors, tumors of skeletal muscle, and vascular lesions (see later).[1] Primary mesenchymal tumors of the colon and rectum must be distinguished from mesenchymal differentiation within a high-grade carcinoma. The reader is directed to the section on soft tissues for more detailed discussions of these entities.

GISTs of the colon and rectum are rare and usually show high-grade features using the National Institutes of Health consensus approach for classification.[178] Approximately 75% of colon and rectum GISTs have shown aggressive clinical behavior.[179] Overexpression of c-*kit* using CD117 immunostaining must be ascertained, preferably as part of a panel of immunostains that includes CD34, smooth muscle actin, desmin, cytokeratin, S-100 protein, and melan A to verify GIST and to exclude other differential diagnostic possibilities.[180]

Schwannoma in the colon and rectum is rare and is usually encountered in the absence of a predisposing condition. Schwannomas are rarely seen in patients who have neurofibromatosis syndrome or multiple endocrine neoplasia type IIB (MEN2B) and must be distinguished from GISTs in that setting.[1,181,182]

Neurofibromas can manifest as an isolated mass lesion or nodule but are more commonly seen as a diffuse infiltration of the bowel wall in the setting of neurofibromatosis.[1] Care must be taken to distinguish neurofibroma from schwannoma and GIST, which also occur in neurofibromatosis.[1,183,184]

Granular cell tumor can manifest as a polyp or nodule frequently in the distal rectum and anal canal where it can mimic a hemorrhoid. The tumor is composed of masses of histiocytic-like cells with granular eosinophilic or amphophilic cytoplasm, which can sometimes be spindled (Fig. 23-36). The cytoplasmic granules stain positive on PAS and stain intensely for S-100 protein.[1,185]

True smooth muscle tumors are rare but leiomyomas of the muscularis mucosae are commonly encountered in

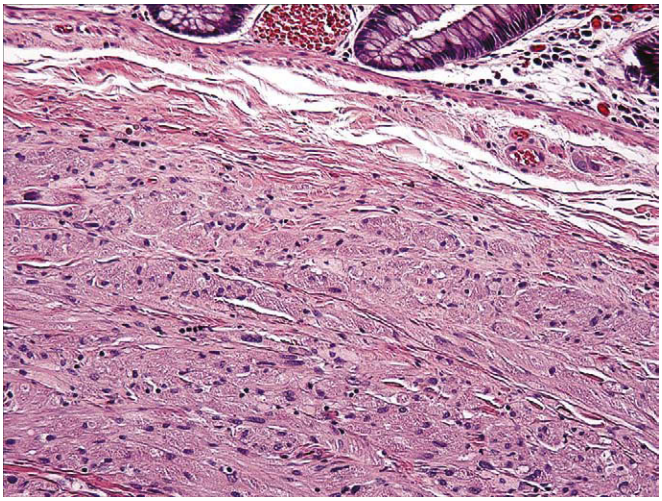

Figure 23-36 ■ Granular cell tumor involving the muscularis mucosae and submucosa composed of histiocyte-like cells with granular eosinophilic cytoplasm.

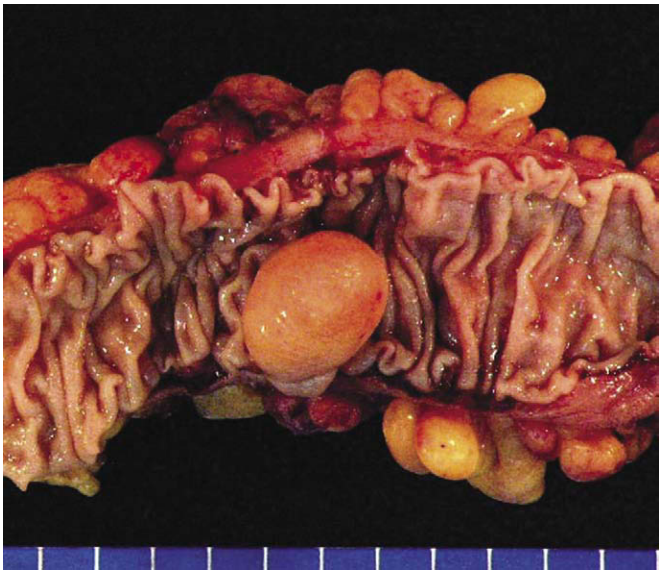

Figure 23-37 ■ Lipoma of large bowel in a resection specimen showing the characteristic polypoid and yellow appearance.

biopsy specimens.[1] These tumors are usually small, less than 5 mm to 10 mm in greatest cross dimension, and are composed of smooth muscle cells. Atypical mitoses and necrosis typical of leiomyosarcoma are not seen and the reported behavior has been benign.[186]

Primary glomus tumors of the colon and rectum are exceptionally rare[187,188] and can manifest as a polyp or mucosal thickening. Microscopically, these tumors are composed of lobules of small round cells intimately related to vascular spaces and usually show positive immunoreactivity for smooth muscle actin and vimentin. The cases reported so far have acted in a benign fashion.

Lipohyperplasia of the ileocecal valve, which can be accentuated in obese persons, is the most common fatty tumor of the colon.[1,189] Occasionally, the fat may produce a more localized tumor. Patients are usually asymptomatic and the degree of lipohyperplasia generally correlates with body weight.

Lipomas are frequently encountered during colonoscopy. These tumors are composed of benign adipose tissue. Most are small and asymptomatic but larger ones can bleed, can be subject to trauma or prolapse, cause abdominal pain, and may lead to resection (Fig. 23-37). Lipomas are usually recognized at colonoscopy by their yellow color and pliability (pillow sign). Atypical lipomas and even liposarcoma have rarely been described.[1] Rare examples of malignant fibrous histiocytoma, rhabdoid tumor, and rhabdomyosarcoma have been reported in the large bowel.[1]

Vascular "Lesions" of the Colon and Rectum

Numerous classifications for intestinal vascular lesions have been proposed.[190,191] We find it useful to divide the vascular lesions into two groups, those isolated to the GI tract and those associated with recognized clinical syndromes (Tables 23-6 and 23-7).[1]

Isolated Colorectal Vascular "Lesions"

Table 23-6 is a list of isolated intestinal vascular abnormalities.

VASCULAR ECTASIA OF THE RIGHT COLON

Vascular ectasia of the right colon has numerous synonyms, including angiodysplasia, arteriovenous malformation, and the type I lesion of Moore and colleagues.[1,190,192,193] Vascular ectasia of the right colon is a well-defined clinicopathologic entity with a distinct type of lesion and pathogenesis. Patients are typically elderly and present with episodes of recurrent low-grade lower GI bleeding. Approximately 15% of patients present with massive GI hemorrhage. The lesions nearly always manifest in the cecum or right colon and are often multiple. Vascular ectasia of the right colon is usually not associated with other conditions. Reports linking vascular ectasia of the right colon to aortic valvular disease have been criticized.[194,195] However, bleeding vascular ectasias may be associated with aortic stenosis and associated abnormalities in von Willebrand factor (deficiency of the largest multimers).[196]

Colonoscopic and radiographic examination will show almost all lesions. Endoscopically, vascular ectasias appear

TABLE 23-6

Isolated Intestinal Vascular Abnormalities

Vascular ectasia of right colon
Other sporadic vascular ectasias of the colon or small intestine
Hemangiomas
Capillary
Cavernous
Arteriovenous
Venous
Mixed
Hemangiolymphangioma
Lymphangioma
Phlebectasia (varicosities)

TABLE 23-7
Recognized Syndromes Associated with Intestinal Vascular Abnormalities

Hereditary hemorrhagic telangiectasia
Progressive systemic sclerosis
Blue rubber bleb nevus syndrome
Turner's syndrome
Klippel-Trénaunay-Weber syndrome
Pseudoxanthoma elasticum
Ehlers-Danlos syndrome

as erythematous mucosal macules or papules measuring 0.1 mm to 10 mm in diameter (Fig. 23-38). They may be round, oval, or stellate. A "feeding" vessel may be visible. Angiographic signs of vascular ectasia include the densely opacified, slowly emptying vein, an opacified vascular tuft, early opacification (filling) of a draining vein, or, rarely, extravasation of contrast media into the lumen. Vascular ectasia is usually treated primarily by the endoscopist (heat probe or other endoscopic ablation technique) or by the radiologist (vasopressin infusion or transcatheter embolization) at the time of diagnosis.[197,198] The typical curative surgery, right hemicolectomy, is rarely performed and is often reserved for those cases in which endoscopy or radiography could not be performed or treatment was not successful or for perforative complications of endoscopic or angiographic treatment.

Vascular ectasia is notoriously difficult to identify by standard pathologic techniques in resection specimens. Demonstration of the lesion usually requires some form of vascular injection. Boley and Brandt's technique employs injection of the fresh specimen vasculature with a silicon rubber compound. The specimen is then fixed in formalin, dehydrated in graded alcohols, and cleared with methylsalicylate.[192] This technique produces a transparent specimen in which the vasculature can be examined by epi-illumination and transillumination under a dissecting microscope. Using this technique, the vascular ectasias appear as "coral reef–like" arrangements measuring 0.1 cm to 2.0 cm in diameter contrasted against the honeycombed pattern of the normal colonic mucosal vasculature. Histologic examination reveals abnormal thin-walled ectatic veins, venules, and capillaries localized to the mucosa and submucosa. The lesions are thought to result from repetitive partial obstruction to venous drainage caused by contraction of the muscularis propria. Wall tension is directly proportional to lumen diameter, a finding that may explain the lesion's predilection for the right colon, where the diameter is the greatest. Obviously, vascular injection techniques require preparation in terms of materials. If caught unprepared, one may still demonstrate larger ectasias by carefully and gently washing off the mucosal surface of the specimen with water. Sometimes, a blood clot adheres to the bleeding point and this may direct the histologic sectioning. We have been disappointed with injection of contrast media and specimen radiography but have had success demonstrating right-sided vascular ectasia by injecting brightly colored ink into the ileocolic artery. Some investigators have reported success by bluntly dissecting the mucosa from the muscular wall of the formalin-fixed bowel followed by dehydration and transillumination.[199]

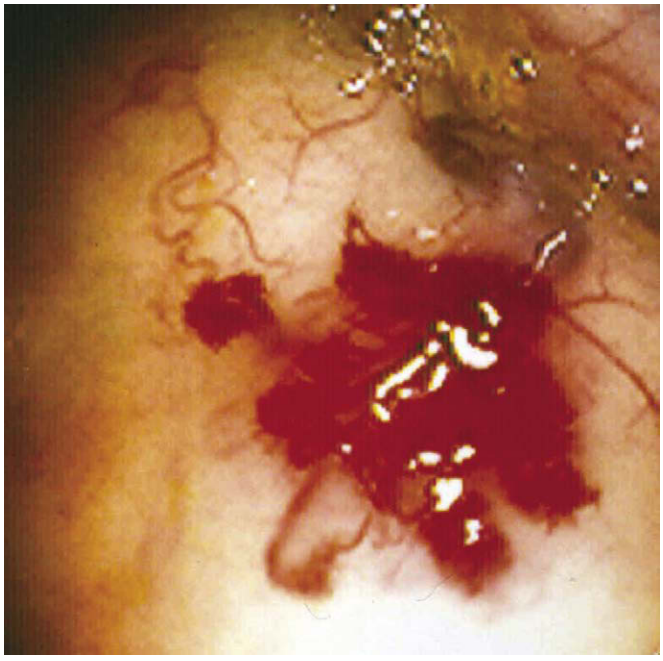

Figure 23-38 ■ Endoscopic photograph of right-sided vascular ectasia showing an irregularly shaped erythematous mucosal macule.

HEMANGIOMAS

Many isolated hemangiomas may be classified on the basis of the predominant vessel type as capillary, cavernous, venous, arteriovenous, or mixed.[1] *Capillary hemangiomas* are typically small, rarely multiple, and composed of small, closely packed capillaries. These lesions may be found in the colon but are usually encountered in the small intestine, appendix, and perianal skin.[200] Some lesions reported as capillary hemangiomas may, in fact, be vascular ectasias (see earlier). Capillary hemangiomas rarely cause clinical symptoms. Cavernous, venous, arteriovenous, and other mixture hemangiomas occur in localized or diffuse forms[201-204] and have the same clinical significance regardless of vessel type (Fig. 23-39).

Cavernous hemangiomas are composed of blood-filled, sinus-like spaces supported by connective tissue.[191,201] The stroma occasionally contains smooth muscle. Cavernous hemangiomas can occur in the small bowel but have a predilection for the colon and rectum. Patients may present with symptoms of a mass or with rectal bleeding. Localized cavernous hemangiomas can be treated by excision, fulguration, or sometimes radiation therapy, whereas diffuse forms of hemangiomas may be unresectable and treatment must be directed toward controlling complications.

A lesion composed of abnormal proliferating veins and arteries with evidence of arteriovenous shunting is referred to as an *arteriovenous hemangioma*.[1] *Venous hemangiomas* are characterized by large, thick-walled vessels that resemble normal veins but occasionally have more disorganized smooth muscle in their walls. Arteriovenous and venous hemangiomas have the same distribution and significance as cavernous hemangioma.[191] Rare reports have noted tumors composed of admixtures of dilated vascular chan-

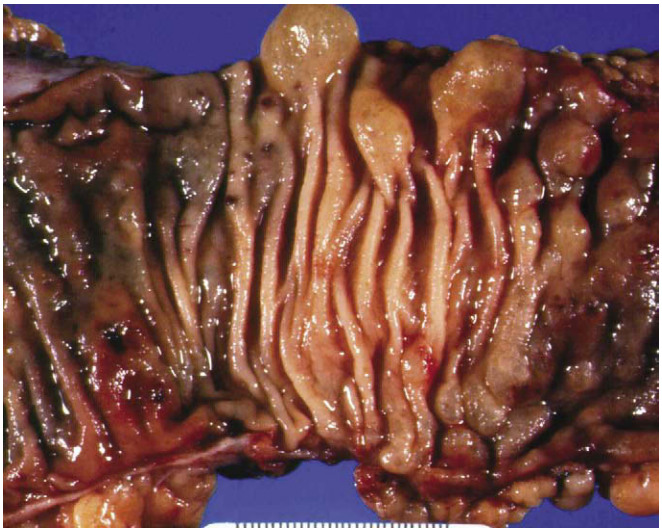

Figure 23-39 ■ Gross photograph of resected hemangiolymphangioma showing numerous mucosal cystic nodules.

nels and lymphatics. These tumors can be referred to as hemangiolymphangiomas, lymphaticovenous malformations, or even generically as vascular malformations.[1,205] These lesions have the same clinical significance as cavernous hemangiomas.

Pure lymphangioma of the large bowel is extremely rare. Depending on size and location, these lesions may be asymptomatic or they may cause pain, diarrhea, or bleeding.[206] Reported size has varied to up to 10 cm. Microscopically the lesions are composed of thin-walled, anastomosing endothelial-lined channels that are bloodless but usually contain eosinophilic material.

PHLEBECTASIA

The term *phlebectasia* defines a non-neoplastic venous varicosity.[191] These lesions may occasionally cause severe GI bleeding. The most frequent site of bleeding caused by phlebectasias associated with portal hypertension is the lower esophagus. Other sites have been reported, especially the rectosigmoid colon[207] and rarely the small intestine.[191] We have also seen cases of idiopathic colonic varices in children. Because phlebectasias are encountered rarely, if ever, in surgical specimens, they are not considered further.

Colorectal Vascular Lesions Associated with Recognized Clinical Syndromes

Table 23-7 is a list of recognized syndromes associated with intestinal vascular abnormalities.

HEREDITARY HEMORRHAGIC TELANGIECTASIA

Hereditary hemorrhagic telangiectasia (HHT) is inherited as an autosomal dominant trait.[191,208] Two disease-causing genes have been identified, endoglin and ALK-1.[209] Vascular lesions occur in the skin, mucous membranes, and internal organs, including liver, genitourinary tract, meninges, eyes, and spinal cord. The mucocutaneous lesions appear in the second and third decades of life. Many patients present with recurrent epistaxis in childhood. Approximately 15% of patients with HHT, usually older patients, have GI bleeding. The histopathologic pattern of the colorectal lesion is simple dilatation of normal vascular structures (i.e., telangiectasia) and in general resembles the lesions of right-sided vascular ectasia (Fig. 23-40).

PROGRESSIVE SYSTEMIC SCLEROSIS

Progressive systemic sclerosis can be associated with GI tract telangiectasias.[191,210] A predilection exists for the stomach, rectum, and colon. Intestinal bleeding develops only rarely.

BLUE RUBBER BLEB NEVUS SYNDROME

The blue rubber bleb nevus syndrome can occur as an autosomal dominant trait or in a sporadic form. The characteristic histologic lesion is a cavernous hemangioma that can involve the skin, GI tract, and other viscera.[211-213] The skin lesion is typically blue and tender and ranges in size from 0.1 cm to 2.0 cm. The lesion empties on digital pressure to leave a wrinkled blue sac that in time refills with blood. The preferred site of involvement in the GI tract is the small intestine but colorectal lesions have been reported.

TURNER'S SYNDROME

Turner's syndrome is characterized by numerous somatic abnormalities associated with a 45 XO karyotype. Telangiectasias of the small and large intestine have been described in this disorder and may cause GI bleeding.[214]

KLIPPEL-TRÉNAUNAY-WEBER SYNDROME

Klippel-Trenaunay-Weber syndrome occurs sporadically. Patients demonstrate unilateral soft tissue and bony hypertrophy associated with a port-wine hemangioma. GI cavernous hemangiomas have been described in these patients.[191,215]

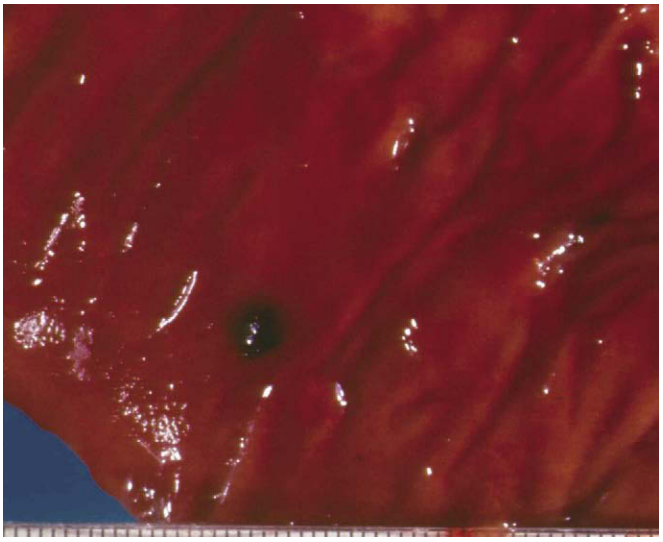

Figure 23-40 ■ Resected right-sided colonic vascular ectasia from a patient with the hereditary hemorrhagic telangiectasia syndrome.

PSEUDOXANTHOMA ELASTICUM

Pseudoxanthoma elasticum shows marked clinical and genetic variability.[191] Clinically, "plucked-chicken" skin and angiomatoid streaks in the retina have been described. Bleeding in the GI tract may occur from ruptured blood vessels caused by the abnormalities in elastic structure. Patients usually bleed from the stomach.[216] Arteriovenous hemangiomas have also been described.[191,217]

EHLERS-DANLOS SYNDROME

The term *Ehlers-Danlos syndrome* describes more than 11 subclasses of metabolic disorders associated with abnormal collagen synthesis.[218] Most patients demonstrate hyperelasticity of skin and joints (i.e., the circus rubber man). Vascular ectasias or proliferative vascular lesions have not been described, but spontaneous arterial or intestinal rupture has been reported in some forms (especially type IV [vascular Ehlers-Danlos syndrome with mutations of *COL3A1* gene[219]]) of Ehlers-Danlos syndrome.[218-224]

Kaposi's Sarcoma Involving the Intestinal Tract

Kaposi's sarcoma characteristically cause pigmented skin nodules predominantly on the lower extremities. Currently, an aggressive variant of Kaposi's sarcoma in patients with acquired immunodeficiency syndrome (AIDS) is most commonly seen[225-227] and has been linked to infection with human herpesvirus 8.[228]

The GI tract of patients with AIDS is frequently involved by Kaposi's sarcoma.[227] Investigators have estimated that about half of the patients with cutaneous or lymph node Kaposi's sarcoma have concomitant GI tract involvement.[229-231] Rarely, the GI tract can be involved without skin lesions. GI tract Kaposi's sarcoma is typically asymptomatic but occasional GI Kaposi's sarcoma can cause bleeding, obstruction, perforation, or protein-losing enteropathy.[1,232]

GI Kaposi's sarcoma has numerous appearances grossly and endoscopically.[1] Although red macules have been described, Kaposi's sarcoma more characteristically causes a red or purple nodule or plaque measuring 15 mm or more.[229] Some patients with GI Kaposi's sarcoma have large tumors. Despite the vascular nature of the neoplasm, lesions can be sampled for biopsy and in most instances bleed surprisingly little. The diagnostic yield with biopsy has been notoriously low[227]; in one report, only 13% of upper GI specimens and 36% of sigmoidoscopic specimens tested positive.[229] Usually, the low yield is attributed to the preferential submucosal location of Kaposi's sarcoma that may not be sampled in an endoscopic biopsy specimen. That said, examples of Kaposi's sarcoma are easily overlooked by even experienced pathologists, because the sarcoma is subtle and can be dismissed as granulation tissue.

In positive biopsy specimens, Kaposi's sarcoma typically causes an expansion of lamina propria by a spindle cell proliferation that may not be very atypical. The spindle cells are usually not extremely mitotically active and at first glance may suggest granulation tissue (although macrophages and mononuclear inflammatory cells are typically absent) or the fibromuscular obliteration of the lamina propria associated with the solitary rectal ulcer syndrome (prolapse or trauma-related change). Generally, GI Kaposi's sarcoma is histologically similar to Kaposi's sarcoma seen elsewhere.[227] The histologic pattern shows spindle cells, vascular clefts, extravasated red blood cells frequently associated with hemosiderin deposits, and occasionally tumor necrosis (Fig. 23-41). Kaposi's sarcoma cells usually stain with antibodies directed against factor VIII–related antigen but more consistently stain positive with endothelial markers such as CD34 and CD31.

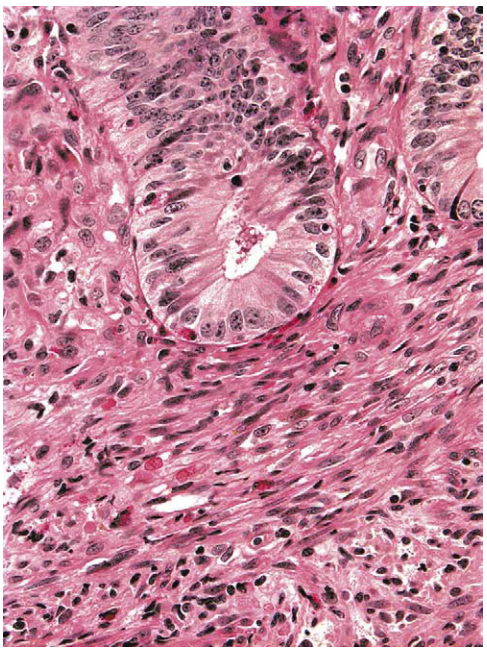

Figure 23-41 ■ Kaposi's sarcoma showing expansion of the lamina propria and obliteration of the muscularis mucosae by a spindle cell proliferation showing occasional vascular clefts.

As mentioned earlier, the changes are subtle and diagnosis can be difficult. Important clues to the proper diagnosis include (1) knowledge of the clinical situation, (2) knowledge of the endoscopic appearance, (3) recognition of crowding and hyperchromasia in the spindle cell nuclei, (4) recognition of slits and spaces containing red blood cells, and (5) recognition of the tendency for Kaposi's sarcoma cells to overrun or obliterate the muscularis mucosae.[1]

Aggressive antiretroviral therapy is now considered the first-line treatment for GI Kaposi's sarcoma.[233,234] Other forms of treatment are reserved for symptomatic tumors.[232] Surgical procedures are performed for obstruction or severe bleeding. Chemotherapy approaches have improved but the treatment is risky in an already immunocompromised patient. These therapies offer palliation at best. Treatment with zidovudine (formerly azidothymidine [AZT]) does not have an effect on GI Kaposi's sarcoma.[235,236] Immunomodulation has been tested but is not used.[232,237,238] The addition of taxanes (paclitaxel and docetaxel) to aggressive antiretroviral therapy appears promising.[239,240]

Angiosarcoma

Angiosarcomas are only rarely encountered in the colon and rectum.[241] The varied histologic spectrum ranges from well-formed vascular structures to sheets of malignant polygonal or spindle cells. Grossly and endoscopically, angiosarcomas form red-gray polypoid masses. An immunohistochemical

panel including CD31 and factor VIII–antigen can be useful in diagnosis.

Caliber Persistent Artery (Dieulafoy's Lesion)

The term *Dieulafoy's lesion* refers to an inappropriately large artery located directly beneath the mucosa where it can erode and cause profuse bleeding. Although typically described in the stomach, similar lesions are found in the colon and rectum.[242]

Metastatic Tumors to the Colon and Rectum

Metastatic neoplasia to the colon and rectum come principally from the lung, breast, ovary, and skin (melanoma).[1] Advanced prostate carcinoma can cause confusion with primary rectal carcinoma or with neuroendocrine carcinoma. Sometimes perirectal lymph node metastases in resections performed for colorectal carcinoma contain metastatic deposits from prostate carcinoma.

GASTROINTESTINAL POLYPOSIS SYNDROMES AND OTHER LARGE BOWEL POLYPS

Familial Adenomatous Polyposis and Variants

FAP is inherited as an autosomal dominant trait. Bussey recognized that 100 or more colorectal adenomas (recognized grossly) phenotypically identified patients with FAP and distinguished them from patients with multiple adenomas in whom inheritance was not seen.[243,244] In typical FAP, hundreds to thousands of adenomas develop within the colon (Fig. 23-42). The adenomas begin to appear in the second or third decades of life and are surprisingly asymptomatic considering their usually large numbers. Symptomatic patients present with signs and symptoms of increased bowel motility and the passage of blood or mucus, or both, which often heralds the onset of carcinoma. The average age of patients with colon cancer and FAP is 39 years.[66] Two thirds of patients with these so-called propositus cases present with carcinoma and nearly one half of them have more than one carcinoma in the colon. This high risk of invasive cancer in symptomatic patients forms the basis for polyposis registries and the extensive screening of asymptomatic kindred at risk for FAP.

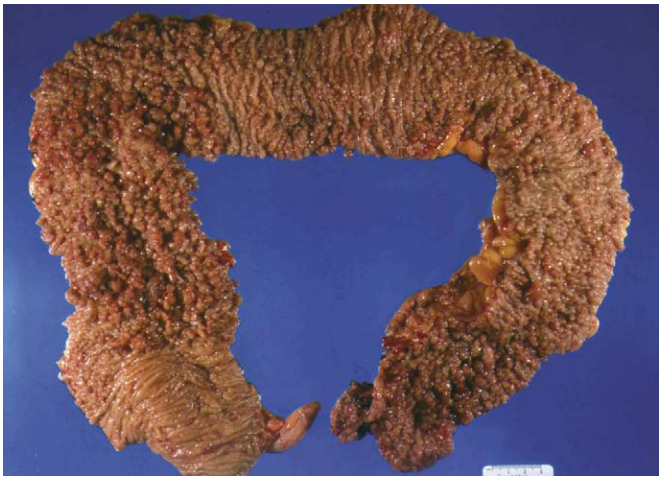

Figure 23-42 ■ Familial adenomatous polyposis syndrome in resection specimen. The mucosa is carpeted by thousands of adenomas.

Screening recommendations have evolved with increased genetic information. Genetic testing should be considered for FAP, attenuated FAP, and mutY homologue (MYH)–associated polyposis (MAP) when 10 or more colorectal adenomas are found in a patient during a single examination or over time.[66] Screening of first-degree relatives of affected individuals should begin at the age of 10 years.[63] In the absence of genetic testing, endoscopic screening is still useful to detect FAP. All affected patients have adenomas within the range of a flexible sigmoidoscope. It is therefore recommended that screening sigmoidoscopy begin at age 14 years with re-examination every 2 years. The diagnosis of FAP must be confirmed with biopsy because lymphoid polyposis and hyperplastic polyposis can mimic FAP grossly and endoscopically. Once a diagnosis of FAP has been established, prophylactic proctocolectomy is recommended. Most investigators recommend sigmoidoscopy for mutation-negative kindred at age 12 years just in case the genetic test is erroneous. Thyroid examination for associated thyroid lesions (usually papillary carcinoma with cribriform pattern[245]) and determination of serum alpha fetoprotein (to screen for hepatoblastoma) are recommended.

Regular upper endoscopy should also be performed. Gastric and duodenal polyps develop in 30% to 90% of patients with FAP.[246] The gastric lesions are usually fundic gland polyposis, whereas the duodenal polyps are usually adenomas. The fundic gland polyps can develop a peculiar surface epithelial atypia called *foveolar dysplasia*,[247] but progression to carcinoma is extremely rare.[229] The incidence of duodenal adenomas in FAP increases with increasing age. Duodenal adenomas have a propensity to develop in the periampullary region. Adenomas anywhere in the GI tract can proceed through the dysplasia-carcinoma sequence. The relative risk of duodenal or periampullary carcinoma in patients with FAP is approximately 125 to 350 times that seen in the general population, and duodenal or periampullary carcinoma has become the major cause of morbidity and mortality in patients with FAP in the post–prophylactic colectomy era.[248]

The gene responsible for FAP (*APC* gene) has been localized to the long arm of chromosome 5 (5q21-q22) and has been cloned.[249-253] Some *APC* gene mutation–negative cases may be caused by mutation of MYH (see later).[254] Mutation in most patients with FAP creates a stop codon resulting in a truncated protein product. The *APC* gene is a tumor suppressor gene and the APC protein is part of the Wnt-signaling pathway[66,255] involved in cell growth control. When the *APC* gene is mutated, beta-catenin accumulates, thus altering expression of certain genes affecting proliferation, differentiation, migration, and apoptosis.[256]

Most patients are now diagnosed by DNA sequencing, which has largely replaced the assay to detect the truncated

APC protein (PTT).[63,256] Monoallelic mutation analysis (MAMA) examines the two APC alleles independently and can detect more than 95% of patients with FAP. Another test, multiplex ligation-dependent probe amplification (MLPA), is useful in detecting large deletions.[256]

More than 700 disease-causing *APC* gene mutations have been reported.[256] Localization of mutations within the *APC* gene locus correlates with phenotype. For example, germline mutations between codon 1250 and codon 1464 are associated with very large numbers of colonic adenomas, whereas mutations elsewhere, especially near the 5′ end or the 3′ end of the *APC* gene and an area of exon 9, yield lesser numbers of colonic adenomas (see the later discussion of attenuated FAP).[63,256-258]

In *Gardner's variant,* in addition to colonic adenomas and upper GI polyps, patients can exhibit extraintestinal manifestations such as osteomas, epidermal inclusion cysts and other benign skin tumors, desmoid tumors of the abdomen or abdominal wall, fibrosis of mesentery, dental abnormalities, carcinoma of the periampullary region or duodenum, and carcinoma of the thyroid. Patients with Gardner's syndrome have *APC* gene mutations; however, no particular *APC* mutation distinguishes FAP from Gardner's variant. Even within a "Gardner's family," Gardner's stigmata can be variably expressed and can skip generations.[253] Therefore, some unknown disease-modifying factors are required for phenotypic expression of the extraintestinal manifestations.

Turcot's syndrome has been the subject of some controversy. In many investigators' zeal to publish, the phenotypic spectrum has been unduly broad with colonic manifestations ranging from a single adenoma to a virtual carpeting of the colonic mucosa with polyps. Furthermore, the brain tumors have comprised almost every histologic type. Molecular studies done on 14 families with Turcot's syndrome have clarified the situation.[259] Families with Turcot's syndrome and germline mutations of the *APC* gene have a typical FAP colonic phenotype and develop medulloblastomas. Other patients originally thought to have Turcot's syndrome have mutations in the DNA MMR genes that are characteristic of Lynch's syndrome. The brain tumors in this group have varied, with many reported as glioblastoma.

Mutations of the *APC* gene near the 5′ end and 3′ end and in a particular region of exon 9[66] result in fewer adenomas (<100; average, 30), a tendency for the adenomas to be macroscopically flat, and a propensity for these adenomas to cluster in the right colon. Originally reported as *hereditary flat adenoma syndrome,* this form is now more accurately referred to as *attenuated FAP* (AFAP).[63,258] As in typical FAP, these patients can develop fundic gland polyposis, duodenal adenomas, and periampullary carcinoma. The risk of colorectal carcinoma is increased in these patients albeit to a lesser degree than in the other form of FAP and the cancers tend to occur later in life (average age, 49 years).

Inherited variants of a base-excision repair gene *MYH* have been associated with colorectal polyposis with an autosomal recessive mode of inheritance.[254,260,261] Some cases phenotypically resemble FAP or attenuated FAP and are referred to as *MYH polyposis* or MAP.[254] Of those patients with a phenotype typical of FAP or suspected AFAP in whom an *APC* gene mutation is not found, 10% to 20% will have mutation of the *MYH* gene.[66] Approximately 80% of affected persons have one of two specific *MYH* mutations (Y165C or G382D). If one is found, then sequencing is done to find the mutation on the other allele because MAP is biallelic.[66] These patients should be treated and followed similarly to patients with FAP.

Juvenile Polyps and Juvenile Polyposis Syndrome

Juvenile polyps can occur in a sporadic form or can be part of juvenile polyposis syndrome. In the sporadic form, juvenile polyps have their peak prevalence in children between 1 and 7 years of age. Some evidence indicates that juvenile polyps once formed can regress; they can certainly be seen in adults. Sporadic juvenile polyps typically occur singly but patients can have up to five, usually located in the rectum. Juvenile polyps typically range in size up to 2 cm and can be associated with overt prolapse (Fig. 23-43).[262] Because these polyps are often attached by a small pedicle, they are prone to autoamputation. Histologically, typical juvenile polyps consist of a hamartomatous overgrowth of the lamina propria accompanied by elongation and cystic dilatation of colonic crypts lined by nondysplastic colonic epithelium (Fig. 23-44).[66] Osseous and cartilaginous stromal metaplasia can occur (Fig. 23-45). The inflammatory component of juvenile polyps can be quite prominent with neutrophils and lymphoid follicles within the lamina propria. Frequently, the distinction between juvenile polyps and inflammatory polyps of primary IBD cannot be made on histologic grounds alone and requires clinical correlation. Nonsyndromatic juvenile polyps appear to have no malignant potential.[263]

Juvenile polyposis syndrome can be familial or nonfamilial and usually becomes clinically apparent within the first

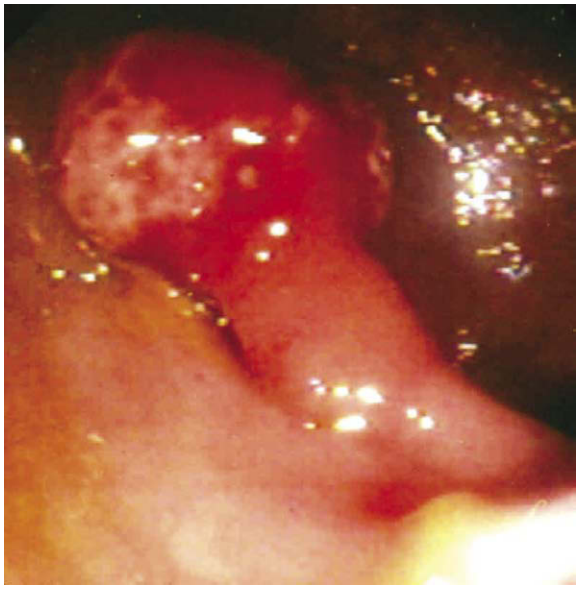

Figure 23-43 ■ Endoscopic photograph of a sporadic juvenile polyp. The polyp head is erythematous with scattered surface exudate and is attached to the bowel by an elongate pedicle.

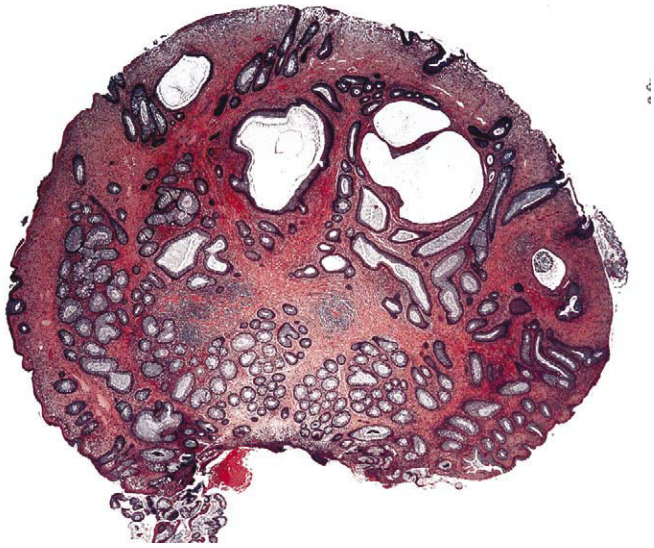

Figure 23-44 ■ Sporadic juvenile polyp showing the edematous and inflammatory expansion of the lamina propria with glandular cyst formation.

decade of life with painless rectal bleeding, prolapse, iron deficiency anemia, or passage of an autoamputated polyp.[244] Patients are considered to have juvenile polyposis syndrome if they have six or more juvenile polyps in the colon and rectum, have juvenile polyps throughout the GI tract, or have any number of juvenile polyps in association with a positive family history.[262,264] In the nonfamilial forms of juvenile polyposis syndrome (≈30% of the total), patients frequently have associated abnormalities, such as cardiac defects, hydrocephalus, gut malrotation, undescended testes, and skull abnormalities.[244] Patients with the familial forms usually lack these extraintestinal manifestations. Inheritance has varied although almost all are considered autosomal dominant with variable penetrance.[244] Familial forms of juvenile polyposis syndrome appear to be associated with an increased risk of colorectal carcinoma.[264] Prophylactic colectomy may be prudent in juvenile polyposis syndrome. Patients may also have an increased risk of gastric, small intestinal, and pancreatic carcinoma.[265] Juvenile polyposis syndrome coexisting with HHT (Osler-Weber-Rendu syndrome) is rarely reported.[265]

The number of polyps in juvenile polyposis syndrome typically ranges from a few dozen to several hundred (Fig. 23-46). Phenotypically, juvenile polyposis syndrome appears to occur in three varieties: (1) polyps limited to the colon, (2) polyps limited to the stomach, and (3) polyps throughout the entire GI tract.[266-268] The mucosal polyps found in the context of juvenile polyposis syndromes are often unusual histologically. In addition to the typical juvenile polyps described earlier, one can find juvenile polyps with atypical features such as more epithelium than lamina propria. In addition, mixture polyps (juvenile polyps with areas of adenoma or dysplasia) are quite frequent.[244,264] A family showing an autosomal dominant inheritance of atypical juvenile polyps, adenomas, hyperplastic polyps, and polyps showing a mixture of all three types (hereditary mixed polyposis syndrome)[269] may have a variant of juvenile polyposis or they may have MAP.[265,270,270a]

Two genes have been identified to cause familial juvenile polyposis syndrome, *MADH4* (mothers against decapentaplegic homologue 4, also known as *SMAD-4* [18q21.1] and *DPC-4*) seen in approximately 15% of patients and *BMPR1A* (bone morphogenetic protein receptor type 1A [10q22.3])[265,271-273] seen in 25% of cases. One should consider genetic testing for juvenile polyposis syndrome when three or more juvenile polyps have occurred in one individual or when juvenile polyps are found outside the colon.[66] *MADH4* and *BMPR1A* are both components of the signaling pathway for transforming growth factor-β and the bone morphogenetic proteins. Patients with *MADH4* gene mutation are more likely to have gastric juvenile polyposis.[265,274,275] Juvenile polyps can be found in patients with other hamartomatous syndromes of the colon, such as intestinal ganglioneuromatosis or ganglioneurofibromatosis (see later),[276-278] although some of these syndromes are now

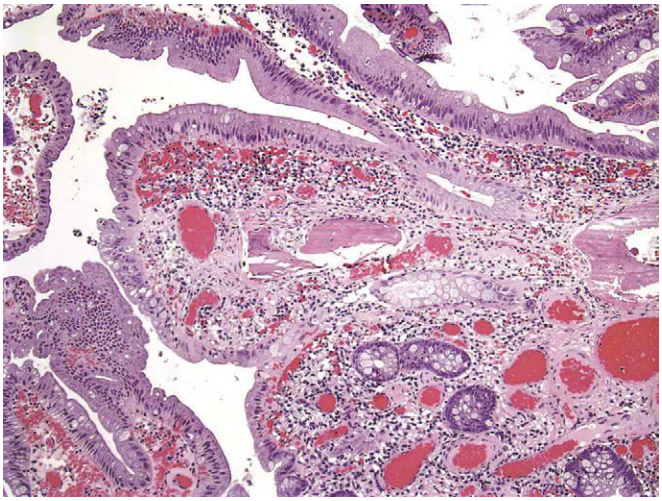

Figure 23-45 ■ Area of stromal bone formation within the lamina propria of a juvenile polyp.

Figure 23-46 ■ Resection specimen of juvenile polyposis syndrome. Although some polyps grossly resemble sporadic juvenile polyps, many have an unusual frondlike configuration.

best classified as PTEN (phosphatase and tensin homologue) syndrome (see later).

Patients can sometimes be managed with endoscopy and polypectomy (every 1 to 3 years); however, colectomy must be considered for patients with large numbers of polyps or polyps with dysplasia or for patients with complications (e.g., bleeding, obstruction). Screening colonoscopy every 3 years should commence with symptoms or in the early teenage years in an asymptomatic patient.[66,279] Upper endoscopy is also recommended in patients with juvenile polyposis syndrome. Esophagogastroduodenoscopy and small bowel examination (every 2 years) should begin at age 15 years.[66,279]

Ruvalcaba-Myhre-Smith Syndrome (Bannayan-Zonana Syndrome, Riley-Ruvalcaba Syndrome, Bannayan-Ruvalcaba-Riley Syndrome)

Ruvalcaba-Myhre-Smith syndrome consists of macrocephaly, mental deficiency, unusual craniofacial appearance, pseudopapilledema, pigmented macules on the penis, and hamartomatous polyps in the GI tract. The syndrome appears to be passed on as an autosomal dominant condition.[280] The GI polyps have been indistinguishable from juvenile polyps and in rare instances intestinal ganglioneuromatosis has also been described. The syndrome has been linked to mutations or deletions in the *PTEN* gene (10q23.3)[267,271,281] and with Cowden's syndrome and can be considered as one of the PTEN polyposis syndromes.[265]

Peutz-Jeghers Syndrome

Peutz-Jeghers polyps can be found throughout the GI tract, either sporadically or as part of the Peutz-Jeghers syndrome.[1,282,283] The polyp itself is characterized by fairly normal epithelium and lamina propria lining an abnormal arborizing network of smooth muscle that represents hamartomatous overgrowth of the muscularis mucosae (Fig. 23-47).[1,282,284] *Peutz-Jeghers syndrome,* usually inherited as an autosomal dominant trait, is the combination of skin hyperpigmentation and Peutz-Jeghers polyps in the GI tract. The diagnosis of Peutz-Jeghers syndrome is considered definitive if the patient has a Peutz-Jeghers polyp and at least two of the following criteria: (1) family history, (2) mucocutaneous hyperpigmentation, and (3) small bowel polyposis.[265,283] The pigmentation consists of clusters of brown or black freckles about the lips, buccal mucosa, and perianal and genital region. Pigmented areas can occasionally be seen on the fingers and toes. The spots appear in the first year of life and tend to fade toward middle age. The polyps usually number only in the dozens and can be found throughout the GI tract. These polyps have a propensity to form in the small intestine where they often cause intussusception. In rare kindred, Peutz-Jeghers polyps have been limited to the large bowel. Cases of complicating GI carcinoma have been reported.[285,286] Approximately 5% of female patients with Peutz-Jeghers syndrome have a peculiar ovarian tumor, sex cord tumor with annular tubules (SCTAT).[287] The rate of detection may increase if the ovaries are carefully examined,[287,288] and some tumors may be associated with sexual precocity.[289] Male patients with Peutz-Jeghers syndrome occasionally have unilateral or bilateral Sertoli cell tumors of the testes.[290,291] Adenoma malignum and pancreaticobiliary tract carcinomas are reported to occur at increased rates.[292]

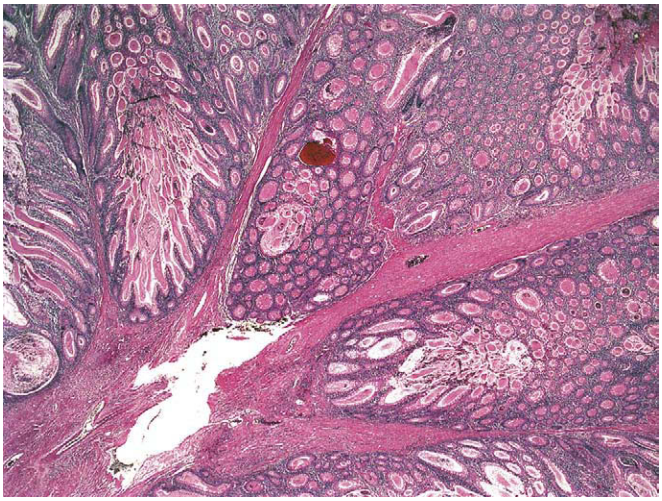

Figure 23-47 ■ Colonic Peutz-Jeghers polyp illustrating the arborizing hamartomatous overgrowth of the muscularis mucosae.

The Peutz-Jeghers syndrome has been linked to the *STK11* (serine/threonine-protein kinase 11, also known as *LKB1*) gene on chromosome 19p13.3[293-296] and can be demonstrated in 70% of cases.[265] This is a tumor suppressor gene involved in transduction of intracellular growth signals.[66] Investigators have suggested that genetic testing be considered for Peutz-Jeghers syndrome when any Peutz-Jeghers polyps or typical perioral pigmentations are found.[66]

Meta-analysis of cancer risk in an evaluation of patients with known mutations of the *STK11* gene have shown increased lifetime risk for cancer of the esophagus, stomach, small bowel, colon, pancreas, and breast.[283,297] Putting this into perspective, the risk for breast cancer in Peutz-Jeghers syndrome is similar to the risk seen in individuals with germline mutations of *BRCA1* and *BRCA2* and Peutz-Jeghers syndrome is the strongest known risk factor for pancreatic carcinoma except for hereditary pancreatitis.[283]

Screening at-risk individuals (first-degree relatives of a patient with Peutz-Jeghers syndrome) should begin at birth with an annual history and physical examination to look specifically for melanotic spots, precocious puberty, and testicular tumors. Asymptomatic at-risk individuals without stigmata by age 8 years should be tested for *STK11/LKB1* gene mutations. If mutation is not found in the family, small intestinal contrast radiography every 2 years until age 25 years is recommended. Other investigators suggest that upper and lower endoscopy with small bowel series should be done at ages 12, 18, and 24 years.[283]

Esophagogastroduodenoscopy and upper GI radiographic series with small bowel follow through are recommended in patients with Peutz-Jeghers syndrome commencing at age 8 years and repeated every 2 years thereafter.[283,298] Colonoscopy every 3 years is recommended

starting with symptoms or by age 18 years if symptoms have not occurred.[66,283] Testicular examination, pelvic examination by age 20 years, mammographic examination by age 25 years, and endoscopic ultrasound examination of the pancreas by age 25 to 30 years have been recommended.[229,283] Annual transvaginal ultrasound examination and serum CA-125 determination are also recommended commencing at age 25 years.[283]

Intestinal Ganglioneuromatosis

Intestinal ganglioneuromatosis is defined as proliferation of ganglion cells, neurites, and supporting cells that can affect any layer of the GI wall (Fig. 23-48).[280] These proliferations often manifest as mucosal polyps in the colon. Although these lesions most often occur as an isolated phenomenon, the importance of intestinal polypoid ganglioneuromatosis is in recognizing the other settings in which it can occur, such as von Recklinghausen's disease (*NF1* gene mutation), MEN2B (*RET* gene mutation), Cowden's syndrome (*PTEN* mutation), Ruvalcaba-Myhre-Smith syndrome (*PTEN* mutation), and tuberous sclerosis (*TSC1* [9q34] or *TSC2* [16p13] mutation).[299-303] Intestinal ganglioneuromatosis can coexist with juvenile polyps although these patients may be better classified as having PTEN polyposis.[276-278]

Cowden's Syndrome

Cowden's syndrome describes an autosomal dominant multiple hamartoma syndrome in which patients have multiple orocutaneous hamartomas (e.g., facial trichilemmomas, mucosal papillomas, acral keratosis, subcutaneous lipomas), fibrocystic disease of the breast, an increased risk of breast carcinoma, thyroid abnormalities, and hamartomatous polyps in the stomach, small intestine, and colon. Polyps of the GI tract, when described, often have shown an abnormal proliferation of the smooth muscle in the lamina propria and generally have resembled the polypoid variant of solitary rectal ulcer syndrome.[304] Some juvenile polyp–like proliferations have been described.[265] Intestinal ganglioneuromatosis has also been reported.[302] Other associated abnormalities include macrocephaly, high arched palate, hypoplastic mandible and maxilla, microstomia, supernumerary nipples, pectus excavatum, hemangiomas, ovarian cysts, and uterine leiomyomas.[265,303] The gene (*PTEN*) for Cowden's disease has been mapped to chromosome 10 (10q22-23).[272,305,306] Cowden's syndrome and Ruvalcaba-Myhre-Smith syndrome are sometimes referred to as the *PTEN polyposis syndromes*. Genetic testing is suggested when features of this syndrome are present.[66] Esophagogastroduodenoscopy and small bowel examination every 2 years beginning at age 15 years is recommended.[66]

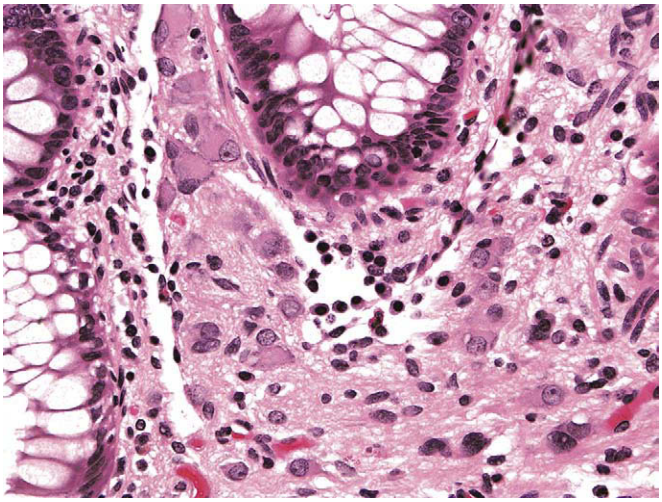

Figure 23-48 ■ Colonic ganglioneuroma is composed of ganglion cells, neurites, and supporting cells.

Cronkhite-Canada Syndrome

Cronkhite-Canada syndrome is an acquired nonfamilial syndrome characterized by intestinal polyposis, dystrophic changes of the fingernails, alopecia, and cutaneous hyperpigmentation.[307,308] Patients first present with diarrhea, abdominal pain, and anorexia that progresses to weight loss and protein-losing enteropathy. Many patients complain of loss of taste (hypogeusia) and loss of smell. As a rule, the ectodermal changes occur weeks to months after the other symptoms. The nail dystrophy consists of thinning, splitting, and separation from the nail bed (onycholysis). Onychomadesis (complete loss of the nail) can also occur. The hair loss is rapid and may be seen in the scalp, eyebrow, face, axilla, or pubic region. The cutaneous hyperpigmentation ranges from small macules to confluent areas of hyperpigmentation that can be 10 cm or more. Histologically, the pigmented macules result from increased melanin in the basal layer.

Cronkhite-Canada polyps are found throughout the GI tract but are most commonly seen in the stomach and large bowel. Grossly, they are sessile; a few are pedunculated. The polyps tend to occur on a background of diffuse mucosal thickening (Fig. 23-49). Histologically, the polyps themselves are identical to juvenile polyps. However, the mucosa between polyps is abnormal and shows edema, congestion, and inflammation (chronic inflammation often with prominent eosinophils) of the lamina propria coupled with glandular ectasia (Fig. 23-50). Carcinomas of the colon and stomach have been described rarely in patients with Cronkhite-Canada syndrome. The malabsorption in this syndrome is usually progressive and with no specific therapy available, the prognosis is generally poor. Death results from anemia, septic shock, bleeding, or postoperative complications. Treatment consists of supportive therapy, antibiotics, corticosteroids, and surgery. Within the stomach, Cronkhite-Canada syndrome closely mimics Ménétrier's disease. Ménétrier's disease, however, is confined to the stomach and has no associated ectodermal changes.

Other Large Bowel Polyps

Mucosal Heterotopia

Heterotopic gastric, pancreatic, sebaceous, and salivary gland tissues have been described in the colon and rectum. These ectopic tissues can be found throughout the GI tract

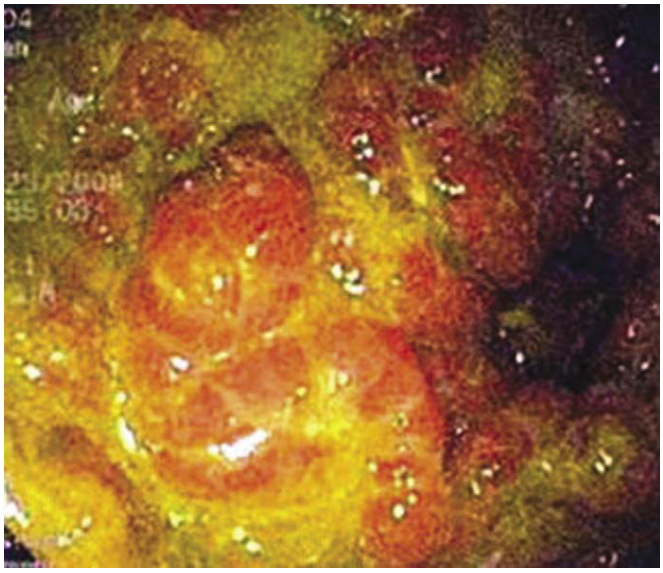

Figure 23-49 ■ Endoscopic photograph of the colon from a patient with Cronkhite-Canada syndrome. The broad-based sessile polyps are situated on a background of diffuse mucosal thickening, nodularity, and exudate.

but are most often seen in the rectum where they can cause a plaque, polyp, or mass (Fig. 23-51).[309-311]

Inflammatory Fibroid Polyp

Inflammatory fibroid polyp is most commonly found in the stomach but can be encountered throughout the GI tract including the colon and rectum.[1,312-314] Symptoms include abdominal pain and bleeding. The polyp is usually solitary. It can be sessile or pedunculated and typically has a solid pale tan cut surface.

Microscopically one sees a loose myxoid fibrous tissue background containing regularly distributed blood vessels, some of which show hyalin change in their walls. The fibrous tissue can layer in a whorl-like fashion around these

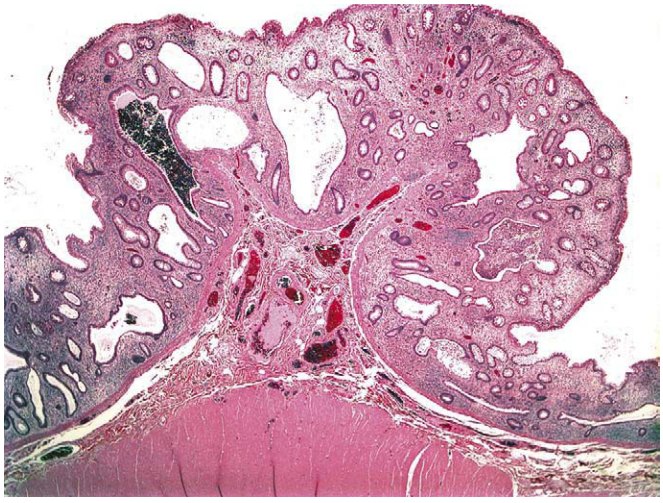

Figure 23-50 ■ Cronkhite-Canada syndrome polyps resemble juvenile polyps because they are composed of edematous and inflammatory expansion of the lamina propria with glandular cyst formation. In contrast to juvenile polyps, the adjacent nonpolypoid mucosa shows similar lamina propria abnormalities and mucosal atrophy.

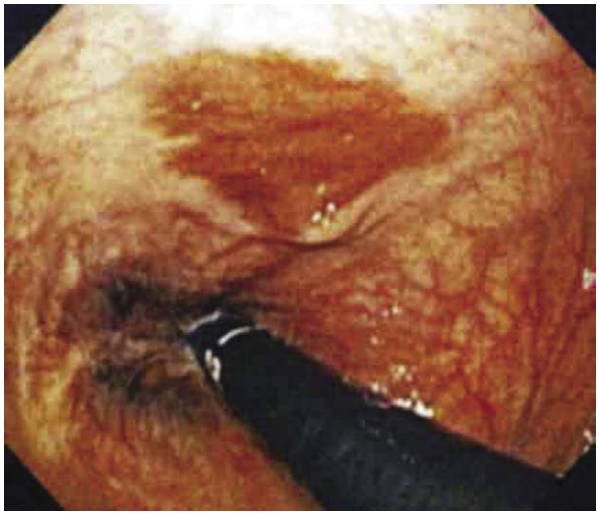

Figure 23-51 ■ Endoscopic view of gastric heterotopia. This photograph taken with the endoscope retroflexed for a view of the rectum shows a plaquelike area of erythema.

vessels in an onion-skin pattern. Most lesions are rich in inflammatory cells including plasma cells and eosinophils (Fig. 23-52). Scattered macrophages and Touton-type giant cells can also be seen. The stroma in most lesions is positive for CD34 but negative for CD117. Mutations in platelet-derived growth factor receptor alpha gene have been described.[314a] The mucosa overlying these typically submucosal tumors can be ulcerated, presumably by trauma, and can show areas of inflamed granulation tissue. The ulcerated surface can contain bizarre stromal cells, which are also seen in a variety of inflammatory polyps with chronic ulceration (e.g., IBD, trauma or prolapse, and radiation injury). The inflammatory fibroid polyp is benign and typically does not recur.

Malakoplakia

Malakoplakia, an abnormal immune response to gram-negative bacteria, can cause a tumor or polyp in any site

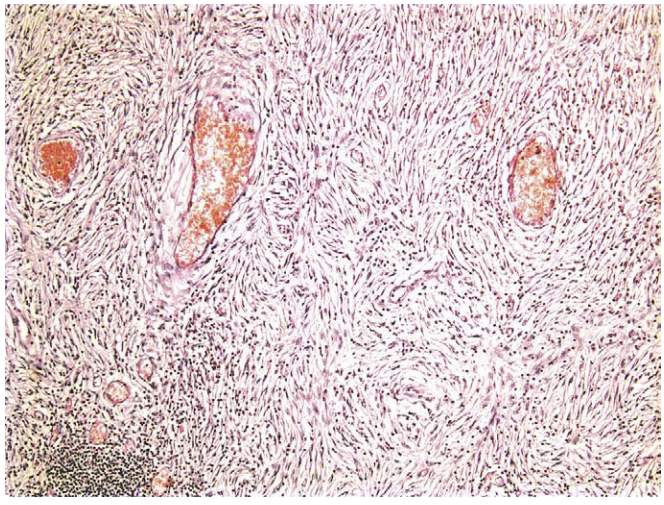

Figure 23-52 ■ Inflammatory fibroid polyp. The lesion is histologically composed of loose myxoid fibrous tissue and blood vessels. The fibrous tissue is layered around the vessels and contains inflammatory cells.

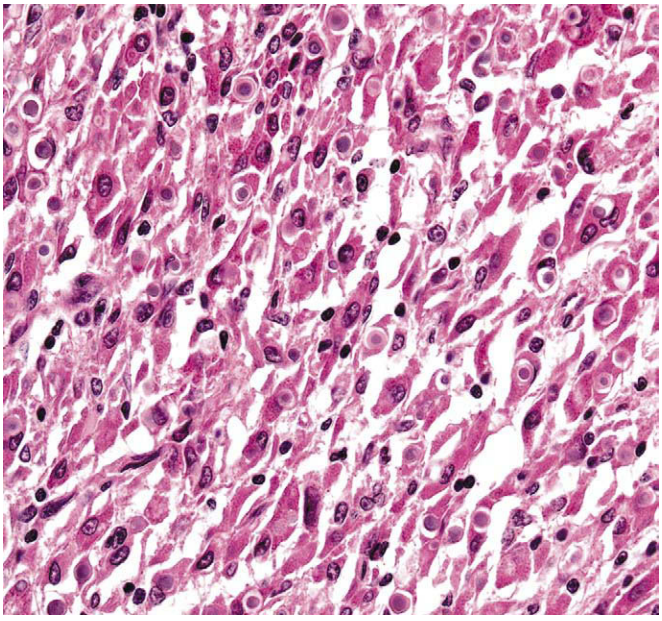

Figure 23-53 ■ Malakoplakia. The xanthogranulomatous inflammatory reaction contains numerous Michaelis-Gutman bodies.

of the GI tract, including the large bowel. Histologically, it is characterized by xanthogranulomatous inflammation accompanied by the pathognomonic Michaelis-Gutmann body (Fig. 23-53).[1] The partially digested bacteria accumulate in macrophages and lead to deposition of calcium and iron on the residual bacterial glycolipids.[315] An association between colorectal malakoplakia and colorectal neoplasia may exist.[315]

Endometriosis

Defined as the presence of endometrial glands or stroma usually with hemorrhage and hemosiderin deposits in an extrauterine location, *endometriosis* tends to affect sites closest to the female genital tract such as the sigmoid colon and rectum.[1] Symptoms include episodic abdominal pain. Hematochezia can occur with mucosal involvement. Endometriosis usually involves the serosa and muscularis externa and can cause smooth muscle proliferation and stricture. Mucosal and submucosal involvement can cause mucosal polyps.[316] Endometriosis must be distinguished from müllerian adenosarcoma and endometrial stromal sarcoma. The glandular component can be confused with colitis cystica profunda and adenocarcinoma. Immunohistochemical analysis for CD10, which highlights endometrial stromal cells, can be helpful in the differential diagnosis as can recognition of ciliated epithelial cells. Differential cytokeratin immunostaining can also help because endometriosis commonly stains positive for CK7, whereas colorectal epithelium usually expresses CK20. Examples of malignant transformation (mostly endometrioid carcinoma and clear cell carcinoma) in endometriosis have been reported.[316]

Oleogranuloma

Injection of materials containing lipid bases into the lower rectum and anus can cause a mass or polyp referred to as an *oleogranuloma*. The lesion is composed of lipid-containing cysts surrounded by a foreign body giant cell reaction.[1]

Benign Fibroblastic Polyp/Colorectal Perineurioma

Benign fibroblastic polyps and perineurioma have been described in the colon and rectum where they may represent the same or a similar lesion.[317-319] These mucosal polyps are usually solitary but can be multiple and have been reported throughout the GI tract, most commonly in the colon and rectum. Histologically, these polyps contain proliferations of small tightly packed spindle cells within the lamina propria that often orient themselves parallel to the muscularis mucosae. This lesion frequently coexists with hyperplastic polyp–like epithelial proliferations, and indeed the polyp could represent a trauma-related change seen in the otherwise typical hyperplastic polyp or sessile serrated polyp (Fig. 23-54). The spindle cells test negative for immunoreactive S-100 protein and other neuromarkers; they can express immunoreactive epithelial membrane antigen by immunohistochemical analysis.

Elastosis and Elastofibromatous Change

Areas of increased elastin fibers in the submucosa and muscularis mucosae are referred to as *elastosis* or *elastofibromatous change* and can cause polyps in the colon and rectum. Histologically, the elastosis appears as finely granular or fibrillar amphophilic material usually with a fibrous component and is often centered around prominent blood vessels (Fig. 23-55). The change could also be a manifestation of mucosal trauma or prolapse. Elastosis can be confused with amyloid deposits but results of Congo red stains have been negative.[320]

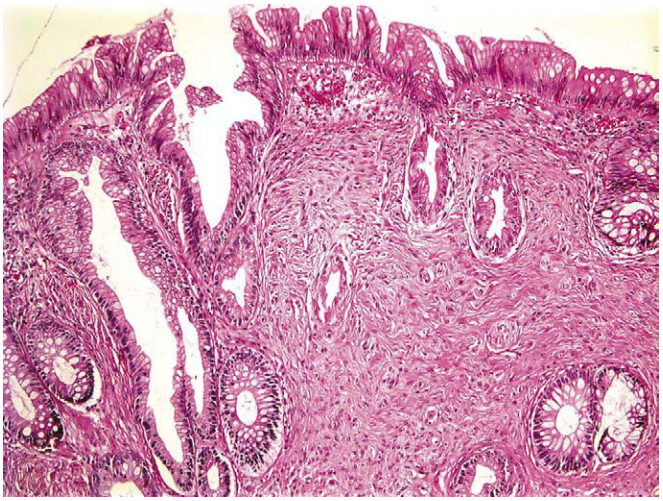

Figure 23-54 ■ Benign fibroblastic polyp/colorectal perineurioma. The lesion is composed of small, tightly packed spindle cells within the lamina propria. Note the alignment of the superficial spindle cells parallel to the muscularis mucosae. Mucosal hyperplastic polyp–like changes are often present in these lesions.

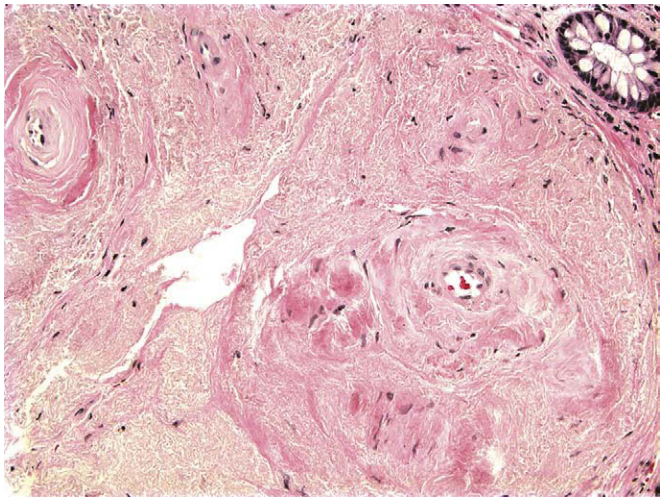

Figure 23-55 ■ Elastofibromatous change can be seen within mucosal polyps of the colon and rectum. The finely granular and fibrillar eosinophilic material is often centered around blood vessels.

Mucosal Neuroma/Schwann Cell Hamartoma

Benign spindle cell proliferations that express immunoreactive S-100 protein can manifest as mucosal polyps in the colon and rectum and are usually termed *mucosal neuromas*[1] or *Schwann cell hamartomas*. Care must be taken not to overlook ganglion cells, which would indicate a ganglioneuroma. These lesions can be seen in patients with neurofibromatosis but most occur sporadically and are unassociated with syndromes.[321]

LARGE BOWEL INFLAMMATION

Colonic Biopsy in Inflammatory Bowel Disease

With increased availability of total colonoscopy and flexible sigmoidoscopy, pathologists can expect an ever-increasing number of colorectal biopsy specimens. The pathologist plays a critical role in the diagnosis and management of patients with colitis and suspected colitis.

When evaluating a colorectal biopsy specimen, it is useful to scan the tissue at low magnification and ask several questions. Are abnormalities present? If present, are the changes diffuse or focal? Is the luminal border of the specimen straight or irregular? Is intraepithelial mucin (the goblet cell population) preserved or depleted? If intracellular mucin is depleted, is this change focal or diffuse? Are inflammatory cells increased in the lamina propria or epithelium? Is this increase diffuse or focal? What kind of inflammatory cells are they? Is the lamina propria obliterated by fibrous or fibromuscular tissue? Are crypt abscesses present? Are colonic tubules straight? Do the colonic tubules reach the muscularis mucosae or are they short, branched, or budded? With careful consideration of the features outlined earlier, one can often recognize a pattern of abnormality that when coupled with clinical and endoscopic information can lead to a fairly specific diagnosis in a large number of patients.

Patterns of Colorectal Inflammation

The following patterns of inflammation can be identified in mucosal biopsy specimens: chronic colitis, diffuse active colitis, focal active colitis, ischemic-type injury, trauma-related change, apoptotic colopathy, and intraepithelial lymphocytosis. Identification of an inflammation pattern can be helpful in assessing patients by creating a clinically relevant differential diagnosis.

CHRONIC COLITIS

Quiescent UC best typifies the *chronic colitis* pattern of injury. The predominant features are mucosal atrophy and architectural distortion (Fig. 23-56).[322-325] The luminal border is often irregular and the number of crypts decreased. The remaining crypts typically appear short (i.e., they do not touch the muscularis mucosae), they lose their parallel arrangement, and they become branched and budded. The goblet cell population is usually preserved. Chronic inflammatory cells including plasma cells are increased in the lamina propria. Paneth cells may be present. The muscularis mucosae is usually hypertrophied. The foregoing changes, although consistent with a diagnosis of chronic UC, must be interpreted in light of the clinical, radiologic, and endoscopic findings because similar changes can be seen in focal, healed, or healing areas of other chronic colitides such as Crohn's disease, ischemia, chronic irradiation injury, tuberculosis, and schistosomiasis.

Care must be taken when interpreting biopsy specimens obtained from the normal mucosa adjacent to lymphoid follicles, from normal mucosa containing the innominate groove, and from the lower portion of the rectum near the transition zone. These areas normally show some loss of crypt parallelism and should not be misinterpreted as evidence of chronic colitis.[2,7] Conversely, histologically normal biopsy specimens must not be reported as showing "chronic nonspecific inflammation" consistent with UC. Unless one or more of the features discussed in the preceding para-

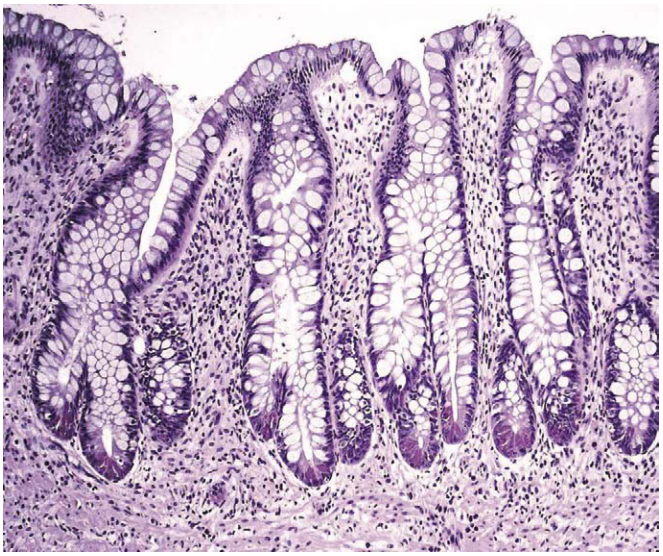

Figure 23-56 ■ Quiescent ulcerative colitis. The predominant feature is the loss of the crypt parallel arrangement. The luminal border is irregular. The remaining crypts are atrophic, shortened, branched, and budded.

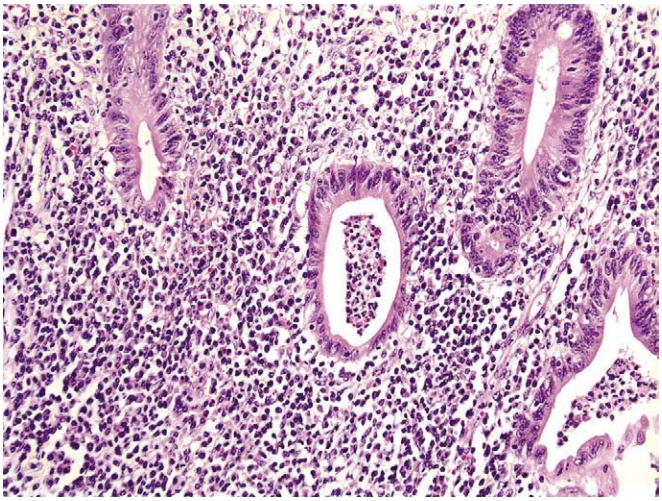

Figure 23-57 ■ Ulcerative colitis in an active phase showing architectural distortion, diffuse goblet cell depletion, basal plasmacytosis, and crypt abscess formation.

graph are also present, it is a good rule not to diagnose primary IBD based only on an evaluation of inflammatory cells within the lamina propria.

DIFFUSE ACTIVE COLITIS

The term *active colitis* describes inflammatory conditions in which neutrophils are present within the lamina propria, within epithelial cells (cryptitis), or within the lumen of crypts (crypt abscesses). Included under this heading are UC in an active phase, most examples of Crohn's disease, and infectious colitis or acute self-limited colitis.[326,327]

UC in an active phase represents the prototype diffuse active colitis. Biopsy specimens usually demonstrate diffuse abnormalities, meaning that changes are of approximately the same intensity in all areas of the tissue submitted from a particular region of the colon. The luminal border of the mucosa is irregular.[323-329] Increased numbers of chronic inflammatory cells are present in the lamina propria and may occasionally spill over into the superficial portion of the submucosa. Intracellular mucin in goblet cells is diffusely depleted.[330] Cryptitis and crypt abscess formation are often prominent (Fig. 23-57). It is surprising that even in UC of extremely short overt clinical duration, atrophy, branching, and budding of crypts are already apparent in many specimens.[7,324-329] This crypt distortion coupled with *basal plasmacytosis,* which is defined as increased plasma cells in the lower fifth of the mucosa, has been proposed as the most useful histologic criterion to differentiate primary IBD from infectious colitis or acute self-limited colitis.[323,326-328]

Remember, the most a pathologist can conclude from a biopsy specimen showing this pattern of injury is that the changes are consistent with UC in an active phase. The diffuse active colitis pattern of injury can also be seen in some examples of Crohn's disease[324,328] and in some cases of documented infectious colitis,[331] although we think it is likely that these cases represent an infectious exacerbation of an underlying, albeit clinically latent, primary IBD. The diffuse active colitis pattern of injury has been reported in a form of colitis associated with diverticular disease.[332] However, this entity can be distinguished from classic UC by virtue of its rectal sparing and the presence of inflammation only in areas of diverticula.

FOCAL ACTIVE COLITIS

The *focal active colitis* pattern of injury refers to the patchy distribution of architectural or acute inflammatory change in mucosal biopsy specimens. Chronic colitis showing diffuse chronic changes as described earlier, coupled with patchy acute inflammation, is not considered focal active colitis but is classified as *chronic colitis showing mild activity*. The focal active colitis pattern consists of limited areas of increased inflammatory cells sometimes coupled with focal minimal architectural distortion (Fig. 23-58). Characteristically, some areas of the biopsy specimen from a region of the colon must maintain an essentially normal appearance. The focal active colitis pattern of injury is usually not seen with UC and when present suggests Crohn's disease,[7,333,334] injury related to nonsteroidal anti-inflammatory drugs (NSAIDs), or infectious colitis or acute self-limited colitis (see later).[7,323,327,330,334,335] The focal active colitis pattern of injury, however, can be seen in resolving UC under active medical management.[330,336] Areas previously involved in the colon and rectum in UC can return to an almost normal histologic appearance with therapy.

Granulomas typically found in Crohn's disease should be sought in all biopsy specimens, but especially those showing the focal active pattern. Although serial sectioning of biopsy specimens is advocated by some investigators for the detection of granulomas,[337] in our experience, granulomas are rarely missed. That said, germinal centers, tangential cuts of blood vessels, tangential cuts of the pericryptal fibroblastic sheath, and an inflammatory reaction to extravasated mucin (so-called mucin granulomas) are often misinterpreted as the granulomas of Crohn's disease. In the absence of true granulomas, biopsy specimens from patients with Crohn's disease often show the focal active colitis pattern of injury without neutrophils in the lamina propria. Some examples of Crohn's colitis can be indistinguishable from resolving mucosal UC in biopsy specimens.[323,328]

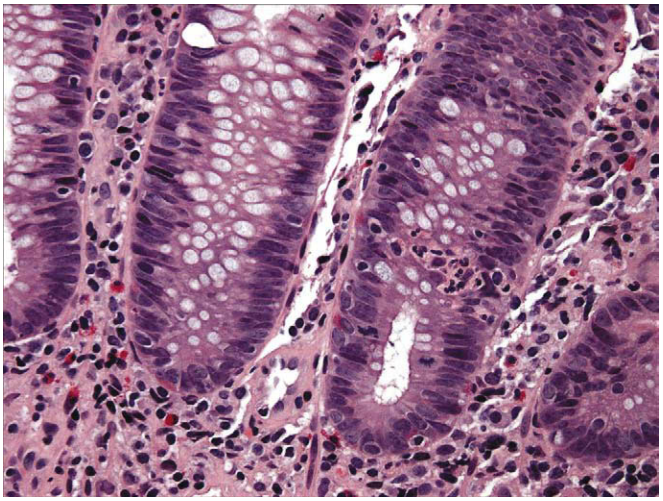

Figure 23-58 ■ Focal active colitis pattern of injury. The focal area of cryptitis is associated with no architectural change in this example.

A fibrinopurulent exudate in the specimen overlying but separate from the mucosa is always abnormal. The clinician should be informed that ulcers are likely to be present in a more proximal location in the bowel. On a practical note, all inflammatory exudates should be examined under high magnification for trophozoites of *Entamoeba histolytica,* because this is their preferred location and these organisms are easy to overlook.

The definitive classification of colonic inflammation depends on clinical pathologic correlation. In our opinion, the task of the pathologist is to convey the histologic pattern of injury to the clinician who then collates that information with the clinical history and data obtained from endoscopic, radiologic, and laboratory examination.

Antineutrophil cytoplasmic antibodies (ANCAs) have been identified in patients with IBD.[338-340] The immunofluorescence pattern (perinuclear) differs from the diffuse cytoplasmic reaction detected in patients with Wegener's granulomatosis. Although initially thought to be specific for UC, ANCAs more likely reflect inflammatory conditions involving the colon. In one study, up to 70% of patients with presumed UC had ANCA positivity with a 46% prevalence in patients with colonic Crohn's disease and a 5% prevalence in patients with infectious-type colitis.[328] Another antibody, anti–*Saccharomyces cerevisiae* antibody (ASCA), has been closely linked to Crohn's disease. ASCAs can be identified in up to 60% to 70% of patients with Crohn's disease, as opposed to 10% to 15% in UC and 5% of controls.[341,342] Some investigators have proposed the use of ANCA and ASCA together to increase specificity.[343] These tests clinically have demonstrated low sensitivity (≈50% to 60%) but have been reported to be highly disease specific. These tests may have value in classification of indeterminate colitis but this remains to be proved.[344]

Infectious-Type Colitis/Acute Self-Limited Colitis

The following histologic appearances have been described in culture-proved or toxin-proved infectious colitis: normal colon, nonspecific increases in chronic inflammatory cells, the diffuse active colitis pattern of injury[331] (although these likely represent infectious exacerbations of an underlying primary IBD), ischemic-like changes,[345,346] and the focal active colitis pattern of injury. Although colonic mucosal biopsy appearance in infectious colitis can vary greatly, many specimens have the focal active colitis pattern. In general, invasive organisms cause greater changes in morphology than those producing their effects by toxins.

Histologic evaluation, although helpful in suggesting infection and ruling out primary IBD, can only rarely suggest a specific cause. The definitive diagnosis of infectious colitis requires laboratory identification of the serologic features of the offending organism.

Even after extensive microbiologic workup, a subset of patients presumed clinically to have infectious colitis will experience spontaneous recovery in less than 6 months and will have biopsy specimens that demonstrate the focal active colitis pattern of injury without an identifiable infectious cause. The term *acute self-limited colitis* has been used to describe such patients.[326-328,330] We prefer the term *infectious-type colitis* to acute self-limited colitis because some examples of acute self-limited colitis may not be self-limited.[7] Other investigators prefer the term *nonrelapsing colitis.*[327,329]

THE ISCHEMIC PATTERN

The characteristic pattern of *acute ischemic-type injury* consists of hemorrhage into the lamina propria associated with superficial epithelial coagulative necrosis, with relative sparing of the deep portions of the crypts (Fig. 23-59).[3,346,347] These changes can occasionally be associated with more extensive necrosis of epithelium with inflammatory pseudomembrane formation. Surprisingly, acute and chronic inflammatory cells, especially plasma cells, are typically scant in ischemic-type damage and this feature can help differentiate ischemic-type damage from primary IBD.

The differential diagnosis of ischemic-type damage is wide and includes all causes of true ischemia such as inadequate perfusion, narrowing of blood vessels, obstructing lesions of the bowel, and bowel distention. Ischemic-type change is also associated with a variety of drugs, including vasopressors, oral contraceptives, NSAIDs, cocaine, and glutaraldehyde, which is sometimes used to clean endoscopes.[348-351] Some infectious agents typically cause ischemic-type damage, including cytomegalovirus (CMV), *Clostridium difficile*, *Clostridium septicum,* and the enterohemorrhagic *Escherichia coli* (EHEC).[346]

THE TRAUMA PATTERN

Trauma-type histologic changes frequently coexist clinically with mucosal ulcers or erosions. The characteristic trauma-type histologic pattern is found in the mucosa adjacent to ulcers or in polypoid mucosa areas and consists of fibro-

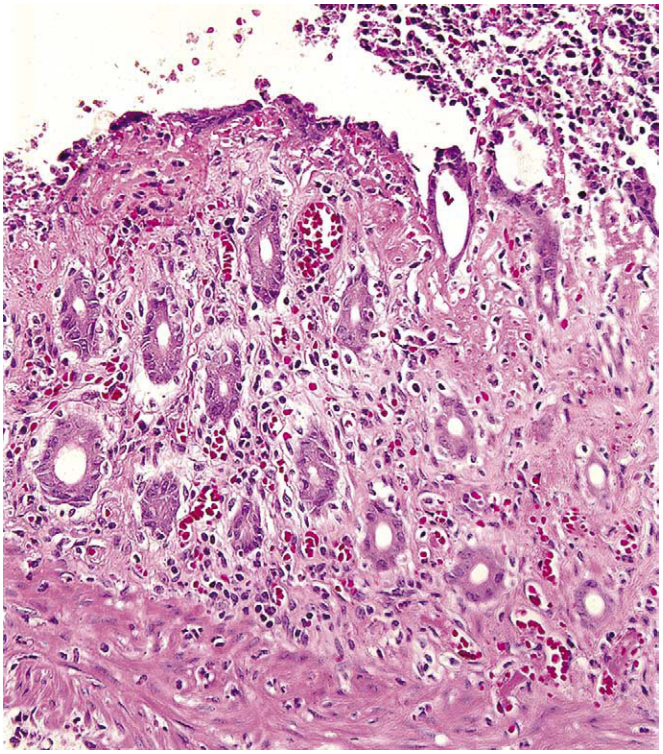

Figure 23-59 ■ Acute ischemic pattern of injury showing hemorrhage into the lamina propria associated with coagulative necrosis of the surface epithelium and inflammatory pseudomembrane formation. Regenerative changes are present at the crypt bases.

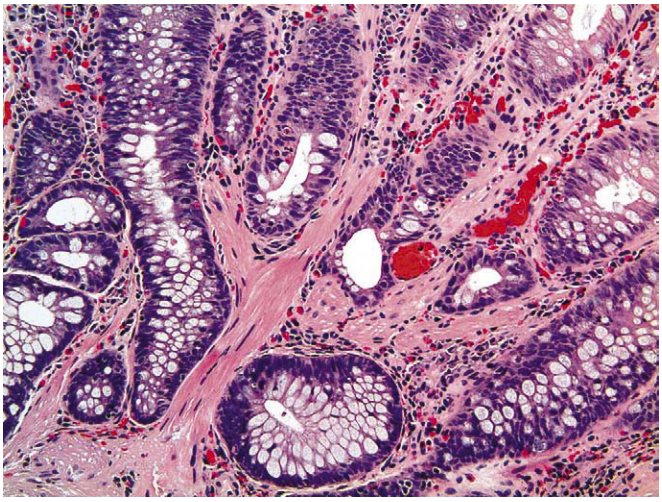

Figure 23-60 ■ Solitary rectal ulcer syndrome showing the traumatic pattern of injury. Sections show fibromuscular obliteration of the lamina propria associated with mucosal architectural changes, inflammation, and capillary ectasia.

muscular proliferation within the lamina propria associated with mucosal architectural distortion and intramucosal capillary ectasia (Fig. 23-60).[352-355] The trauma-type histologic features can be seen in the solitary rectal ulcer syndrome, localized colitis cystica profunda, inflammatory cloacogenic polyp, the mucosa adjacent to orifices of colonic diverticula,[356] and inflammatory cap polyposis[357] and are frequent findings adjacent to neoplasia and in the vicinity of the ileocecal valve.[358]

APOPTOTIC COLOPATHY

Surface colonic epithelial apoptosis and karyorrhectic debris within the superficial lamina propria are commonly seen in mucosal biopsy specimens and are widely attributed to bowel preparation. Apoptotic bodies in the deep crypt are only rarely seen (<1 per 20 crypts) outside of pathologic conditions. Increased deep apoptotic bodies can be seen in ischemic-type damage, CMV infection, chemotherapy or radiation, and in association with mycophenolate mofetil (CellCept) (Fig. 23-61).[359] Although associated with a variety of injurious agents, apoptosis is the characteristic form of cell death in cell-mediated immune cytotoxicity as demonstrated in graft-versus-host disease (GVHD),[360] other immune deficiency syndromes[361,362] and thymic neoplasia.[363] Many patients with AIDS with diarrhea demonstrate deep apoptosis in the absence of pathogens, a finding suggesting that primary immune-mediated apoptotic colopathy may cause some of the diarrhea and wasting seen in AIDS.[364,365]

INTRAEPITHELIAL LYMPHOCYTOSIS

Collagenous and Lymphocytic Colitis

The term *collagenous colitis,* first coined by Lindström in 1976,[366] describes a distinct clinicopathologic syndrome causing watery diarrhea, predominantly in middle-aged or older (mean age, 59 years) women (male-to-female ratio, 1:7.5).[367,368] Results of colonoscopic and barium enema examination in these patients are usually normal. Therefore, diagnosis depends on recognition of characteristic changes in biopsy specimens. The primary histologic change of collagenous colitis consists of a patchy increase in the thickness of the subepithelial collagen plate (Fig. 23-62).[367,368] The normal colonic epithelial collagen layer measures approximately 5 μm in thickness, but in collagenous colitis it may increase to 10 μm or more. We use 15 μm as a morphologic cutoff point for collagenous colitis. A mild to moderate increase in chronic inflammatory cells including plasma cells and eosinophils expands the lamina propria. Patchy injury to the surface epithelium characterized by increased numbers of intraepithelial lymphocytes, epithelial degeneration, and sloughing also occur. Atrophy, mucosal architectural distortion, and acute inflammation are usually not present or are minimal.[367,369,370]

Read and colleagues[371] introduced the term *microscopic colitis* to describe patients with chronic watery diarrhea of unknown origin occurring in middle-aged (mean, 54 years) patients. As in collagenous colitis, the colonoscopic appearance and the barium enema were usually described as

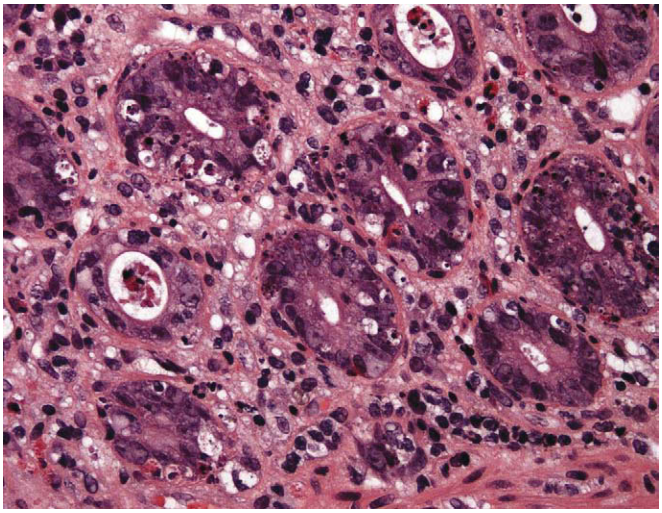

Figure 23-61 ■ Acute graft-versus-host disease, grade 2, showing numerous apoptotic bodies and scattered crypt abscesses.

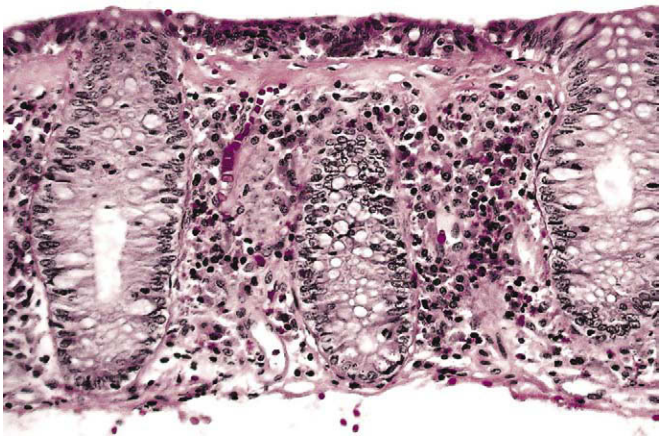

Figure 23-62 ■ Collagenous colitis. Sections show benign colonic mucosa without architectural distortion. Increased numbers of inflammatory cells including plasma cells and eosinophils are present within the lamina propria. Surface epithelial lymphocytosis is evident. The subepithelial collagen plate is increased in thickness.

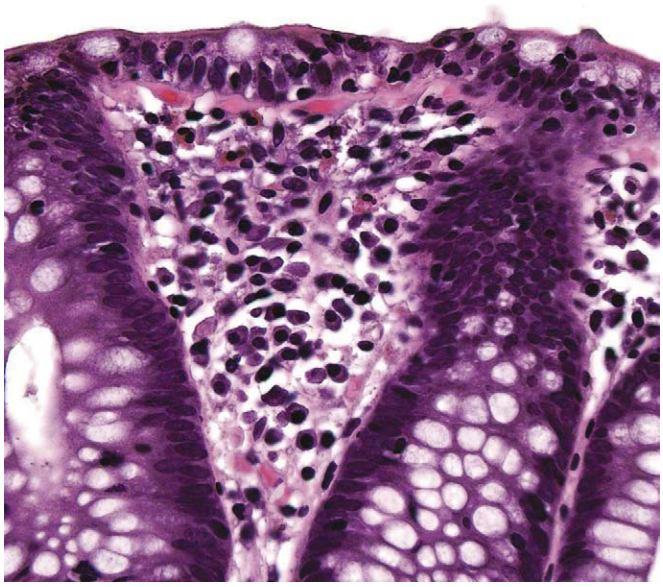

Figure 23-63 ■ Lymphocytic colitis. The sections show little architectural change but a marked increase in inflammatory cells within the lamina propria and within the surface epithelium.

normal. Biopsy specimens demonstrated increased inflammatory cells in a pattern not specific for any established entity.[371] Since this initial report, investigators have refined the clinical and especially the histologic diagnostic criteria of lymphocytic colitis.[370,372] The histologic changes include increased chronic inflammatory cells in the lamina propria and surface epithelium, degenerative changes of the surface epithelium, minimal architectural change, and minimal acute inflammation (Fig. 23-63). The changes of lymphocytic colitis in general resemble the surface epithelial and lamina propria changes of collagenous colitis, and indeed changes identical to lymphocytic colitis are seen in biopsy specimens from patients with collagenous colitis when areas where the collagen plate is not well developed are sampled.

The similarities between lymphocytic colitis and collagenous colitis are striking. They share similar symptoms and endoscopic findings. The histologic similarities include increased intraepithelial lymphocytes, surface epithelial damage, and increased chronic inflammatory cells within the lamina propria.[369,370,373] Both collagenous colitis and lymphocytic colitis can be associated with other autoimmune phenomena such as thyroid disease, enteropathic arthritis, rheumatoid arthritis, myasthenia gravis, and celiac sprue.[374,375] Some cases of lymphocytic colitis demonstrate thickening of the subepithelial collagen plate, and distinguishing lymphocytic colitis from collagenous colitis may not be so clear-cut in all cases.[373] It appears likely that lymphocytic colitis and collagenous colitis are either the same or very similar conditions, perhaps representing different morphologic phases of one disease process.[370,374]

Some minor differences between lymphocytic colitis and collagenous colitis deserve mention, however. Collagenous colitis has been reported predominantly in women, whereas lymphocytic colitis affects men and women equally.[370,376] Differences in human leukocyte antigen (HLA) haplotypes between collagenous colitis and lymphocytic colitis have been described.[376] Finally, collagenous colitis and lymphocytic colitis differ histologically with the presence of the thickened collagen plate.

Pathogenesis of the Diarrhea

Lymphocytic colitis and collagenous colitis are associated with net fluid secretion in the colon that is responsible for the diarrhea.[377] Several investigators could find no association between the thickness and extent of the collagen plate and the amount of diarrhea.[373] Therefore, most investigators conclude the damage to the surface epithelial cells and the inflammation, rather than the collagen deposits, cause diarrhea. The presence and thickness of the subepithelial collagen plate appear unrelated to the patient's age or the duration of disease.[373] Some patients have also demonstrated evidence of small bowel dysfunction such as salt wasting, fatty acid malabsorption, small bowel net secretion, and rarely a small bowel villous lesion that resembles celiac sprue (see later).[376]

Treatment and Prognosis

Spontaneous resolution of collagenous and lymphocytic colitis has occurred, thus rendering evaluation of therapeutic regimens difficult.[378] A few patients with these colitides have presented with relatively mild diarrhea and have achieved medical control with dietary restriction (elimination of caffeine and lactose-containing foods), bulking agents, and antimotility drugs (loperamide hydrochloride, diphenoxylate hydrochloride, atropine). A trial of bismuth compounds is worthwhile. Many times, symptomatic therapy has failed, thus necessitating the addition of anti-inflammatory agents. Approximately 80% to 90% of patients eventually respond to therapy with sulfasalazine, prednisone, or budesonide.[368,378,379]

Etiology and Pathogenesis

NSAIDs and ticlopidine have been linked to some occurrences of collagenous colitis,[380,381] and lymphocytic colitis has been reported in patients receiving *Ruscus* extract (Cyclo 3 Fort),[382] ranitidine,[383] ticlopidine, and flutamide.[381] However, most cases cannot be linked to drug ingestion and the bulk of the evidence suggests that lymphocytic and collagenous colitis share common immune-mediated etiology and pathogenesis. Both conditions have a striking histologic similarity to celiac sprue, a condition known to be autoimmune and possibly having a viral or infectious trigger.[370] In addition, both lymphocytic and collagenous colitis have been linked to other conditions thought to have autoimmune pathogenesis such as Crohn's disease, hypothyroidism, hyperthyroidism, inflammatory arthropathies, pernicious anemia, small bowel villous atrophy, iritis, diabetes mellitus, and myasthenia gravis.[374,384,385] Both conditions respond dramatically to anti-inflammatory agents.[378,379] The finding of "lymphocytic colitis–like" histologic features reported in an epidemic outbreak of Brainerd diarrhea linked to a water tank aboard a cruise ship supports an infectious trigger for some cases of lymphocytic colitis (see later).

Associations with Celiac Disease

The association between lymphocytic colitis or collagenous colitis and celiac sprue and spruelike lesions deserves

special attention. In the experience of DuBois and associates[386] and Wolber and colleagues,[387] approximately 25% of patients with "celiac sprue" who had colonic biopsies also showed changes of lymphocytic colitis. Colonic microscopic abnormalities in patients with celiac sprue occur after experimental exposure to wheat or gliadin enemas, a finding suggesting that the entire intestinal tract may be susceptible to gluten-induced injury. It is possible that in some patients with true celiac sprue (responsive to gluten withdrawal), occult dietary gluten reaches the colon and induces the histologic changes of lymphocytic colitis. However, approximately one half of the patients with spruelike small bowel lesions and lymphocytic colitis have not responded to gluten withdrawal. The term *lymphocytic enterocolitis* has been coined to describe this refractory spruelike condition associated with colonic intraepithelial lymphocytosis.[386]

Aberrant Histology

As more cases are investigated, it is not unusual to see variations in histologic pattern commingled with the classic changes of lymphocytic and collagenous colitis. These variations include architectural change, cryptitis, Paneth cell metaplasia, ulcers, and inflammatory membranes.[388-391] Approximately one third of patients demonstrate cryptitis. Rarely, one encounters inflammatory pseudomembranes. Neither histologic pattern correlates strongly with infection. Approximately 2% of patients have ulcers, and architectural abnormalities have been reported in 5% of patients. Paneth cell metaplasia is seen in 14% to 44% of patients, most often in collagenous colitis in which it may correlate with increased severity of diarrhea. Acute inflammation is seen with increased frequency in patients taking antibiotics. Ulcers have been linked with concomitant NSAID usage. Some investigators have suggested that the "stiff" colon seen in collagenous colitis could be at increased risk for the development of ulcers and perforation during colonoscopy.[388] Other variants with subepithelial giant cells have been described (Fig. 23-64).[392] Histologic features, aberrant or otherwise, do not seem to correlate with symptoms, results of medical treatment, or outcome.[393] No patient with unusual histologic features, including architectural change and Paneth cell metaplasia, has yet to develop primary IBD (e.g., Crohn's disease or UC).

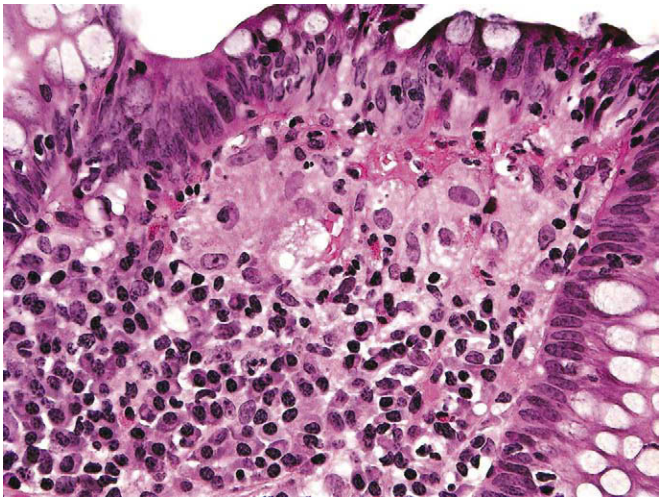

Figure 23-64 ■ Lymphocytic colitis with subepithelial giant cells.

Brainerd Diarrhea

The term *Brainerd diarrhea* has been applied to outbreaks of diarrhea of unknown origin characterized by acute onset and prolonged duration.[394] The disease was named after Brainerd, Minnesota, where in 1984 122 residents developed watery diarrhea after drinking unpasteurized milk. A second outbreak occurred in Henderson County, Illinois in 1987, when 72 people developed watery diarrhea associated with drinking contaminated well water at a roadside restaurant. In each outbreak, patients underwent extensive diagnostic evaluations including comprehensive microbiologic studies of their stool and the implicated exposure site. Despite the workup, no causative agent was identified. The clinical and epidemiologic characteristics were typical of point-source epidemic infectious diarrhea. However, unlike in typical infectious diarrhea, these patients developed a chronic watery diarrhea syndrome with symptoms lasting longer than 6 months and often lasting for years.

In general, the small bowel biopsy specimens from patients with Brainerd diarrhea were histologically normal. Colonic biopsy specimens revealed surface epithelial lymphocytosis without distortion of mucosal architecture, surface degenerative changes, or thickened subepithelial collagen plate. The degree of surface epithelial lymphocytosis was similar to that seen in cases of collagenous and lymphocytic colitis.[370,394,395]

Many experts believe that patients with the clinical syndrome of chronic watery diarrhea of unknown origin and patients reported as having lymphocytic colitis represent a heterogeneous group that may contain persons with unrecognized Brainerd diarrhea. With long-term follow-up, cases of Brainerd diarrhea appear to be self-limited, and patients recover in less than 3 years. From a practical standpoint, surface epithelial lymphocyte counts should be performed on all colonic biopsy specimens from patients with chronic diarrhea, especially chronic watery diarrhea. Currently, Brainerd diarrhea cannot be recognized outside the setting of an epidemic.

MUCOSAL PROLAPSE SYNDROMES

The solitary rectal ulcer syndrome, localized colitis cystica profunda, inflammatory cloacogenic polyp, prolapsing mucosal folds in areas of diverticular disease, and inflammatory cap polyposis are closely allied conditions that have been linked to large bowel mucosal prolapse and trauma.[352-356,396-400] Affected patients with solitary rectal ulcer, localized colitis cystica profunda, and inflammatory cloacogenic polyp often demonstrate abnormal function of the anal and pelvic floor musculature during defecation[352,401,402] that leads to rectal mucosal prolapse or even intussusception. The resulting trauma is thought to cause the clinical symptoms and the pathologic changes. The term *solitary rectal ulcer syndrome* is quite a misnomer because the ulcers are often multiple, a preulcer polypoid phase is reported, and similar lesions occur in the anal canal and proximal colon.[352,356,396,397] The terms *colitis cystica profunda* and *inflammatory cloacogenic polyp* are also misnomers. Because all three conditions share a common histologic

appearance, clinical presentation, clinical course, and pathogenesis, we prefer to consider them together under the heading *mucosal prolapse syndromes*.

Patients with mucosal prolapse syndrome range in age from 10 to 83 years with the majority presenting in the third and fourth decades of life. The condition occurs more commonly in women. All patients report difficulties in defecation. Other common symptoms include rectal bleeding, passage of mucus, anal and abdominal pain, and intermittent bowel habits in which periods of constipation interrupt bouts of loose stools. Furthermore, surprising numbers of patients admit to the use of digital manipulation, spoons, or other instruments to assist in rectal evacuation.

The diagnosis of mucosal prolapse syndromes can be difficult because the history often suggests primary inflammatory or ischemic bowel disease. In addition, mucosal prolapse is often covert requiring special techniques such as evacuation cine proctography and defecography to demonstrate abnormalities in these patients.[352,356,401,403]

Ulcers, when present, typically occur on the anterior or anterolateral wall of the rectum, are irregular in shape, and often appear well demarcated. In patients without ulceration, the mucosa appears polypoid, roughened, or erythematous. Inflammatory cloacogenic polyp[398,399] involves the lower rectum and anal transition zone. The clinical impression in patients with mucosal prolapse syndromes is often incorrect and includes ulcer, Crohn's disease, nonspecific proctitis, carcinoma, and villous adenoma.[355]

The characteristic histopathologic changes are found in the mucosa adjacent to the ulcers or in the polypoid areas and consist of fibromuscular obliteration of the lamina propria associated with mucosal architectural distortion often with a hyperplastic or villiform appearance (see Fig. 23-60).[352-355,397] Inflammation is typically mild or absent and mucosal capillaries can be ectatic. Superficial erosions occasionally occur and can be associated with acute inflammation and the formation of inflammatory pseudomembranes. On occasion, colonic glands may be misplaced into the muscularis mucosae or submucosa, a histologic pattern referred to as *localized colitis cystica profunda*. Submucosal vessels may also be ectatic and hyalinized. The histologic features of specimens obtained from ulcerated areas appear nonspecific and usually show fibrinopurulent debris, fibrosis, and granulation tissue.

Differential diagnostic considerations include mucinous adenocarcinoma, chronic UC, Cowden's disease, and ulcers resulting from ergotamine suppositories. The misplaced glands of mucosal prolapse syndrome (colitis cystica profunda) simulate pseudoinvasion seen in adenomas; these glands can be associated with dissecting mucous pools and easily can be mistaken for invasive mucinous adenocarcinoma. Table 23-2 illustrates histologic features that aid in this differential diagnosis.

The mucosal abnormalities of mucosal prolapse syndrome also closely mimic chronic UC. Knowledge of the clinical picture and recognition of the characteristic fibromuscular obliteration of the lamina propria (not usually present in IBD) are helpful in this distinction. The histologic appearance of colorectal polyps from patients with Cowden's disease appears identical to the histologic features seen in mucosal prolapse syndrome.[304] Mucosal prolapse syndrome and Cowden's disease must be separated on clinical grounds. Clinical history is also required to separate the rectal ulcers associated with the use of ergotamine suppositories from mucosal prolapse. These lesions can be grossly and microscopically identical to those seen in mucosal prolapse syndrome.[404]

The few studies with long-term follow-up report a chronic, stable appearance to the lesions.[352,396,405] Most patients with mucosal prolapse syndrome tolerate their symptoms following reassurance that they do not have cancer, the addition of fiber to the diet, and instruction to reduce straining and to avoid digital manipulation. The rare patient with severe bleeding or obstruction requires excisional therapy. Medical remedies such as sulfasalazine, local or systemic corticosteroids, and antibiotics are useless.[352,355,396] Unusual patients with severe, incapacitating symptoms have been treated by resection, diverting colostomy, or rectal prolapse repair. Results of these operations have varied and because approximately 100 different operations have been described for mucosal prolapse syndrome, comparisons are difficult.

Classification of Inflammatory Bowel Disease in Resection Specimens

Inflammatory conditions of the colon can be caused by specific agents or conditions, such as bacteria or ischemia, or can be nonspecific. After specific causes of colitis have been ruled out, one is left with a group of diseases referred to as *nonspecific or primary IBD*. These include UC, Crohn's disease, and IBD type indeterminate (unclassified colitis). In most cases, careful examination of gross and microscopic features will allow categorization of these nonspecific IBDs into either UC or Crohn's disease.[406] Approximately 10% of cases will cause significant differential diagnostic problems by illustrating ambiguous features. These cases are best classified as IBD type indeterminate (see later).

Pouches and Fulminant Colitis

Evolving surgical techniques have changed the pathologist's role in the analysis of IBD. Patients with UC have several surgical options that either create continence through ileostomy (Kock ileostomy) or preserve anal sphincter function and restore continuity to the bowel (ileal pouch–anal anastomosis).[406-408] These operations have in common the creation of a pouch or reservoir formed by interconnecting loops of terminal ilium. In general, these pouch procedures are contraindicated in patients with Crohn's disease because of increased morbidity such as fistula and abscess.[409] Furthermore, complications requiring pouch removal can result in loss of considerable lengths of small bowel, sometimes enough to cause short-bowel syndrome. In our experience, there is nothing quite like a pouch to bring out the Crohn's disease in someone. These cases highlight the limitations of the current pathologic classification especially in the setting of fulminant clinical disease.

Accurate pathologic diagnosis of colonic IBD contributes greatly to patient care. In patients who have had subtotal colectomy, relaxed and thorough pathologic examination of the colectomy specimen to rule out Crohn's disease is pos-

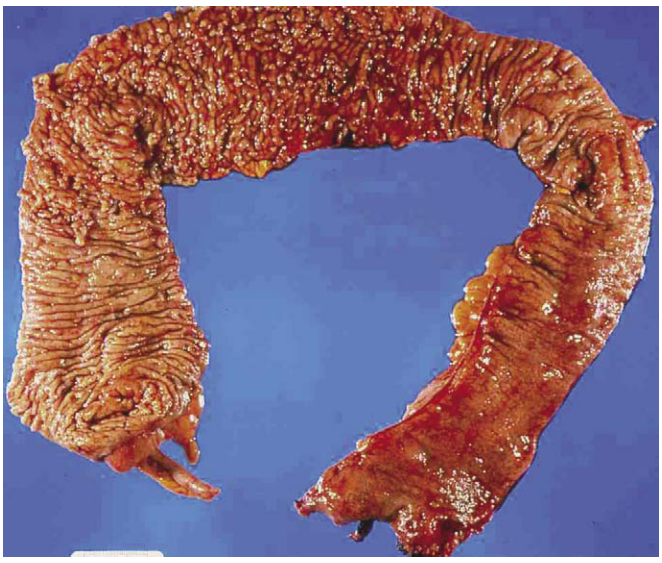

Figure 23-65 ■ Ulcerative colitis in a resection specimen. The distal margin is involved by the inflammatory process. More proximal inflammation occurs in continuity with an involved rectum. No skip areas, no deep ulcers, and no mural sinuses are present.

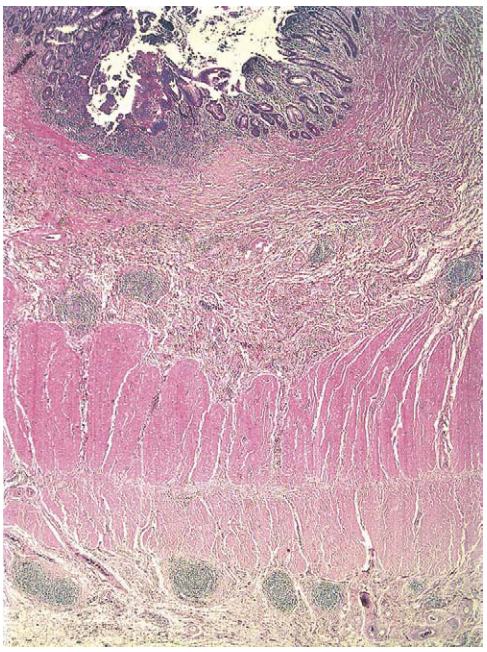

Figure 23-66 ■ Colonic Crohn's disease showing transmural lymphoid aggregates in an area not deeply ulcerated.

sible. A staged resection of the large bowel is still the safest and most advisable approach for patients with severe or fulminant colitis, even though it requires an additional operation to remove the rectum and a period with a temporary ileostomy. Although pathologic assessment and interpretation are more difficult in fulminant disease, the two-stage procedure still allows for a complete examination of the colectomy specimen before any contemplated pouch construction with ileal-anal anastomosis. Some surgeons do not consider two-stage proctocolectomy necessary for selected patients with colonic IBD. The one-stage operative approach therefore requires accurate preoperative diagnosis and emphasizes the importance of clinical evaluation, radiologic examination, endoscopic analysis, and proper interpretation of mucosal biopsy specimens (see earlier).[406]

Pouch complications include inflammation, fistula, obstruction, incontinence, and anastomotic leaks.[406,407] Although many complications result from surgical and mechanical difficulties, and others relate to the development of "primary" inflammation in the pouch (see "Pouchitis," later), some of these complications represent pouch recurrence of initially unrecognized Crohn's disease. These cases illustrate the inability to differentiate UC from Crohn's disease reliably in severe colitis, even after thorough examination of the colectomy specimen.[410] All reports of surgical experience with ileal pouch–anal anastomosis for presumed UC contain approximately 2% to 7% of patients in whom the final diagnosis proves to be Crohn's disease.[406,409-412]

We recommend use of a three-tiered classification system for primary IBD in colon resection specimens: UC, Crohn's disease, and IBD of indeterminate type. The definitive diagnosis of UC requires all the following features: diffuse disease limited to the large intestine, involvement of the rectum, more proximal colonic disease occurring in continuity with an involved rectum (i.e., no gross or histologic skip lesions), the absence of deep fissural ulcers, the absence of mural sinuses, and the absence of transmural lymphoid aggregates or granulomas (Fig. 23-65).[406,413,414] The definitive diagnosis of Crohn's disease requires histologic verification with the demonstration of transmural lymphoid aggregates in an area not deeply ulcerated or the presence of non-necrotizing granulomas (Figs. 23-66 and 23-67).[406,413-416] When the gross and clinical features suggest Crohn's disease by the presence of skip lesions, linear ulcers, cobblestoning, fat wrapping, or terminal ileal inflammation, extensive histologic sampling to find the definitive histologic features of Crohn's disease is suggested (Fig. 23-68).

The term *primary IBD of an indeterminate type* is used for cases of idiopathic colonic IBD that have ambiguous pathologic features in the resection specimen and are inconclusive for a diagnosis of UC or Crohn's disease.[406,410,413-418]

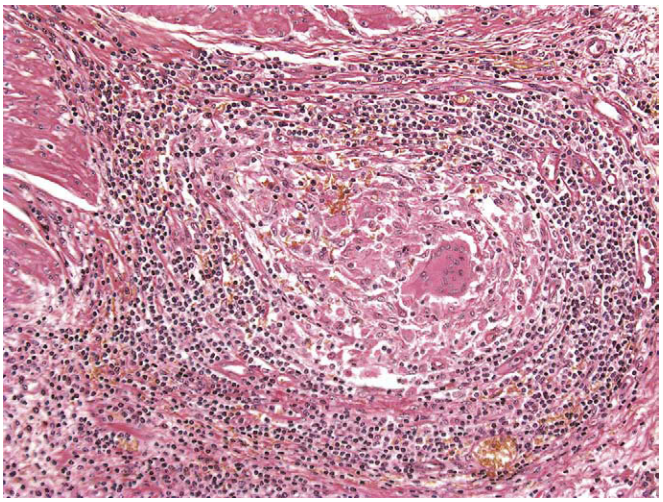

Figure 23-67 ■ A non-necrotizing granuloma in a patient with Crohn's disease.

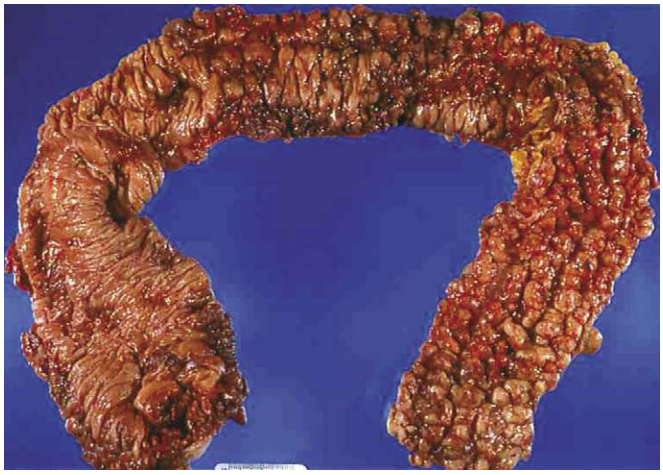

Figure 23-68 ■ Resection specimen of colonic Crohn's disease. The cobblestoning within the descending colon gives way to patchy areas of ulcer with intervening normal mucosa in the right colon.

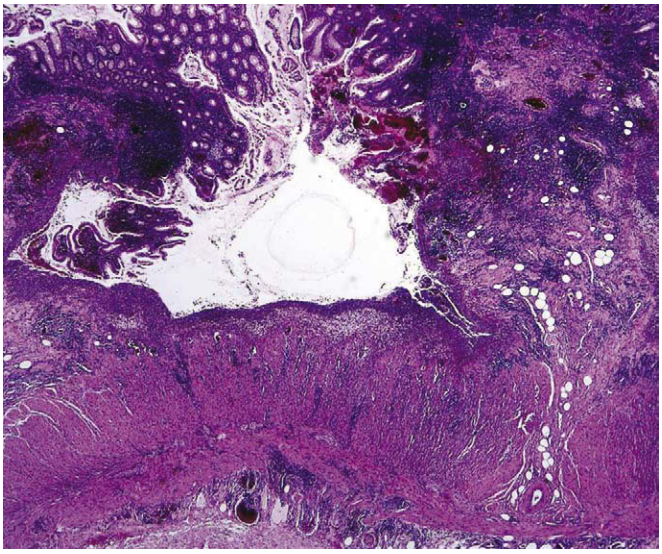

Figure 23-70 ■ Fulminant primary inflammatory bowel disease, type indeterminate. Deep ulcers extend into the muscularis externa and are associated with transmural lymphoid aggregates.

These cases are usually accompanied by fulminant clinical colitis, a setting in which transmural inflammation and deep fissural ulcers (features usually associated with Crohn's disease) can be found in patients with a clinical course that indicates UC (Figs. 23-69 and 23-70).

The classification system has prognostic significance. The pouch failure rate in indeterminate colitis (≈19%) is intermediate between that seen with Crohn's disease (≈48%) and that reported in UC (≈8%). Even so, patients without clinical, endoscopic, or radiologic evidence suggestive of Crohn's disease in whom the final pathologic results are indeterminate generally are considered suitable for ileal pouch–anal anastomosis.[406,414,418-423]

Lesions Associated with Surgery for Inflammatory Bowel Disease

DIVERSION COLITIS

Colon and rectum surgically placed out of circuit acquire histologic changes associated with defunctioning alone, regardless of the original reason for diversion.[424-427] The changes reflect a physiologic response to stasis and the loss of trophic factors in the feces, most notably short-chain fatty acids.[428] Most patients are asymptomatic. The mucosa of the diverted segment appears erythematous, granular, and friable (Fig. 23-71). Histologic changes include marked lymphoid hyperplasia with germinal center formation, usually accompanied by mild colitis with crypt abscess formation (Fig. 23-72). These changes may be indistinguishable from follicular proctitis (ulcerative proctitis or localized UC).[429] With time, the muscularis mucosae hypertrophies, the submucosa shows fatty and fibrous tissue infiltration, the muscularis propria thickens, and the lumen becomes progressively smaller.[406] The mucosal lymphoid hyperplasia may be accompanied by lymphoid aggregates scattered in the deep submucosa and muscularis externa and may occur in diverted segments in patients without IBD. Care must be taken not to base a diagnosis of primary IBD, especially

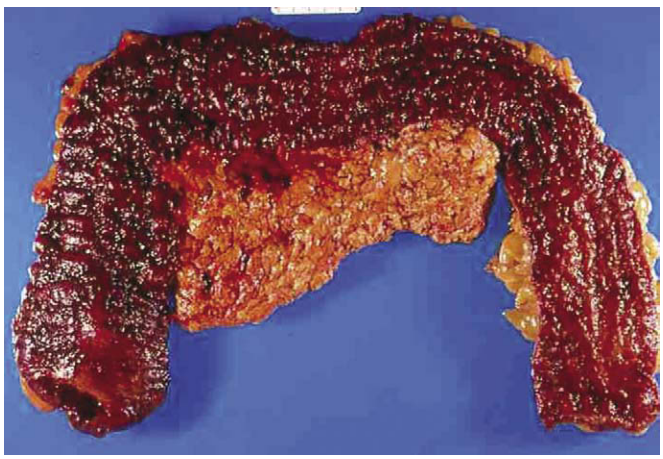

Figure 23-69 ■ Fulminant primary inflammatory bowel disease of an indeterminate type showing deep linear ulcers and areas of serositis.

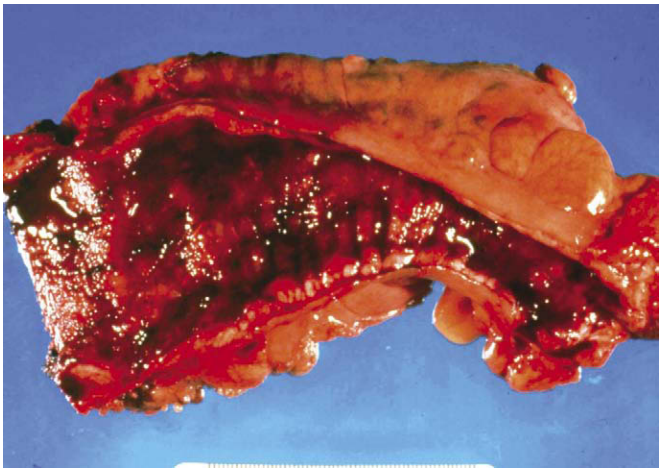

Figure 23-71 ■ Defunctioned rectum showing an erythematous and granular mucosa with mural thickening.

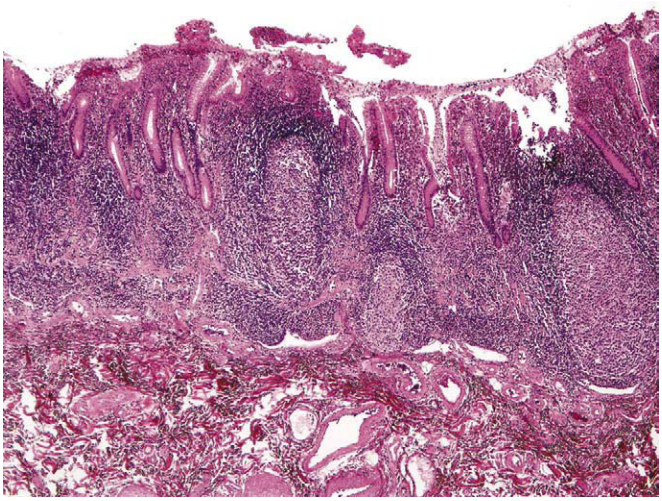

Figure 23-72 ■ Microscopic sections from defunctioned rectum showing mucosal architectural distortion and marked mucosal lymphoid hyperplasia.

Crohn's disease, solely on the histologic changes seen in diverted specimens. In many patients, the rectum is placed out of circuit during an operation for primary IBD. In these instances, the rectum can show changes of both IBD and diversion. The histologic changes in a defunctioned rectum do not correlate with the original diagnosis or clinical outcome.[430]

ILEAL RESERVOIRS (POUCHES) AND POUCHITIS

A late complication of Kock pouch and ileal pouch–anal anastomosis is the development of "primary" inflammation in the pouch with its associated clinical syndrome termed *pouchitis*.[431,432] The reported incidence ranges from 8% to 46%. This wide range may be the result of the lack of an accepted case definition of pouchitis. Patients generally experience nausea, vomiting, malaise, fever, and abdominal cramping. The increased effluent/stool from the pouch may be watery, foul smelling, or grossly bloody. Patients frequently become incontinent. Pouch bacterial ecology is often altered and many patients respond to antibiotics such as metronidazole and ciprofloxacin, a finding that suggests a bacterial cause in some cases. Some patients have required 5-aminosalicylates, sulfasalazine, corticosteroids, immunomodulators, or even pouch excision to manage symptoms.[432]

Pouch biopsy may be performed to confirm the presence of inflammation or to evaluate the possibility of Crohn's disease.[433] Pouch biopsy specimens from nondysfunctional pouches can show mild villus shortening and increased chronic inflammation with augmented crypt proliferation. Most specimens from pouches that are functioning well resemble normal terminal ileum. A few neutrophils within surface epithelium and within the lamina propria are commonly seen in pouches that are functioning well.[432-436] In contrast, pouches with classic pouchitis show decreased epithelial mucin and decreased or absent lymphoid follicles. The most consistent finding in this classic form of pouchitis has been ulcers with granulation tissue and patchy accumulations of neutrophils within crypt epithelium and within the lamina propria with deep crypt abscess formation.[432,433,435,437,438] To define pouchitis more precisely, Sandborn proposed the Pouchitis Disease Activity Index.[432,434] In this system, up to 12 points are awarded for various clinical and endoscopic findings. The amount of neutrophilic infiltration and the degree of ulceration are graded on a scale of 1 to 3 points each. Histologic findings are weighted in this system because pouchitis is diagnosed in patients who have 7 or more points.

Many investigators report an inconsistent relationship between endoscopic and histologic changes in the pouch and patients' symptoms. Therefore, many clinicians diagnose pouchitis on clinical criteria and reserve endoscopic examination with biopsy for those patients with refractory pouchitis or possible Crohn's disease.[432,433,439,440] Unfortunately, no reliable endoscopic or histologic criteria are available to differentiate most examples of pouchitis from a new onset or recurrence of Crohn's disease in the pouch. Confusion over pouchitis is easily understood when one considers that the clinical syndrome of pouchitis probably represents at least six different conditions (Table 23-8).[406,432,433]

The two variants of antibiotic-responsive pouchitis syndromes are classic pouchitis and jejunal bacterial overgrowth.[432,433,441] *Classic pouchitis* is associated with endoscopic and histologic findings that support the pouch as the source of clinical symptoms.[431-434,436,439] Patients with classic pouchitis usually respond to antibiotics such as metronidazole and ciprofloxacin. Occasional patients with clinical symptoms of pouchitis have had endoscopically and histologically negative pouches but have responded to antibiotics.[431,432] Although rare, some of these patients have had *proximal jejunal bacterial overgrowth,*[442] probably as a result of pouch distention causing an *ileal brake phenomenon* that decreases motility in the proximal intestine.[442,443] This decreased motility may predispose some individuals to proximal small bowel bacterial overgrowth.

Pouchitis syndromes refractory to antibiotic therapy include irritable pouch syndrome, short-strip pouchitis ("cuffitis"), Crohn's disease, and chronic primary refractory pouchitis.[432,433] Patients with irritable pouch syndrome may have severe clinical symptoms but demonstrate normal pouch endoscopy and histology. Some of these patients respond to dietary fiber supplements and antidepressant therapy.[432] To obtain a better-functioning pouch, many surgeons have abandoned rectal mucosectomy in the ileal pouch–anal anastomosis procedure.[432,444] In short-strip pouchitis, clinical symptoms may be caused by exacerbation of UC in the small retained rectal segment.[432,445] Many patients with this form of pouchitis have responded to topical corticosteroids or mesalamine.

TABLE 23-8

Pouchitis Syndromes: Proposed Classification

Antibiotic-Responsive Pouchitis Syndromes
Classic pouchitis
Proximal jejunal bacterial overgrowth
Chronic and Refractory Pouchitis Syndromes
Irritable pouch syndrome
Short-strip (segment) pouchitis
Crohn's disease (refractory pouchitis with Crohn's-like histology)
Chronic primary refractory pouchitis

Although debated,[446] missed Crohn's disease is likely to manifest as a late pouch fistula or abscess rather than as refractory pouchitis. In occasional reported cases of refractory pouchitis, pouch biopsy specimens contained granulomas or the excised pouch showed histologic criteria for Crohn's disease.[414,433,436] Invariably, the original colectomy showed either missed Crohn's disease or colitis of an indeterminate type.[414] These cases are best classified as Crohn's disease.[406,414,433] Patients with chronic pouchitis should be investigated with endoscopy and biopsy to rule out Crohn's disease or CMV infection, which has been linked to some cases of refractory pouchitis.[432,447] Routine biopsy specimens of the pouch should be examined as well as biopsy specimens of the afferent limb. Afferent limb ulcers tend to correlate with Crohn's disease and, in patients who do not have Crohn's disease, with the use of NSAIDs.[448]

We have seen cases of refractory pouchitis requiring surgical removal of the pouch. After careful pathologic evaluation, no specific infection and no criteria for Crohn's disease can be found in either the excised pouch or the original colectomy specimen.[414,433,436] These cases are best categorized as *primary refractory pouchitis*. The causes of classic pouchitis and primary refractory pouchitis are unknown but are probably related to a combination of stasis, bacterial overgrowth, the abnormal immune response of patients with IBD, or perhaps associated colonic-type metaplasia, which is reported to occur in a minority of pouches (see later).[432,433,449]

Some investigators have identified histologic patterns of mucosal adaptation in pouches.[450-452] Approximately 50% to 60% of patients exhibit what has been called *type A mucosa* with normal small bowel biopsy histology or only mild mucosal atrophy with no or minimal inflammation. *Type B mucosa,* characterized by transient atrophy with temporary moderate to severe inflammation followed by normalization of intestinal mucosa, is seen in 30% to 40% of patients. *Type C mucosa* with permanent persistent atrophy and severe inflammation occurs in up to 10% of pouches. Colonic-type features have been reported at least focally in pouches of all types by routine morphology, mucin histochemistry, immunohistochemistry, lectin binding, or electron microscopy. This colonic-type change is best developed in type C mucosa but is not complete. All pouches seem to retain mostly small bowel properties regardless of mucosal type or the duration of the pouch.

POUCHES AND DYSPLASIA

With long-term follow-up, it appears that epithelial dysplasia can rarely develop in the pouch. This extremely rare complication seems to be limited to the subgroup of patients (<10%) in whom refractory pouchitis and colonic-type metaplasia develop (type C mucosa).[450-452] Most investigators suggest yearly pouch surveillance once type C mucosa is established. However, until further information on cancer risk is available, it would seem prudent to survey types A and B mucosa as well, perhaps every other year.[433,453]

Dysplasia can also develop in the small retained rectal segment (often incorrectly referred to as the anal transition zone) in patients who have had restorative proctocolectomy and stapled ileal pouch–anal anastomosis.[454] Annual endoscopic surveillance with biopsy for these retained rectal segments seems prudent. The incidence of dysplasia is rare (<3% of patients), correlates with the original colectomy specimen containing dysplasia or cancer, and can be safely treated by completion mucosectomy.[454-456]

COLOSTOMY CHANGES

Specimens from colostomy revisions usually show changes associated with trauma and mucosal prolapse such as erosions, ulcers, hemorrhage, acute and chronic inflammation, and fibromuscular obliteration of the lamina propria. One often encounters peri-intestinal fibrosis and suture granulomas. Inflammatory polyps can be seen as well.

Other Forms of Colitis

Eosinophilic Colitis and Proctitis

Infiltration of the large intestine by large numbers of eosinophils can be seen in *eosinophilic gastroenteritis*. These patients usually show peripheral blood eosinophilia and have a clinical history of atopy.[457-460] The entity that has been termed *allergic proctitis* is in our opinion a form of UC.[461] Whenever large numbers of eosinophils are encountered in a colorectal biopsy specimen, this finding should prompt thorough search for parasites, especially *Strongyloides* species. The most common form of allergic proctitis or colitis occurs in infants as a result of dietary protein–related allergy. These children present typically with rectal bleeding, sometimes with diarrhea.[462,463] Colorectal biopsy specimens show increased numbers of eosinophils within the lamina propria, occasionally with focal active colitis. Biopsy specimens that contain more than 60 eosinophils per 10 high-power fields are suggestive of this disease.[463]

Graft-versus-Host Disease

Allogeneic bone marrow transplantation can be complicated by acute or chronic GVHD.[360,464-467] The changes of acute GVHD (apoptotic colopathy) in mucosal biopsy have been described and various grading systems for acute GVHD are used.[360,466,467] Grade 1 acute GVHD correlates with increased apoptosis alone. Grade 2 changes include crypt abscesses as well as apoptotic bodies (see Fig. 23-61). Total necrosis of crypts is classified as grade 3, whereas denudation of areas of bowel is considered grade 4.[360] Biopsy specimens should be carefully examined for CMV infection. CMV may also cause apoptotic change that can mimic GVHD and occasionally both conditions can coexist.[467]

Apoptosis is seen with damage associated with chemotherapy and irradiation. Patients receiving bone marrow transplantation for malignant conditions are prepared with chemotherapy and irradiation; therefore, distinguishing the effects of therapy from GVHD without a clinical history is impossible. Histologic changes associated with chemotherapy and irradiation typically resolve in 7 to 10 days.[464,466] Apoptotic colopathy identical to grade 1 GVHD can be seen in immunodeficiency syndromes, in patients receiving mycophenolate mofetil, and in primary AIDS-related colitis. Grade 4 GVHD cannot be distinguished from ischemic damage without a clinical history.

Chronic GVHD usually spares the colon but a few examples have been described. The pathologic changes include

submucosal fibrosis, mucosal calcification, and fibrosis of the lamina propria.[360,464,467] Chronic colitis–like changes have been seen in a subset of patients with GVHD; the relationship between this condition and chronic GVHD requires more study.[468]

Ulcerative Proctitis

A localized form of UC with a better prognosis has been described as *mucosal proctosigmoiditis, follicular proctitis,* or *ulcerative proctitis.*[469-471] The gross and endoscopic mucosal appearance resembles that seen with more extensive forms of UC. Mucosal biopsy specimens typically show changes of UC but some have shown prominent mucosal lymphoid aggregates (follicular proctitis) (Fig. 23-73).[429] Most patients respond to the local administration of corticosteroids or 5-aminosalicylates; approximately 10% of patients develop more extensive colitis.[469,470] Some evidence suggests that patients with prominent lymphoid follicles are less likely to respond to treatment.[429]

Inflammatory Bowel Disease and Diverticular Disease

Inflammatory changes are relatively common in patients with diverticular disease and are often related to trauma or prolapse.[356] IBD and diverticular disease are both common and occasionally coexist. UC-like inflammation in association with diverticular disease has been described.[332] Crohn's disease and diverticular disease share similar features such as focal mucosal inflammation, stricture, and fistula. Frequently, the pathologist will ascribe all the changes to one disease (usually diverticular disease) and overlook the concurrent IBD (usually Crohn's disease). Features that suggest Crohn's disease in this setting are the presence of fissural ulcers, patchy active mucosal inflammation outside diverticula, granulomatous inflammation, and internal fistulas other than colovesical or colovaginal fistula. Approximately 15% to 20% of patients develop other bowel lesions of IBD on follow-up.[472-477]

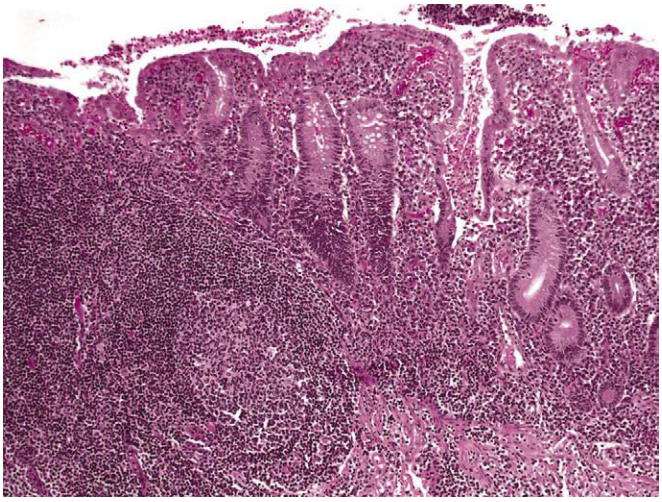

Figure 23-73 ■ Follicular proctitis showing typical changes of ulcerative colitis (crypt distortion, mucin depletion, and crypt abscesses) along with prominent mucosal lymphoid aggregates.

Mast Cell Disease

Systemic mastocytosis is a rare disorder characterized by the infiltration of mast cells and eosinophils in the skin, bones, lymph nodes, and other organs such as the GI tract.[478-480] One group of investigators suggested that colorectal biopsy specimens showing more than 20 mast cells per high-magnification field as highlighted by CD117 or mast cell tryptase immunostain should be diagnosed as mastocytic enterocolitis, a disease best treated with antihistamines or mast cell stabilizers.[481] This controversial study did not control for thickness of immunohistochemically stained sections and lacked a treatment control group, thus making such conclusions premature. Mast cells coexpressing CD25 usually indicate neoplastic mast cells.[480]

Dysplasia and Cancer in Inflammatory Bowel Disease

Ulcerative Colitis and Carcinoma

Patients with long-standing UC are at increased risk for colorectal carcinoma.[322] The prevalence of colorectal cancer in patients with UC is estimated to be 3.7% overall and 5.4% for those with pancolitis.[482] Those at greatest risk are patients with extensive colitis[483,484] who have been afflicted for more than 8 to 10 years. The cumulative risk of cancer in a patient with UC is approximately 2% at 10 years, 8% at 20 years, and 18% at 30 years.[482,485] Early age at onset of colitis, family history of colorectal cancer, histologic evidence of active inflammation, and sclerosing cholangitis may also increase the risk.[483-495]

Colitis-associated carcinoma makes up only a small proportion of total colorectal cancer cases, but these tumors are particularly bothersome to the medical community. They frequently occur in young patients and often develop insidiously even while the patient is under active medical care. Many times the carcinomas are not clinically apparent until distant spread has occurred.[488,489] Colitis-associated carcinomas are often flat and infiltrative and difficult to visualize with standard radiographic and endoscopic techniques.[1] Because the symptoms associated with carcinoma mimic those of colitis, diagnosis is often delayed.

The estimated risk of carcinoma complicating UC varies considerably. However, epidemiologic data suggest that patients with UC have 6 to 8 times the risk of developing carcinoma when compared with the general population, and looking at the subgroup of patients with UC who have extensive colitis, the risk is 15- to 19-fold.[483,490] This increased risk poses a management dilemma for physicians caring for patients not sick enough to require colectomy.

Several management options are available. First, the physician can ignore the risk. Many physicians prefer this approach when dealing with an older patient or a patient who is not otherwise a surgical candidate, especially if the actual cancer risk is believed to be low.[491] A second management approach is prophylactic colectomy in patients with colitis for longer than 8 to 10 years.[491] This may be the best approach when dealing with a young patient because of the expected long duration of cancer risk and the possibility that surveillance can fail.[489] Furthermore, the results of ileal

pouch–anal anastomosis are better in young patients. Although prophylactic colectomy theoretically eliminates the cancer risk, several factors have made this approach generally unacceptable. Patients with extensive colitis for more than 8 to 10 years are often asymptomatic or have only mild disease. Such patients often find it difficult to accept the risks associated with major surgery, the possible morbidity associated with mobilizing the rectum, or the social implications of a permanent ileostomy (in the event of a pelvic pouch failure). Besides, most studies suggest that prophylactic colectomy would have been unnecessary in the majority of patients because they would not have developed carcinoma.[1,484]

A third option is colonoscopic surveillance with biopsy. The strategy of such surveillance is to identify a marker that signals a subgroup of patients with colitis who are at increased risk for carcinoma or the detection of carcinoma in an early, curable phase.[1,484,491] Currently, recognition of dysplasia in surveillance biopsy specimens is used as such a marker. Dysplasia, the presumed precancerous epithelial change, has been regularly recognized in colectomy specimens both adjacent to and distant from colitis-associated carcinomas.[1,322] Circumstantial evidence suggests that dysplasia may not only be the marker for carcinoma but also may itself be the carcinoma in a preinvasive phase.[1,322]

Dysplastic epithelium can occur in grossly flat mucosa, in mucosa with a villous or plaquelike configuration, or in a nodular growth resembling adenoma (Fig. 23-74).[1] Dysplasia is recognized by histologic examination of biopsy specimens using well-defined cytologic criteria that include nuclear enlargement with hyperchromasia, increased mitotic figures, and decreased intracellular mucin.[1,322] Most colitis-associated dysplasia resembles adenomas seen in patients without colitis.

The pathologist should use the term *dysplasia* only as a synonym for intraepithelial neoplasia and not in reference to reactive or reparative changes seen with active inflammation. The distinction between repair and dysplasia can be difficult, requires experience, and in certain instances can be impossible. In general, cytologic abnormalities seen in the presence of active inflammation must be interpreted with caution.[1,322]

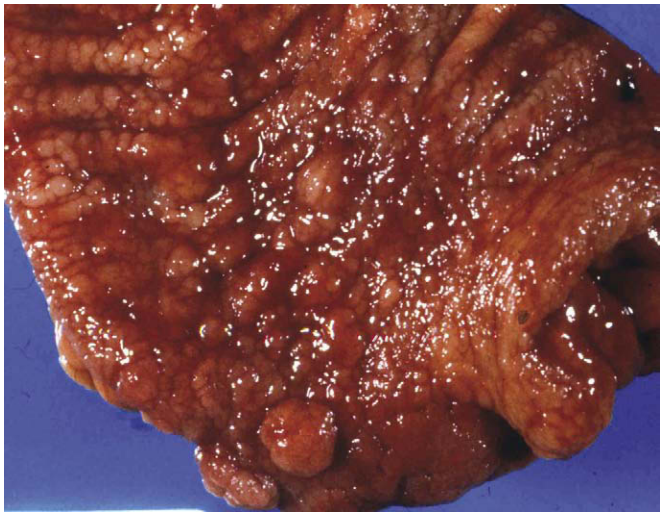

Figure 23-74 ■ Adenoma-like dysplasia lesion in ulcerative colitis. An invasive adenocarcinoma was discovered on histologic examination of the central ulcerated area.

Similar features can be seen in repair and dysplasia and no one histologic feature is absolute in making the distinction.[1] Both conditions are associated with nuclear enlargement and hyperchromasia, increased mitotic figures, and decreased intracellular mucin. Some features favor repair over dysplasia. Although cells undergoing repair demonstrate nuclear enlargement with hyperchromasia, these nuclei are often evenly spaced and not crowded, round to oval with a smooth external nuclear contour, contain granular chromatin with a single or multiple chromocenter or nucleoli, and are remarkably similar to one another in size and appearance. In contrast to dysplasia, the nuclear-to-cytoplasmic size ratio of regenerative cells is often actually decreased, especially in cells adjacent to ulcerated areas. During this phase, the cell cytoplasm is often eosinophilic. Nearby crypt abscesses or neutrophils within epithelium (cryptitis) help to confirm the diagnosis of repair. As a general rule, reparative epithelial change is limited to or accentuated in the crypt base and will not extend onto the surface of the crypt.

Features that favor dysplasia over repair are variable nuclear hyperchromasia, nuclear pleomorphism, irregular external nuclear contours, nuclear stratification with irregular nuclear crowding and overlap, and a loss of nuclear polarity. The changes of dysplasia usually extend onto the surface of the crypt. Major distortions of mucosal architecture also favor dysplasia.

The Inflammatory Bowel Disease–Dysplasia Morphology Study Group proposed a three-tiered classification for biopsy interpretation in IBD: positive, negative, and indefinite for dysplasia.[322] Our experience has shown that this classification is useful and reasonably reproducible.[1,492] Biopsy specimens negative for dysplasia include normal colon and those biopsy specimens showing changes of active or quiescent UC. Positive biopsy specimens are reported as showing high-grade dysplasia or low-grade dysplasia. Most dysplasias histologically resemble adenomas seen in patients without colitis, although some do not.[1] Dysplasias in this latter group are easy to miss.

In low-grade dysplasia, nuclear changes such as crowding, pleomorphism, hyperchromasia, and increased mitotic figures are present, but in general, the nuclei are limited to the basal half of the cell (Fig. 23-75). Usually, intracellular mucin is decreased, but on occasion intracellular mucin can be increased. Dystrophic or signet ring–type goblet cells are common in dysplasia although not pathognomonic. The general mucosal architecture should not be greatly disturbed.

The distinction between low-grade dysplasia and high-grade dysplasia is made largely on the degree of cytologic and architectural change. In high-grade dysplasia, hyperchromasia and pleomorphism are marked (Fig. 23-76). Stratification with loss of nuclear polarity is often present. Nuclei may be found in the luminal portions of the cells. High-grade dysplasia is often associated with a distortion of mucosal architecture, most often taking the form of a villous growth similar to villous adenomas seen in patients without colitis.

Biopsy specimens are classified as showing changes indefinite for dysplasia when cytologic abnormalities are

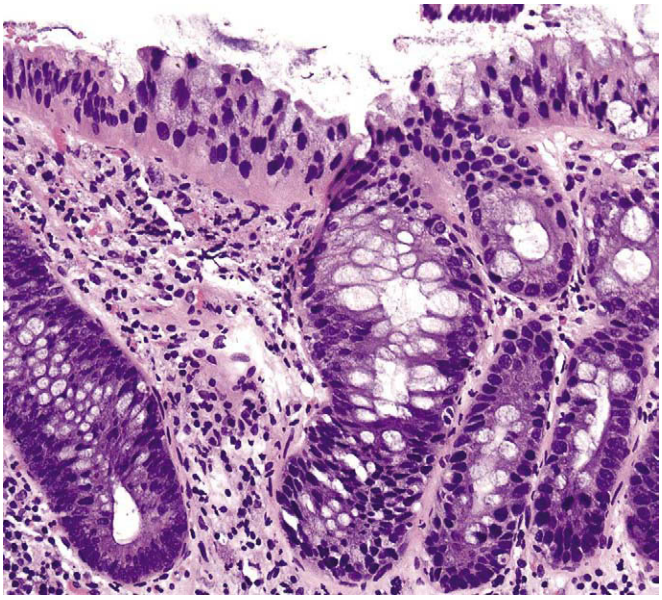

Figure 23-75 ■ Low-grade dysplasia in ulcerative colitis. The nuclei show variable hyperchromasia and pleomorphism but the nuclei for the most part maintain a basal orientation.

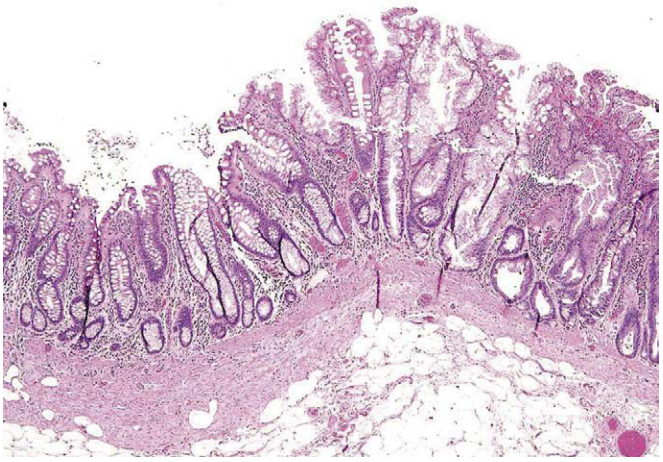

Figure 23-77 ■ This sessile serrated polyp–like lesion in ulcerative colitis is best classified as indefinite for dysplasia.

seen but these changes are of insufficient degree to warrant a diagnosis of true dysplasia. Indefinite changes are usually encountered in a background of active inflammation in which atypical epithelial changes could represent repair or regeneration rather than dysplasia. The indefinite category also includes odd mucosal patterns of growth that have not yet been observed to give rise to carcinoma (e.g., sessile serrated polyp–like change [Fig. 23-77], epithelial changes that resemble gastric foveolar epithelium). The category, *indefinite for dysplasia,* is a legitimate diagnosis alerting the treating physician that worrisome changes are present that may place a patient in a higher risk category that requires more frequent surveillance. The Inflammatory Bowel Disease–Dysplasia Morphology Group originally subdivided indefinite dysplasia into three groups: probably inflammatory, probably dysplastic, and unknown.[322] Obviously, in a category that is already uncertain, subcategorization is cumbersome, subjective, and associated with marked interobserver and intraobserver variation. Therefore, subdivision of biopsy specimens in the indefinite category is not recommended.[1]

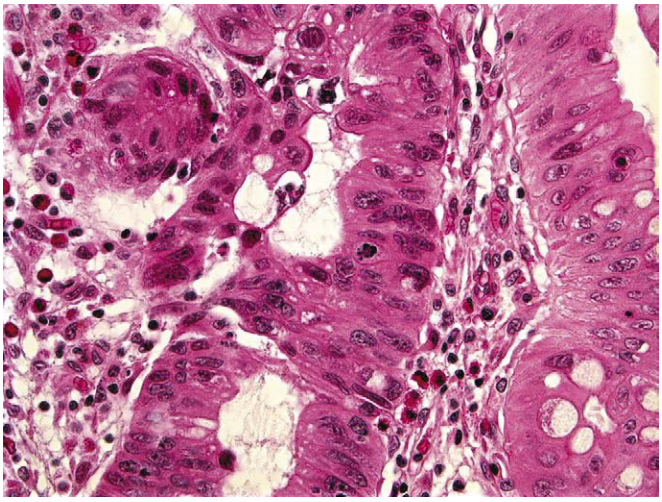

Figure 23-76 ■ High-grade dysplasia in ulcerative colitis showing a high degree of cytologic abnormality with full-thickness stratification of nuclei and with nuclei in the luminal portions of the cells.

COLONOSCOPIC SURVEILLANCE IN ULCERATIVE COLITIS

The use of 5-aminosalicylate compounds decreases the risk of cancer by 53% to 75%,[485,493] as does seeing the physician regularly and having more than one colonoscopy.[493] Most patients and physicians opt for lifelong annual or biannual colonoscopic surveillance.[1,485] Current practice guidelines recommend two to four biopsy specimens obtained every 10 cm throughout the diseased bowel in addition to special sampling of macroscopic lesions.[494] Compliance with this recommendation has been inadequate.[495-498]

Patients whose biopsy specimens remain negative for dysplasia can probably safely continue regular surveillance. Most authorities recommend annual total colonoscopic examination for patients with extensive UC who have had their disease for more than 8 to 10 years.[1,322,492,497] The surveillance interval can be increased to 2 to 3 years for patients with negative initial colonoscopy because in only 2% to 4% of these patients has disease been shown to progress.[489] Patients demonstrating epithelial changes indefinite for dysplasia should have shorter follow-up (e.g., 6 months to 1 year).[488,498] They must not be ignored because 28% of patients in whom the initial biopsy results were indefinite progressed to high-grade dysplasia and 9% progressed to cancer.[489] Management recommendations for patients with low-grade dysplasia in a flat mucosa are difficult because of the paucity of long-term follow-up information. Some clinicians consider it safe to continue short-term follow-up (e.g., 3 to 6 months) for patients with low-grade glandular dysplasia;[488,498] if dysplasia persists[1,497,499,500] or is associated with any suspicious gross lesion or stricture (dysplasia-associated lesion or mass [DALM]), colectomy should be considered.[1,322,484,501] Forty-three percent of reported patients with DALM already had carcinoma in immediate colectomy specimens.[489,501] Increasing numbers of experts have advo-

cated immediate colectomy for low-grade dysplasia.[487-489,502] These experts have stated that 19% of patients with low-grade dysplasia already had complicating carcinomas, and they also have cited a very high rate of progression to high-grade dysplasia or carcinoma with follow-up (54%, St. Marks, London; 53%, Mt. Sinai, New York; 33%, Mayo Clinic, Rochester, Minn).[485] These data are questioned because of case selection bias.[489] If high-grade dysplasia is encountered, then colectomy should be recommended because the risk of concurrent carcinoma is estimated to be as high as 42%.[1,489]

Experience with surveillance biopsy interpretation has shown that truly negative results are rarely interpreted as dysplasia, and dysplasia, especially high-grade dysplasia, is rarely missed.[1,492] That said, variations in interpretation do occur,[1,322,500,502-504] and in general confirmation of a biopsy diagnosis of dysplasia is desirable before colectomy.[1,322] Any one or more of the following may be considered adequate confirmation: finding of dysplasia in a repeat biopsy from the same site, finding of dysplasia in one or more additional sites during the same endoscopic examination, or review and confirmation of the original dysplasia interpretation by another pathologist experienced with the classification system.[1,322,485]

Surveillance endoscopy with biopsy has limitations. No compelling evidence proves that surveillance benefits the patient.[489,491,497,503,505] Participation in a surveillance program does not guarantee that lethal cancer will not develop.[488,489,491,497,500,505,506] Dysplasia is unusual and it is difficult for any one pathologist to acquire extensive experience. Therefore, errors in histologic interpretation can be expected. Dysplasia can be focal and is subject to tremendous sampling error.[1,488,492] Because most authorities consider dysplasia a neoplastic change, it is unlikely that it ever resolves spontaneously. Thus, a clinician should not be lulled into a false sense of security by negative follow-up biopsy results once true dysplasia has been identified.[1]

Although not proved scientifically, it seems likely that patients benefit from surveillance programs because many carcinomas are detected in a curable phase.[1,488,497,498,500,505] In addition, the incidence of carcinoma in patients whose biopsy specimen results have remained negative is low.[489,497,498] It is unclear whether this benefit justifies the large cost of surveillance endoscopy.[489,507] Finally, surveillance programs are pointless unless the patient complies with regular surveillance and agrees to colectomy when the end point (dysplasia) has been reached.[507]

OTHER SURVEILLANCE MARKERS

Many groups have searched for other markers for precancer in UC. Sialomucins predominate in cancer and dysplasia in UC but the role of mucin histochemistry findings is debated.[508] Results of lectin binding, CEA immunohistochemical study, and immunohistochemical analysis for products of c-*myc* and *ras* oncogenes have produced variable results and could not reliably differentiate dysplasia from repair.[1]

Several investigators described a correlation between DNA aneuploidy and dysplasia or carcinoma in UC.[509-511] However, only 80% to 90% of invasive carcinomas and 50% to 80% of dysplasia demonstrated DNA aneuploidy. This finding indicates that DNA analysis by flow cytometry could not be used alone in a cancer surveillance program. Many specimens (≥6%) interpreted as negative or indefinite for dysplasia showed DNA aneuploidy.[510,511] This finding can be interpreted in several ways. It could indicate technical problems linked to false-positive results including failure to disaggregate nuclear clumps, prolonged exposure of the sample to higher temperatures, and debris in the sample.[511,512] Alternatively, this test could identify a subgroup of patients different from the group identified by dysplasia that is showing objective chromosomal abnormalities in the absence of recognizable dysplasia. It is tempting to speculate that this DNA aneuploidy could be used as a marker of some carcinomas complicating UC, although other investigators concluded that the detection of DNA aneuploidy was not useful as a predictor of the presence of concurrent carcinoma in UC.[509-511] Until large prospective studies determine the usefulness of DNA aneuploidy in UC, histologic dysplasia is still the only reliable marker for cancer in a surveillance program.[1,513,514] DNA analysis could benefit some patients. Patients with diploid DNA content and no signs of dysplasia probably can be examined at longer surveillance intervals.[510,511] Approximately 90% of patients would fall into this category and a longer interval surveillance could save considerable amounts of money and time.

Adenomas in Inflammatory Bowel Disease

A special problem concerns the occurrence of adenoma in patients with colitis. Colorectal adenomas and IBD are both relatively common. Therefore, there is probably no reason that both conditions could not coexist. Because most IBD-associated dysplasias resemble adenomas,[1] the distinction in practice is often impossible. Management of patients with UC and adenoma has been controversial. Does the lesion represent a harmless sporadic adenoma or is it a dangerous DALM? In general, a pathologic diagnosis of "adenoma" in a patient with IBD must be carefully evaluated by the treating physician and should at least prompt further consultation with the pathologist because the lesion could represent IBD-associated dysplasia, an ominous change that implies a substantial risk for the development of carcinoma or for coexisting cancer.[1,515]

ADENOMA VERSUS DYSPLASIA-ASSOCIATED LESION OR MASS

Dysplasia in IBD can be broadly classified endoscopically as flat or raised. Raised lesions can be further subdivided into adenoma-like (i.e., discrete, well-circumscribed sessile or pedunculated lesions that resemble sporadic adenomas [see Fig. 23-74]) or non–adenoma-like (i.e., irregular plaque or masslike) lesions (Figs. 23-78 and 23-79).[1,516] Most experts recommend colectomy for flat high-grade dysplasia and endoscopically raised non–adenoma-like dysplasia lesions. Correct management of patients with UC who have endoscopically adenoma-like dysplasia is not clear. The differential diagnosis between conventional adenoma and dysplastic lesions in IBD has been the focus of several publications. Distinction based on pathomorphologic features has been proposed.[517,518] Although lesions can be classified histologically using this system, to date this approach has not been clinically validated. The study of Torres and colleagues[517] suggested that an admixture of normal and

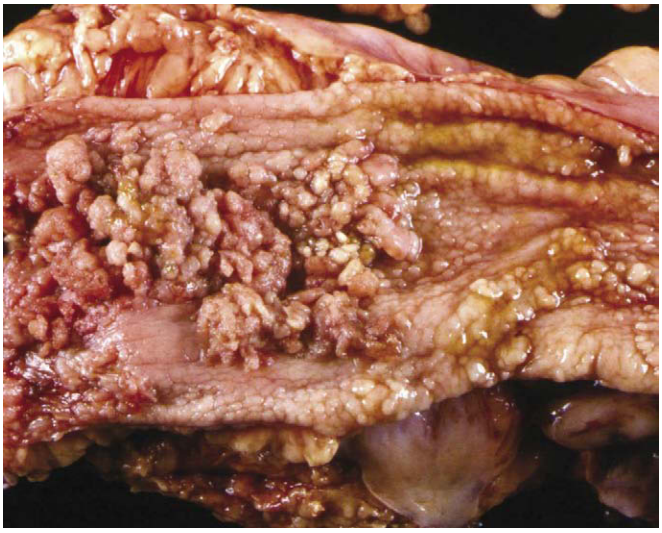

Figure 23-78 ■ Masslike dysplasia-associated lesion or mass (DALM) from a patient with ulcerative colitis.

dysplastic glands at the surface of the lesion could be used to distinguish IBD-associated dysplasia from conventional adenoma. Several drawbacks to this study limit its clinical usefulness. An association with carcinoma or flat dysplasia was definitional for IBD-associated dysplasia in this study. Furthermore, the study had limited clinical follow-up to determine whether the distinction based on this feature (admixture of normal and dysplasia at the surface) was clinically relevant in patients not yet known to have other areas of dysplasia or carcinoma. Many authorities believe that admixtures of normal and dysplastic glands are so highly prevalent in sporadic adenomas that this criterion is not helpful in practice.

Molecular analysis has been applied in an attempt to resolve this diagnostic problem. Odze and associates[519] reported a similar prevalence of 3p, APC, and p16 mutations in adenoma-like dysplasia lesions in UC and sporadic adenomas. However, non–adenoma-like dysplasia in UC showed significantly higher proportions of 3p and p16 mutation, a finding indicating different timing of molecular events in these lesions.[519] Although promising, these molecular approaches are technically difficult, are not generally available, and remain to be validated clinically.

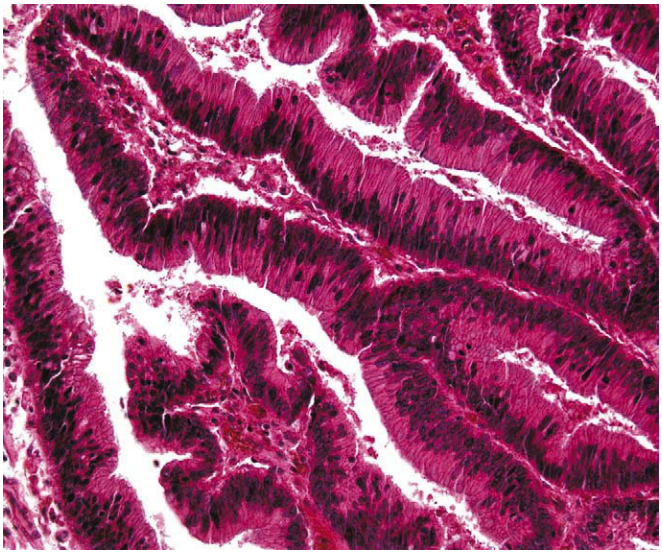

Figure 23-79 ■ Histologically adenoma-like dysplasia in ulcerative colitis. This histologic pattern can be seen in any of the gross or endoscopic configurations of dysplasia.

Immunohistochemistry has also been used in an attempt to discriminate between conventional adenoma and IBD-associated dysplasia.[520,521] p53 overexpression by immunohistochemical analysis that generally correlates with mutation of the corresponding tumor suppressor gene appears to be the most promising. p53 gene mutations reportedly occur earlier in IBD-associated dysplasia than in conventional adenoma or carcinoma. Therefore, strong p53 overexpression tends to correlate with IBD-associated dysplasia. Unfortunately, only 30% of IBD-associated dysplasias overexpress p53 (versus 5% of sporadic adenomas).[520,521] This p53 testing is probably not sensitive enough for routine practice. Combining p53 immunoreactivity with beta-catenin expression (which exploits the relatively low prevalence of *APC* gene mutation in IBD-associated dysplasia) or bcl-2 immunohistochemistry (which is more often overexpressed in sporadic adenomas) does not appear to improve the sensitivity or specificity of this approach.[520,521] Immunohistochemistry is clearly technically easier and more widely available. However, as with the molecular approaches outlined earlier, diagnoses based on immunohistochemistry have not been clinically validated.

PRACTICAL GUIDE TO PATIENT MANAGEMENT

Pathomorphologic, molecular, or immunohistochemical testing could eventually separate harmless sporadic adenomas from the more ominous DALMs in patients with IBD but this remains to be proved. In the meantime, follow-up information is sufficient to guide a careful physician facing this dilemma. The most important criterion for stratification is the topographic relation of the adenoma-like lesion to areas of colitis. Adenoma-like lesions occurring in areas not affected by colitis histologically or endoscopically have not been associated with a high risk of concurrent or subsequent carcinoma. These lesions should be considered conventional adenomas and treated by polypectomy alone.[1,516,517,520,522]

Management of adenoma-like lesions occurring in areas involved by colitis is more challenging. As many as two thirds of patients have had concurrent or subsequent invasive carcinoma at follow-up.[1,515,517,523] From a practical standpoint, we believe that it is prudent to consider all adenoma-like lesions occurring in areas involved by colitis as potentially IBD-associated dysplasia lesions. These lesions must be excised endoscopically and not merely sampled with biopsy.[523] The diagnosis of IBD-associated dysplasia alone in this unique setting (adenoma-like dysplasia in a macroscopic polyp) may not necessarily be an indication for immediate colectomy.[1,323,498,515-517,520,524] Endoscopic polypectomy alone may be adequate treatment provided that careful patient selection criteria are applied, including the following: (1) the patient is in an adenoma age group (>40 years of age), (2) the adenoma-like lesion is discretely defined macroscopically and can be excised in its entirety, (3) excision of the lesion appears complete to the endosco-

pist, (4) no flat dysplasia is identified in the colon, and (5) the colon is easy to survey (i.e., compliant patient without inflammatory polyposis). Current data suggest that the majority of patients managed in this fashion will follow a clinically benign course.[1,515,516,522-524] However, these patients must receive careful short-term surveillance. A 3- to 6-month initial surveillance interval can be increased to 6 months to 1 year following negative results of colonoscopy.[516] Colectomy should be recommended for patients not fulfilling these selection criteria.[515]

Dysplasia and Carcinoma in Crohn's Disease

Increasing epidemiologic and pathologic evidence suggests that patients with Crohn's disease are also at increased risk for the development of carcinoma.[1,525-527] Those patients who are younger than 21 years of age at the onset of Crohn's disease may be at even higher risk.[528]

Colonic carcinomas in patients with Crohn's disease have in general developed after about 20 years of disease.[1,525-532] The diagnosis is usually made clinically because a gross intraluminal lesion can often be visualized (Fig. 23-80). The colonic carcinomas have been better differentiated than their small bowel counterparts in Crohn's disease, with an increased prevalence of mucinous histologic features.[1,525,526,531]

Reports using current histologic criteria almost invariably note dysplasia in the epithelium adjacent to small bowel and colonic carcinomas in Crohn's disease.[1,525-527,531] Dysplasia distant from carcinomas has also been encountered in specimens exhibiting both colonic carcinoma and Crohn's disease. These features suggest that the dysplasia-carcinoma sequence similar to that proposed for UC also occurs in Crohn's disease.[1,526,531] A practice-based surveillance study of 259 patients with Crohn's colitis affecting at least one third of the colon for more than 8 years found that 16% of patients developed dysplasia or cancer at 16 years.[533]

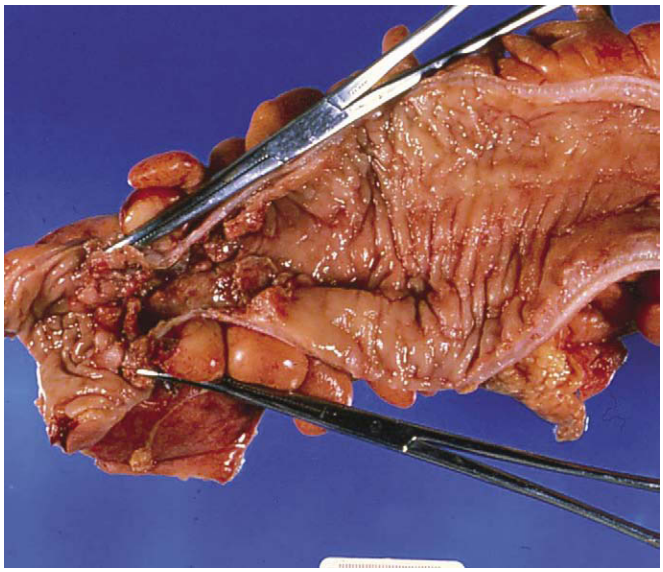

Figure 23-80 ■ Colorectal adenocarcinoma in patients with Crohn's disease often produces luminal lesions. This small, plaquelike area of dysplasia and the underlying carcinoma that is associated with a stricture mimic the inflammatory fibrostenosing lesions of Crohn's disease.

CANCER SURVEILLANCE IN CROHN'S DISEASE

Opinions vary regarding cancer surveillance in patients with long-standing Crohn's disease.[1,525-527,529,531,534] It is possible that surveillance could benefit an occasional patient with colonic Crohn's disease by detecting dysplasia or early carcinoma, but the safety, necessity, and benefit of regular cancer surveillance are questioned.[535] Colonoscopy may be technically impossible or dangerous in some patients with Crohn's disease. Retained rectal stumps are often strictured and inaccessible. The absolute number of colon carcinomas reported in Crohn's disease is still low, so again the expected yield of positive cases in a surveillance program would be quite small. Some experts advocate a UC-like surveillance strategy for patients with at least 8 years of Crohn's colitis involving at least one third of the colon.[485]

Rather than ignoring the risk in Crohn's disease, options are available for a cautious clinician.[1,534,535] A patient with recrudescence of colitis-like symptoms and a background of long-standing inactive Crohn's colitis should be thoroughly investigated for carcinoma.[526] Yearly surveillance of an out-of-circuit rectum seems reasonable considering that approximately 20% of the reported cases of large bowel cancer in Crohn's disease have occurred in such segments.[534,535] It may, however, be better to advise removal of the defunctioned rectum, especially if reanastomosis is not planned, not possible, or contraindicated. The presence of dysplasia in a biopsy specimen from a patient with Crohn's disease must alert the physician to the possibility of coexistent invasive carcinoma. In this situation, management approaches similar to those proposed for dysplasia in UC are recommended.[1,321,526] Clinicians should also recognize that chronic fistula or anal stricture in Crohn's disease may be complicated by squamous carcinoma or adenocarcinoma.[1,530] Any abrupt change in the volume or nature of a fistula discharge or the development of an area of induration or mass near a fistula should be investigated with biopsy.[535]

Diverticular Disease

Left-Sided Colonic Diverticular Disease

So-called left-sided colonic diverticular disease commonly affects middle-aged and older individuals and shows a characteristic muscular abnormality of the bowel wall.[536] The abnormality is characterized by marked thickening of the inner circular layer of the muscularis externa that results in a narrowed lumen and a mucosa thrown up into prominent accordion-like folds. The mucosal abnormality and associated diverticula are most prominent within the sigmoid colon but they may extend proximally for a variable distance and may even involve the entire colon. Diverticula are not seen in the rectum. The diverticula are usually still enveloped by an intact longitudinal muscle layer. Diverticula usually manifest in two longitudinally running rows situated between the mesenteric and two anti-mesenteric taeniae. In severe cases of diverticular disease, diverticula can also be found between the antimesenteric taeniae.

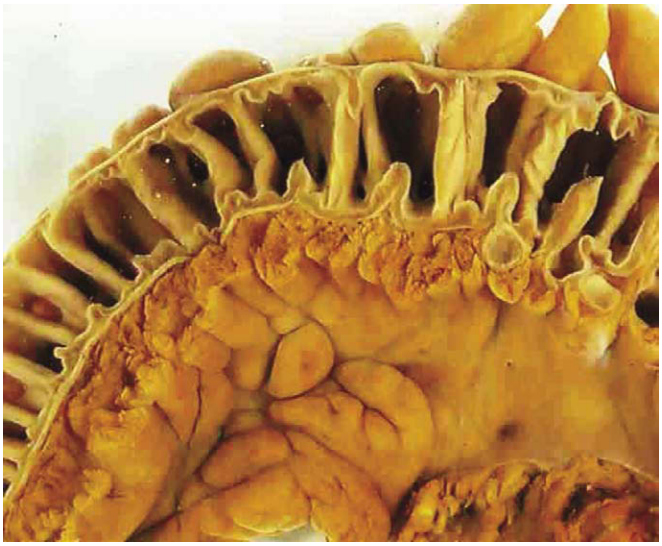

Figure 23-81 ■ Diverticular disease showing a thickened muscularis externa, prominent mucosal folds, and areas of diverticula.

Similar clinical signs and symptoms occur regardless of whether objective inflammatory changes are present; therefore, the term *diverticular disease* is preferred rather than routinely making the distinction between diverticulosis and diverticulitis.

Diverticula are sometimes difficult to demonstrate in freshly resected specimens because of lost muscle tone and intraluminal pressure. As a result the diverticula often evert and are mistaken for polyps. The best way to demonstrate diverticula is to fix an intact specimen with formalin under pressure for at least 1 day before dissection (Fig. 23-81).

Complications of diverticular disease include inflammation within the diverticula (diverticulitis), perforation of diverticula, adhesion, fistula formation, pericolonic abscess with inflammatory mass, hemorrhage, and obstruction.[537] Although colovesical and colovaginal fistula can occur in diverticular disease, other fistula combinations must raise the suspicion of coexisting Crohn's disease. Any granularity or ulceration of the luminal mucosa that is accompanied by microscopic findings of crypt abscesses or deep lymphoid aggregates away from inflamed diverticula must also raise the possibility of coexisting Crohn's disease (see earlier). Likewise, features of colitis distal to the zone of diverticula (e.g., at the distal resection margin) must also raise the question of coexisting Crohn's disease.

Right-Sided Colonic Diverticular Disease

Right-sided diverticular disease is often isolated and usually unassociated with diverticula in the rest of the colon. Right-sided diverticula occur in younger patients and are frequently seen in Asians.[538-541] Clinically, right-sided diverticular disease manifests with symptoms that mimic acute appendicitis. Some authors classify these diverticula as congenital if the outpouching contains all layers of the bowel wall or acquired if the diverticula resemble those seen in the left-sided diverticular disease. Complications include inflammation, hemorrhage, pericolonic abscess, and peritonitis. These diverticula have been implicated in some solitary nonspecific ulcers of the cecum and right colon.

Ischemic Bowel Disease

The clinical diagnosis of ischemic bowel disease can be difficult. Patients usually present with nonspecific symptoms and routine radiographic examinations such as plain abdominal films or barium enemas are rarely of use. Even arteriography may not be helpful because of the poor correlation between angiographic findings and the ultimate diagnosis or clinical outcome.[542] Angiographic demonstration of patent mesenteric blood vessels does not exclude ischemia. Conversely, stenosis or occlusion of mesenteric arteries (even two of the three major vessels) does not establish a diagnosis of ischemia because these are frequent findings in asymptomatic patients. Therefore, the diagnosis of ischemic bowel disease requires a high index of clinical suspicion complemented by continued monitoring of clinical, laboratory, and radiographic information. The pathologist can play an important role in the diagnosis and management of ischemic bowel disease by recognizing the patterns of injury that suggest ischemia in biopsy and resection specimens.

At first glance, intestinal ischemia seems simple, but in reality the topic is almost impossibly complex; the ultimate outcome of the patient depends on complicated interrelationships among temporal, anatomic, and physiologic factors.[543] For example, gradual occlusion of large vessels rarely causes ischemic damage because adequate collateral circulation (e.g., arc of Riolan, marginal artery of Drummond) will develop. In contrast, acute arterial occlusion is likely to result in infarct. Considering anatomic factors, occlusion of a large vessel does not often result in ischemic damage because collateral circulation is usually adequate to protect the bowel. However, occlusion of smaller end arteries frequently results in segmental ischemic damage and infarct.[544] Finally, the mere existence of an entity referred to as *nonocclusive intestinal ischemia* emphasizes the importance of physiologic considerations. Systemic hypotension and bowel distention lead to marked decreases in splanchnic blood flow caused by vasoconstriction and arteriovenous shunting in the bowel wall.[544,545] This phenomenon can result in widespread bowel infarct even in the presence of patent blood vessels.

Ischemic injury to the GI tract occurs whenever the oxygen or vascular supply cannot meet the metabolic demands of the tissue. GI ischemia has many causes, including inadequate perfusion, narrowing of blood vessels from any cause, bowel obstruction and distention, drug effects, and infections that can mimic ischemic damage. The list of differential diagnostic possibilities often overwhelms the pathologist and clinician. Keeping the diagnostic considerations in their proper perspective, almost all cases of mesenteric ischemia result from systemic hypotension or occlusion of a major blood vessel.[544] Knowledge of these relative frequencies can be invaluable in decreasing the pathologist's anxiety and frustration when dealing with these types of specimens and when interacting with the concerned clinician, patient, and family.

Most ischemic episodes result from nonocclusive ischemic bowel disease (low-flow states) and in these cases no vascular lesion or specific cause for ischemia can be demonstrated on pathologic examination. Superior mesenteric artery embolism or thrombosis is usually diagnosed by radiography or at operation. Almost all significant superior mesenteric artery occlusions occur in the proximal 1 cm to 2 cm of the artery,[544] an area not likely to be present in a resection specimen; such occlusive plaques, thrombi, or emboli are either bypassed surgically or removed and submitted separately to the pathology laboratory. Mesenteric venous thrombosis is also diagnosed and identified at laparotomy and treated with thrombectomy. Low-flow states, superior mesenteric artery occlusion, and mesenteric venous thrombosis account for more than 95% of major ischemic events.

Pathology of Ischemic Bowel Disease

Ischemia can result in a wide range of pathologic changes depending on the cause, severity, and duration of the hypoxia. Thus, ischemia can cause little or no change, mucosal plaques or hemorrhages with erosion, discrete or serpiginous ulcers that mimic Crohn's disease, strictures, or at the severe end of the spectrum, hemorrhagic infarct with perforation. Any part or length of bowel can be affected depending on the cause and duration of hypoxia and the state of the collateral circulation. In general, those cases of ischemic bowel disease associated with narrowing of a blood vessel show pathologic changes in the bowel in the corresponding distribution. In contrast, nonocclusive intestinal ischemia causes patchy and irregular distribution of damage not necessarily corresponding to an area supplied by a specific blood vessel (Fig. 23-82). Ischemic damage associated with reduced blood flow shows a propensity to affect "watershed zones" such as the splenic flexure, which is the boundary between the superior mesenteric and inferior mesenteric artery distributions.[3,347]

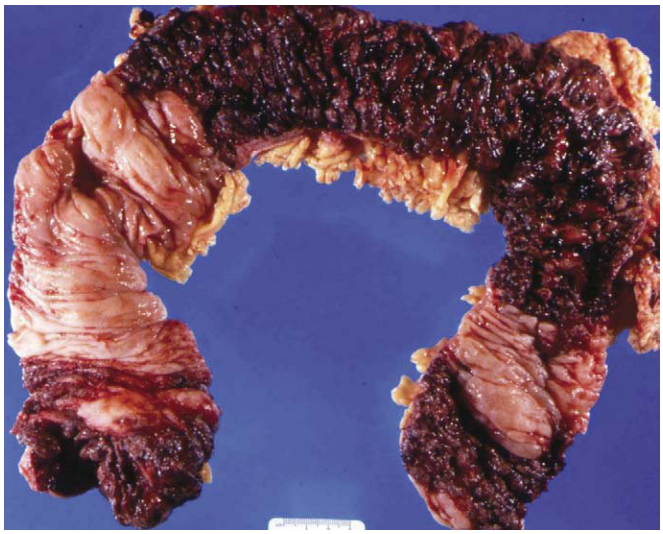

Figure 23-82 ■ Ischemic colitis caused by low flow. Areas of mucosa hemorrhage and ulcer with intervening edematous mucosa can mimic Crohn's disease and primary inflammatory bowel disease of an indeterminate type. The distribution of mucosal damage in this specimen does not correspond to an area supplied by a specific blood vessel.

Acute, organizing, and healed phases of ischemia can be recognized histologically.[347] *Acute ischemic damage* can be focal or diffuse. The characteristic pattern of acute injury consists of hemorrhage into the lamina propria associated with superficial epithelial coagulative necrosis, often with sparing of the deep portion of the intestinal crypt (see Fig. 23-59).[3,347] The mucosal distribution of these changes can be explained by the existence of a countercurrent exchange mechanism that has been suggested for intestinal mucosa. In the mucosa, a central arteriole carries blood luminally in a direction parallel to but opposite to the direction of blood flow in the draining mucosal venule. This situation causes a gradient in oxygen tension to form, with the luminal aspect of the bowel relatively hypoxic when compared with the crypt base.[546,547] The changes of acute ischemia can occasionally be associated with more extensive necrosis of the epithelium, often associated with an attached inflammatory pseudomembrane. Surprisingly, acute and chronic inflammatory cells are typically minimal in acute ischemic damage. This finding helps to differentiate ischemic damage from changes seen in primary IBD. Depending on the severity and duration of the hypoxia, the acute change can be reversible or can proceed to mucosal ulcers, at which point the histologic features become relatively nonspecific.[548] With increasing severity and duration, ischemia can lead to full-thickness infarct with hemorrhage and coagulative necrosis involving all bowel layers.

Granulation tissue and fibrosis with plump fibroblasts predominate in the *organizing phase of ischemic damage*. The histologic change becomes nonspecific. Ischemia should be suspected when an ulcer or area of organizing inflammation in the bowel appears quite bland and is not associated with a marked increase in chronic inflammatory cells with plasma cells and lymphoid aggregates so characteristic of primary IBD. Often, the mucosa of the ulcer edge shows changes similar to those seen in acute ischemic damage, and extensive samplings of these areas can help in diagnostic problem cases. The presence of hemorrhage and hemosiderin deposits in the connective tissues, although not pathognomonic, strongly suggests an ischemic origin.

During the *healing phase,* the colonic mucosa often assumes an architectural appearance similar (if not identical) to chronic UC with atrophy, shortened crypts, and branched and budded glands.[3,347] These changes usually have a patchy distribution in healed ischemic damage but are diffuse in UC. Ischemia usually does not show the basal plasmocytosis of primary IBD. Healed phases of ischemia are often complicated by fibrous stricture in which fibrosis can affect all the layers of the bowel wall including the muscularis externa. Fibrosis of the muscularis externa is distinctly unusual in primary IBD and its presence should raise the suspicion of ischemic bowel disease. Again, hemosiderin deposits can be a helpful clue in recognizing the ischemic nature of the injury.

Ischemic Bowel Disease: Specimen Handling

Most ischemic bowel lesions result from a combination of atherosclerosis and low-flow states and are referred to as *nonocclusive ischemic bowel disease*.[544] Specimens showing ischemic damage or infarct are usually resected on an emergency basis and include relatively short segments of mes-

entery. Large segments of infarct or ischemic damage are usually caused by an occlusive lesion in a proximal segment of a large artery or vein. In other words, the offending vessel is not likely to be present in the resection specimen. Although one is unlikely to see specific vascular abnormality in the resection specimen, the blood vessels should be carefully dissected and many cross sections examined microscopically to detect vascular lesions such as atherosclerosis, embolus, thrombosis, or inflammation (vasculitis). The significance of vascular inflammation in areas of active ulcer and infarct is questionable because this "vasculitis" may be secondary. However, acute inflammation in vascular walls associated with fibrinoid necrosis found in apparently viable areas separated from an ulcerated and necrotic area by a margin of normal tissue may indicate systemic vasculitis.

Vasculitis

GASTROINTESTINAL POLYARTERITIS NODOSA

Polyarteritis nodosa is a multisystem disease characterized by random necrotizing inflammation involving small and medium-sized arteries. Because the distribution and severity of the vascular lesions are haphazard, polyarteritis nodosa produces protean clinical manifestations without pathognomonic signs or symptoms. Abdominal pain, fever, leukocytosis, hypertension, and neuropathy are common in patients with polyarteritis nodosa.[549] According to the American College of Rheumatology, the presence of 3 of the following 10 criteria are considered diagnostic of the disease[550]: weight loss, livedo reticularis, testicular pain or tenderness, myalgia or myopathy, neuropathy, hypertension, renal impairment, hepatitis B infection, abnormal arteriogram, and positive biopsy results.

The diagnostic histopathologic change of polyarteritis nodosa is necrotizing panarteritis with inflammation involving intima, media, and adventitia. The inflammatory infiltrate is composed of neutrophils, eosinophils, plasma cells, and lymphocytes and is often associated with a deposition of fibrin.[551,552] The vascular lesions are usually seen in various stages of development and healing. Disruption of the internal elastic lamina weakens the vascular wall and can lead to aneurysm formation, an important sign used in radiographic diagnosis.

Of patients with polyarteritis nodosa, 14% to 70% have GI tract involvement[553] such as duodenal or gastric ulcer, melena, hematemesis, or small bowel infarcts. GI tract involvement is usually a manifestation of systemic polyarteritis nodosa. However, a growing body of literature has described polyarteritis nodosa apparently limited to one organ, most commonly the skin, gallbladder, or vermiform appendix.[551-555] Only a rare patient with polyarteritis nodosa that is initially diagnosed in the gallbladder or appendix develops systemic vasculitis[552,553,556,557] and those who do frequently have elevated serum rheumatoid factor or antinuclear antibodies.

OTHER FORMS OF VASCULITIS

Phlebitis, Churg-Strauss angiitis, small vessel vasculitis, Buerger's disease, and giant cell arteritis can manifest initially in the GI tract and cause ischemic injury.[553,557] Phlebitis and small vessel vasculitis are frequently associated with drugs and medications and are often self-limited.[553,558]

Special consideration should be given to an entity referred to *as intra-abdominal (lymphocytic) phlebitis*. Rare cases of ischemic damage to the colon have been linked to a curious form of phlebitis reported under numerous synonyms including lymphocytic phlebitis, necrotizing and giant cell granulomatous phlebitis, idiopathic myointimal hyperplasia of mesenteric veins, mesenteric inflammatory veno-occlusive disease, intramural mesenteric venulitis, and idiopathic colonic phlebitis.[553,558-568] Since the original descriptions, approximately 40 additional cases have been described. The patients have ranged in age from 30 to 77 years, and no gender predilection is apparent. Most cases involve the small intestine and colon but involvement of other organs such as the gallbladder, omentum, and stomach have been described.[553,568] Four patients received treatment with the drug rutoside.

Microscopically, specimens show phlebitis and thrombophlebitis mostly involving the submucosal veins and venules (Fig. 23-83). The most prominent lesion is infiltrative lymphocytic phlebitis. In approximately half of these patients, the phlebitis has been necrotizing, and in about one third a granulomatous component has been visible. In approximately half of the patients, myointimal proliferation has been described.[559] Some investigators have proposed that myointimal hyperplasia represents an end stage of lymphocytic phlebitis.[561]

Immunohistochemical analysis has been performed on a few cases and demonstrates a mixture of T cells and B cells with a few macrophages.[559,565] Some of the T cells express the cytotoxic granule-associated protein TIA-1 and granzyme B, findings supporting the contention that the lymphocyte-mediated vascular damage is a central event in the pathogenesis.[565] So far, cases in the literature have had a favorable clinical outcome. The disease usually has been diagnosed and treated by resection in these patients. No patient to date has required repeat resection, nor has any patient developed systemic vasculitis. Some patients con-

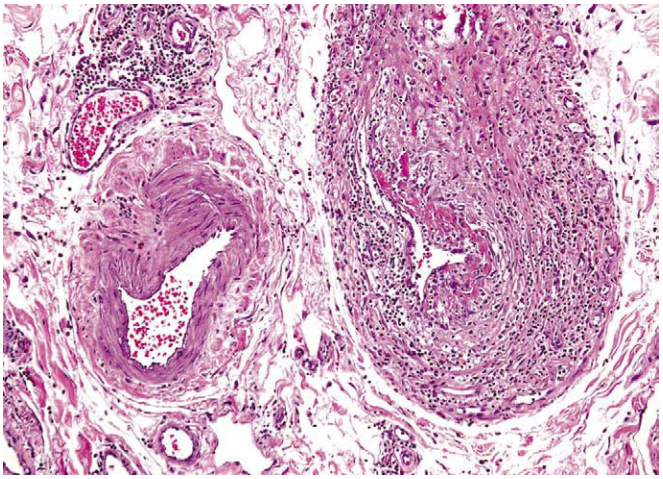

Figure 23-83 ■ Intra-abdominal (lymphocytic) phlebitis. The submucosal vein demonstrates infiltration of its wall by lymphocytes with focal phlebothrombosis. The accompanying artery is normal.

tinue to have abdominal pain, and at least one report noted recurrent phlebitis documented by biopsy.[559]

Other Ischemic Syndromes

Other entities considered part of the spectrum of ischemic bowel disease include necrotizing enterocolitis of the neonate, neutropenic enterocolitis (typhlitis), intestinal Behçet's disease, late irradiation enterocolitis, uremic colitis, stercoral ulcer associated with bowel obstruction, potassium chloride–induced ulcer, stress ulcer and ulcers associated with drugs (e.g., NSAIDs and chemicals), certain infections such as *Clostridium difficile*–associated colitis, and EHEC infection. The pathologic features of these disorders resemble ischemic bowel disease and are generally indistinguishable without knowledge of clinical and laboratory information.

NECROTIZING ENTEROCOLITIS OF THE NEONATE

Necrotizing enterocolitis is a serious form of intestinal injury that resembles ischemic bowel disease. Although many investigators think it part of the spectrum of ischemia, increasing evidence supports a role for infectious agents in the pathogenesis of the lesion.[569] Necrotizing enterocolitis of the neonate generally affects low-birth-weight or premature infants. The disease usually occurs in babies younger than 10 days of age and symptoms usually develop after feeding has begun. The lesions resemble acute ischemic damage.[569,570] Ulcers that can be patchy or diffuse occur and in general may affect any part of the GI tract. Preferred sites of involvement include the terminal ileum, right colon, and stomach. Histologically bland transmural necrosis occurs and may be associated with gas cysts within the bowel wall (pneumatosis cystoides intestinalis [PCI]) (Fig. 23-84). Babies surviving the acute episode may later develop fibrous strictures.

NEUTROPENIC ENTEROCOLITIS (TYPHLITIS)

Neutropenic enterocolitis goes by numerous synonyms, including hemorrhagic necrosis of the GI tract, necrotizing enterocolitis, agranulocytic colitis, typhlitis, and the ileocecal syndrome.[571-574] The condition is fulminant segmental colitis that is often seen in patients with lymphoma or leukemia receiving immunosuppressive drug therapy, but it has also been seen in association with other chemotherapy-induced or non-neoplastic–induced neutropenias such as cyclic neutropenia. Many investigators consider this disorder a form of ischemic bowel disease, but increasing evidence implicates bacteria, especially *Clostridium septicum,* as causative agents.[575-578] The pathogenesis is unclear but is likely to be multifactorial with neutropenia, altered mucosal integrity, ischemia, and infection all playing a role. The lesion can occur anywhere in the GI tract, but the preferred sites are cecum, right colon, and terminal ileum. The histologic picture combines infarct necrosis with profound secondary bacterial or fungal overgrowth and is often associated with a paucity of acute inflammatory cells. The prognosis is grave; however, reports of successful surgical and medical management have been published.[571,572,574,575,579]

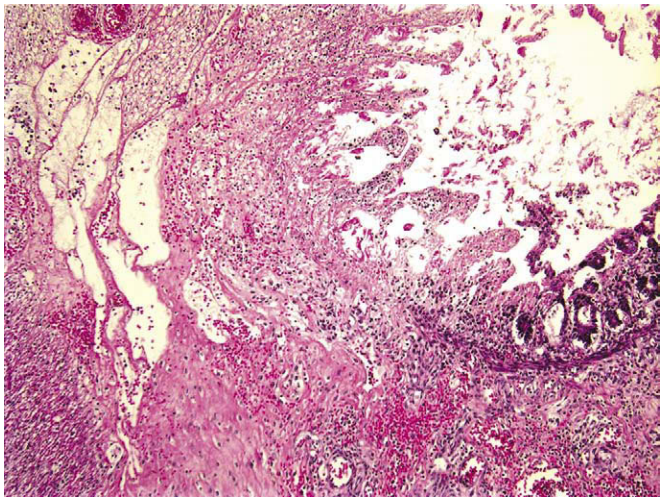

Figure 23-84 ■ Necrotizing enterocolitis of the neonate demonstrating a combination of ischemic-type injury with the acute form of pneumatosis cystoides intestinalis.

NONSPECIFIC ULCERS OF COLON

Investigators have reported benign cecal ulcers and segmental necrosis of the right colon in which the pathologic features are nonspecific or resemble ischemia.[580-582] The cause of many of these ulcers remains unclear.[580] Some may represent inflammatory changes or bleeding vascular lesions in right-sided diverticula.[582,583] Many are associated with end-stage renal disease, hemodialysis, renal or cardiac transplantation, and corticosteroid therapy. Some are clearly related to ischemia caused by low-flow states, which are known to occur in patients undergoing hemodialysis.[581] However, a strong correlation exists among cecal and terminal ileal ulcers, renal or cardiac transplantation, immunosuppression, and CMV infection.[584] The possible role of CMV in these ulcers is unknown. The exact cause of many colonic ulcers cannot be determined at present.[585] NSAID use should also be investigated.[586]

INTESTINAL INVOLVEMENT IN BEHÇET'S DISEASE

The term *Behçet's disease* describes the clinical triad of aphthous stomatitis, genital ulcers, and relapsing iritis. Behçet's disease is seen worldwide, but most cases have been reported from the Mediterranean basin, the Middle East, and Japan.[587] Male patients are twice as commonly affected as female patients and the mean age of onset is in the third decade.[587,588] Behçet's disease is a systemic disorder; only 10% to 15% of patients demonstrate GI tract involvement,[587-589] usually in the form of intestinal ulcers. The ulcers of intestinal Behçet's are described as multiple, deep, and punched-out with a preferential localization in the ileum and cecum. The ulcers often perforate.[588-591] The primary clinical differential diagnosis is Crohn's disease. Intestinal Behçet's disease differs from Crohn's disease in several ways. Behçet's disease is usually not associated with strictures or granulomas. Free perforation, common in Behçet's disease, occurs rarely in Crohn's disease.

Details of histologic pattern in intestinal Behçet's are difficult to find.[590,591] The inflammatory infiltrate of Behçet's ulcer appears nonspecific. The lesions of so-called acute Behçet's ulcer closely resemble acute ischemic bowel disease. The chronic lesion of Behçet's disease resembles Crohn's disease except the transmural lymphoid aggregates in

Behçet's disease contain more germinal centers, the bowel wall can be fibrosed, and granulomas are not usually encountered. Some authors have reported mononuclear cell infiltrates around capillaries and venules with some areas of fibrinoid necrosis.[588,590] Indeed, large vessel inflammation with occlusion and aneurysm formation have been described in 3% to 25% of patients with Behçet's disease.[591,592] Vasculitis may be the common underlying factor producing the GI lesions of Behçet's disease.[590]

LATE IRRADIATION COLITIS

Late complications of irradiation can occur weeks to years after therapy and include colitis, stricture, ulcer, and fistula (Fig. 23-85).[593,594] Many of these abnormalities may be related to ischemia as a result of the effect of radiation on blood vessels. Histologically, the mucosa appears atrophic and similar (often identical) to that seen in chronic UC. Having said that, the basal plasmacytosis in the lamina propria characteristic of primary IBD is usually but not always absent. Ectatic mucosal capillaries with thrombosis and hyalinization are important histologic signs that can point to irradiation effect (Fig. 23-86). Irradiation may be associated with fibrosis of any of the layers of the bowel wall. The fibrosis can appear dense and hyalinized and may contain large, atypical radiation fibroblasts. Vascular changes are often prominent. Blood vessels may be ectatic in the mucosa and submucosa. More commonly, however, one encounters marked intimal fibroplasia with hyaline thickening of the blood vessel walls that leads to luminal stenosis.

STERCORAL ULCER ASSOCIATED WITH BOWEL OBSTRUCTION

Sharply demarcated ulcers sometimes with secondary bacterial overgrowth can often be seen in the colon and rectum proximal to obstructing lesions such as invasive carcinoma, or they can be seen in patients with intractable constipation and fecal impaction.[544,595-597] The ulcer, bland in appearance, is thought to result from ischemia caused by a combination of pressure injury related to the hard fecal mass and the physiologic effects of bowel distention.[544,598]

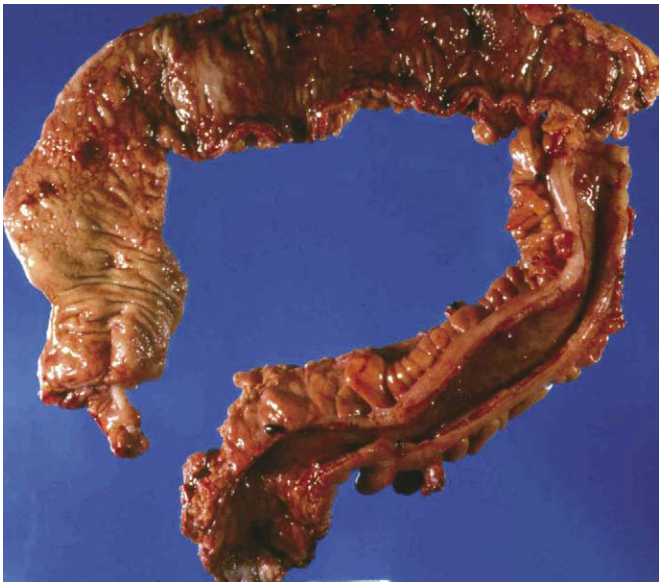

Figure 23-85 ■ Chronic radiation proctocolitis. The mucosal atrophy, erythema, and granularity can simulate ulcerative colitis. The fibrous stricture present in the descending colon can mimic Crohn's disease.

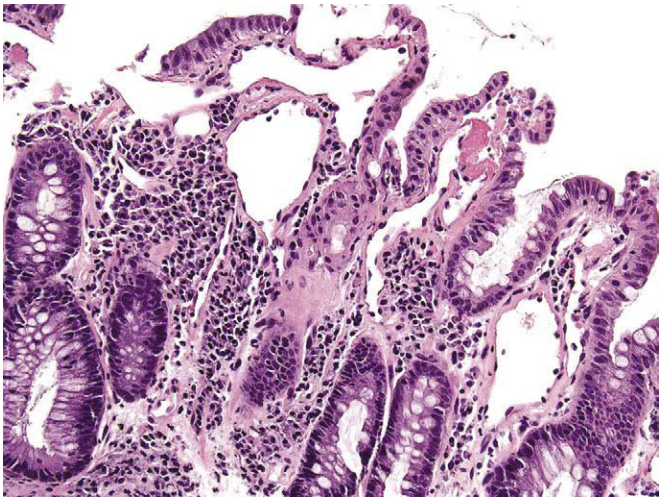

Figure 23-86 ■ Radiation-induced proctitis in a patient treated for prostate adenocarcinoma. Capillary ectasia, fibrosis, and thrombosis are important histologic clues to radiation injury.

DRUG- OR CHEMICAL-INDUCED ISCHEMIC-LIKE LESIONS

Many drugs or chemicals have been associated with ischemic-type changes in the colon, including hydrogen peroxide and glutaraldehyde (used to clean endoscopes),[349] NSAIDs,[350,586,599] cocaine,[350,600,601] oral contraceptives, and estrogen compounds.[348]

Infections of the Large Bowel

Common Bacterial Agents

Colitis can be caused by a host of bacteria including *Campylobacter* species, *Shigella* species, *Salmonella* species, *Neisseria gonorrhoeae*, *Yersinia* species, *Mycobacterium* species, and *Aeromonas* species. Although the histologic features of colonic mucosal biopsy specimens can vary greatly in these infections from essentially normal to lesions mimicking idiopathic IBD, large numbers of specimens show active colitis, as outlined earlier in the chapter, that when seen should suggest infectious-type colitis.[3,323,324,326-328,602-608] The histologic finding usually consists of the focal active colitis pattern of injury with relative preservation of mucosal architecture except for edema. The active inflammation is associated with little or no mucin depletion. Neutrophils can be present within the lamina propria and scattered cryptitis and crypt abscess formation, sometimes with luminal accentuation, can be seen. The definitive diagnosis of infectious colitis requires laboratory documentation by culture, PCR on the paraffin block, or serologic examination. Histologic evaluation, although helpful in suggesting infection, can only rarely point to a specific agent. True granulomas can be seen in tuberculosis, syphilis, *Chlamydia* species infection, and *Yersinia pseudotuberculosis* infection. Microgranulomas are described in infection with *Salmonella* species, *Campylobacter* species,

and *Yersinia enterocolitica*. Isolated mucosal giant cells are nonspecific but have been described in *Chlamydia trachomatis* infection.[330,607]

Some bacterial infections cause little inflammation but can be diagnosed by observation of adherent organisms such as with intestinal spirochetosis and adherent *E. coli* species. Although intestinal spirochetosis (infection with *Brachyspira aalborgi* or *Brachyspira pilosicoli*) can be seen in patients with human immunodeficiency virus (HIV) infection or AIDS,[609,610] it is more frequently encountered in immunocompetent patients in whom its significance remains controversial.[609,611-614] The microscopic appearance is subtle, consisting of a thickening or accentuation of the colonic brush border that stains deeply with hematoxylin. This effect is caused by adherent spirochetes that align in parallel and embed themselves in the absorptive cells. Identification can be enhanced by use of a Warthin-Starry (or other silver) stain. The organism also cross-reacts with *Treponema* species immunostains. Adherent *E. coli* infections, described in HIV/AIDS under the term *diarrheogenic bacterial enterocolitis*, are discussed later.

GI involvement with *Mycobacterium avium-intracellulare* complex (MAIC) is seen in HIV/AIDS usually as part of disseminated infection. The organism is easily cultured from stool and even blood. MAIC can affect any part of the GI tract, including the large bowel.[615,616] The characteristic histologic feature is infiltration of the lamina propria by foamy macrophages that can mimic muciphages. In addition, MAIC stains positive with PAS, a finding further adding to the possibility of misdiagnosis. MAIC is easily diagnosed with an acid-fast stain.

Parasitic Infestations

Cryptosporidium parvum infection can occur in immunocompetent persons but is more often seen in HIV/AIDS[617,618] and occasionally can be seen in the colon (Fig. 23-87). In biopsy specimens, cryptosporidial organisms are identified as basophilic dots measuring approximately 3 μm attached to the surface of the colonocyte. Immunocytochemical methods for identification have been described.[619]

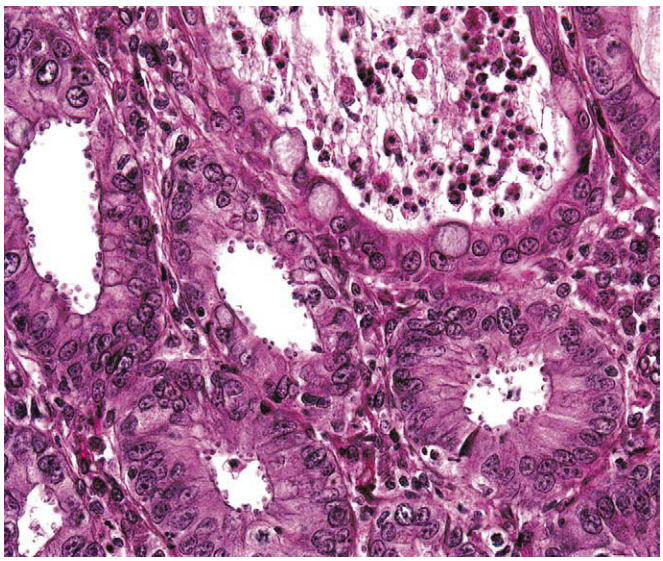

Figure 23-87 ■ Active colitis associated with cryptosporidiosis. Note the numerous basophilic dots on the luminal surface of the colonocytes.

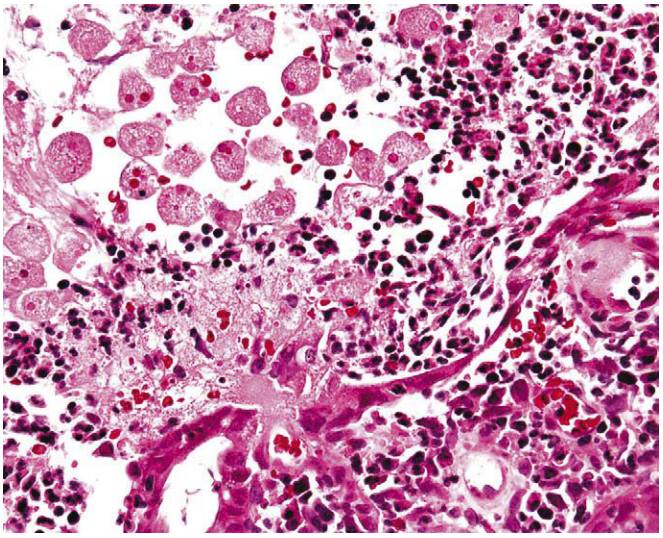

Figure 23-88 ■ Amebiasis. The adherent exudate contains trophozoites of *Entamoeba histolytica*.

Amebiasis (infection with *E. histolytica*) is quite common worldwide and is seen in HIV/AIDS.[620] Clinical disease varies widely from asymptomatic conditions to fulminant colitis. Early lesions consist of a slight mucosal depression and erosion with adherent exudate containing trophozoites of *E. histolytica* (Fig. 23-88). Focal active colitis can also be seen.[608] More severe disease can cause ulcers that have been described as flask-shaped because they undermine the adjacent mucosa. *E. histolytica* is easily distinguished from the much larger *Balantidium coli*, which is only rarely seen in humans.[621] In addition, the trophozoite of *B. coli* is ciliated, the nucleus is much larger and kidney-shaped, and the cytoplasm contains vacuoles.

Schistosoma species infestation is a major cause of colitis worldwide but is rarely seen in North America. The adult worms elicit no inflammatory response. The colitis and the symptoms are caused by the marked inflammatory response to the eggs that can lead to mucosal ulcers (Fig. 23-89). Chronic colitis and inflammatory polyps can be seen in areas of endemic infection.[622]

Strongyloidiasis is usually a self-limiting infection with adult worms residing in the proximal small bowel; the eggs develop into rhabdoid larvae in the lumen that pass in the stool. In immunocompromised patients, the rhabdoid larvae may develop into the infective filiform larvae. These infective larvae may invade intact colonic mucosa or perianal skin and set up a cycle of infection referred to as *autoinfection*. Many such infections are severe and often fatal. In colorectal biopsy specimens the infective larvae can be seen usually associated with marked infiltration of mucosa with the eosinophils (Fig. 23-90).[622] Sometimes an eosinophilic and granulomatous reaction can be seen in biopsy and resection specimens.[623]

Occasionally intraluminal worms are encountered in the colonic lumen and are removed at colonoscopy. These parasites are usually identified as *Trichuris* (whipworm) (Fig. 23-91) or *Enterobius* (pinworm) by examination of the worm and egg morphology.[622]

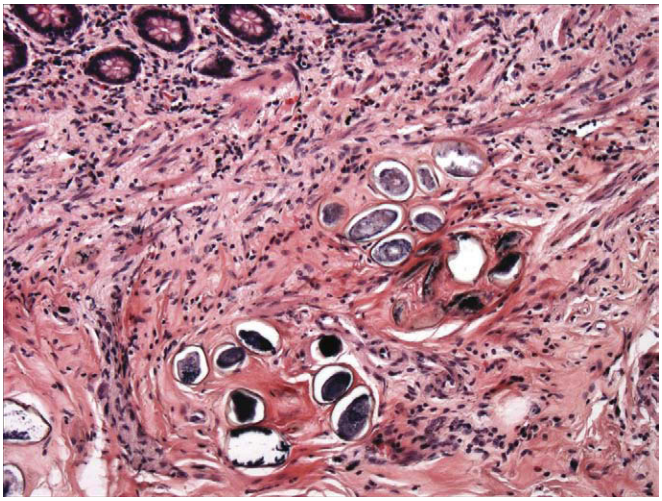

Figure 23-89 ■ Schistosomiasis involving the colon demonstrating a fibrous and chronic inflammatory response to calcified eggs.

Viral Infections

Common viral pathogens include adenovirus, rotavirus, coronavirus, echovirus, enterovirus, astrovirus, and Norwalk virus. Colorectal biopsy is rarely performed in the setting of viral gastroenteritis; therefore, histologic changes are not well documented. Norwalk virus and rotavirus are not known to cause morphologic changes in the colon. Adenovirus can cause diarrhea in HIV/AIDS.[608] Histologic changes affecting epithelial cells include cellular disorder with loss of orientation and degeneration. Eosinophilic viral intranuclear inclusions can be seen in surface goblet cells but are quite subtle. Immunohistochemical analysis can be performed as an aid to diagnosis.

CMV infection is extraordinarily common in patients with HIV/AIDS and in other immunosuppressed patients such as those receiving transplants. The characteristic inclusions are seen in endothelial cells, fibroblasts, and smooth muscle cells and are only rarely encountered in epithelial cells.[624] Severe infection can lead to vascular thrombosis and ischemic-type damage with ulcers (Figs. 23-92 and 23-93).

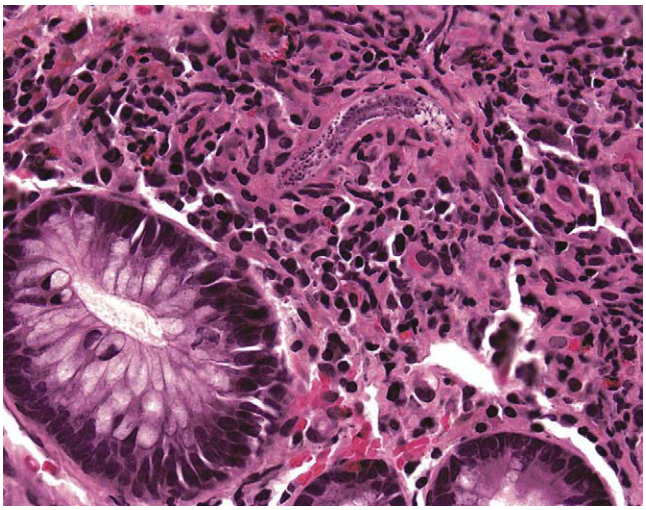

Figure 23-90 ■ Infective filiform larva of *Strongyloides* autoinfection within the colonic lamina propria.

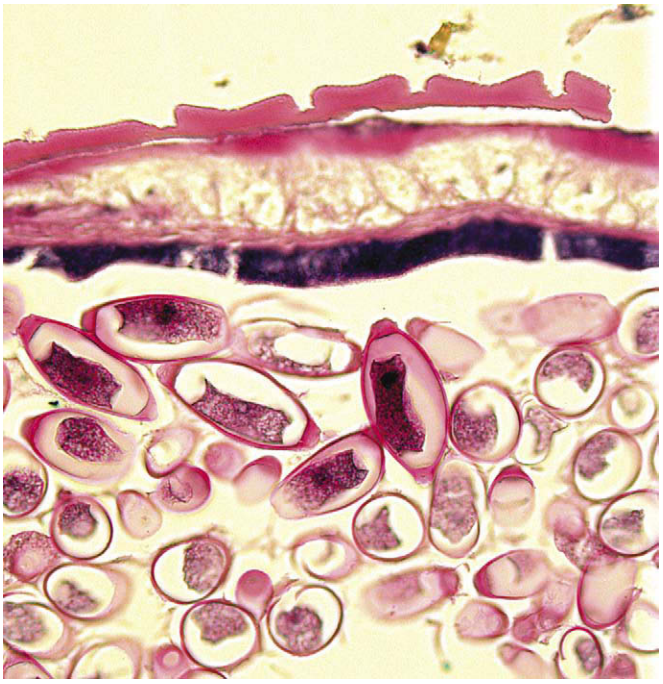

Figure 23-91 ■ Trichuriasis diagnosed by removal of the adult female worm at endoscopy. Sections show a gravid uterus containing the typical egg morphology of *Trichuris* species (bipolar plugs).

Herpes simplex virus infection is associated with painful ulcers in the distal rectum and perianal skin.[625,626] The pathologic changes (ulcer, neutrophils in the lamina propria, cryptitis, and crypt abscess formation) may suggest infec-

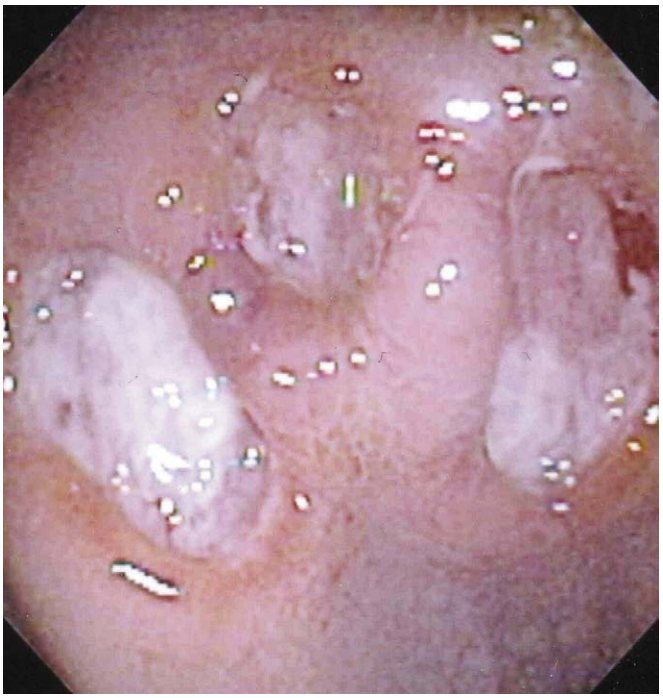

Figure 23-92 ■ Endoscopic view of cytomegalovirus-associated colitis with "punched-out" ulcers.

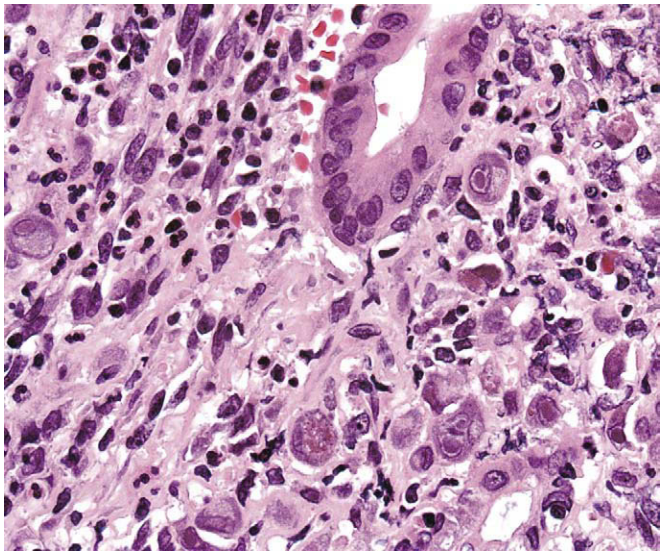

Figure 23-93 ■ Numerous intranuclear and cytoplasmic inclusion bodies of cytomegalovirus within the lamina propria.

tion; however, viral inclusions are not seen in the colon and rectum.

Fungal Infections

Invasive candidiasis can be seen in severely debilitated patients and in patients with HIV/AIDS. This disorder is rarely encountered in colorectal biopsy specimens. Colorectal histoplasmosis can be seen in immunocompetent patients and in immunocompromised patients such as those with HIV/AIDS.[627,628] In disseminated forms one can see collections of foamy macrophages. Some patients demonstrate granulomatous inflammation, which is sometimes suppurative. Diagnosis can be made using Gomori methenamine silver or other fungal stains.

Colonic Infections That Cause Ischemic-Type Damage

CLOSTRIDIUM DIFFICILE–ASSOCIATED COLITIS

Administration of any antibiotic that favors the growth of toxin-producing *C. difficile* can lead to pseudomembranous colitis.[629,630] Early studies linked clindamycin and lincomycin to pseudomembranous colitis, but in terms of absolute numbers, most cases are linked to ampicillin, penicillin, the cephalosporins, and the fluoroquinolones (especially the C-8-methoxyfluoroquinolones gatifloxacin, and moxifloxacin) because of their far more prevalent use.[630,631] Currently, the second- and third-generation cephalosporins and the fluoroquinolones are the leading instigators of *C. difficile*–associated colitis.[630-632] Pseudomembranous colitis has even been associated with antineoplastic chemotherapeutic agents that have antimicrobial activity.[633]

In many cases, the source of *Clostridium difficile* infection is the patient's own gut flora. Alterations of the gut flora allow the patient's own *C. difficile* organisms to multiply. However, the spore-forming organism *C. difficile* is widely distributed in nature. Although cases may be acquired by these routes, increasing evidence indicates that *C. difficile* is often acquired in hospitals.[630,632,634] Indeed, reports of a previously uncommon strain of *C. difficile,* the *NAP1 strain,* showed that it is responsible for severe hospital outbreaks and serious disease in otherwise healthy individuals.[630,635-638] These reports of close-contact transmission, high recurrence rate, young age, bloody diarrhea, and lack of antibiotic exposure suggest changing epidemiologic features.

Advanced age is a risk factor; patients who are older than 65 years old have an approximately 20 times greater risk of developing *C. difficile* infection.[630] Statistically, *C. difficile* is associated with only a minority of cases of antibiotic-associated diarrhea. In GI diseases other than primary IBD, isolation rates are about the same as in healthy adults. *C. difficile* is more frequently identified in patients with IBD and may be linked to exacerbations of IBD and fulminant colitis.[639,640]

Symptoms of pseudomembranous colitis usually develop during the administration of antibiotics but in up to one third of patients, the onset of symptoms can be delayed for up to 4 to 6 weeks; occasionally, no antibiotic exposure has occurred.[630,636,641,642] The characteristic endoscopic and histologic lesion is found early in the course of the disease and only in some individuals. The surface of the mucosa is covered by a plaquelike, cream-colored to yellow pseudomembrane (Fig. 23-94). The intervening mucosa frequently appears normal but can be hyperemic or edematous.[345] With increasing severity, the membranes can become confluent and linear ulcers can develop. Usually the pseudomembranes are evenly distributed throughout the colon but in up to one third of patients, the pseudomembranes can be confined to the right colon. This finding emphasizes the need for total colonoscopy to make an endoscopic diagnosis.

Histologically, patchy necrosis of the superficial colonic crypts is evident that is not unlike that seen in ischemia. The affected crypts become dilated near the surface and an

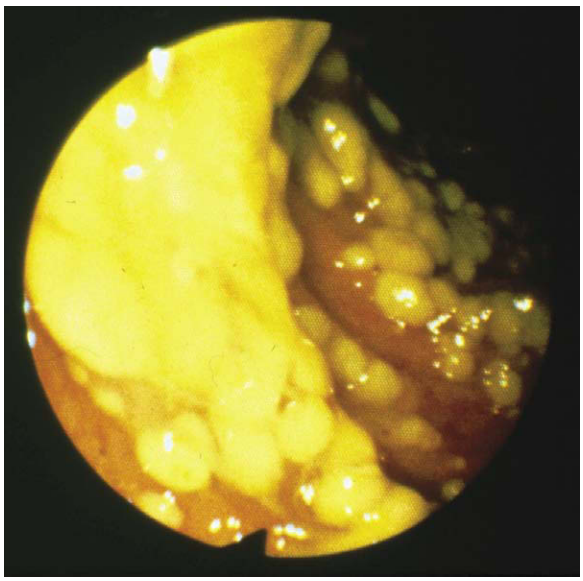

Figure 23-94 ■ Endoscopic view of *Clostridium difficile*–associated pseudomembranous colitis. Plaquelike, cream-colored pseudomembranes overlie erythematous mucosa and have become confluent in the foreground.

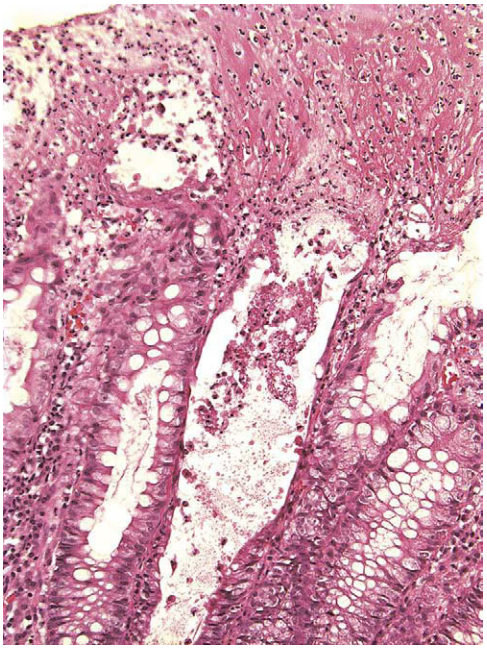

Figure 23-95 ■ Exploding crypt lesion of *Clostridium difficile*–associated pseudomembranous colitis. The affected crypt is dilated with epithelial necrosis. The fibrin, karyorrhectic debris, and neutrophils orient in a curious linear fashion within the inflammatory pseudomembrane.

inflammatory exudate erupts from the surface aspect of the degenerating crypts in an explosive or mushroom-like configuration. The pseudomembrane may cover adjacent virtually normal colonic mucosa (Fig. 23-95). The karyorrhectic debris and neutrophils in the pseudomembranes tend to orient in a curious linear fashion within the fibrin and mucus. Early lesions of *C. difficile* and occasionally the mucosa between diagnostic pseudomembranes can show the focal active colitis pattern of injury frequently described in acute infectious-type colitis (acute self-limited colitis).[326,327,345] Left untreated, some cases of *C. difficile*–associated colitis progress and can become indistinguishable from ischemic bowel disease. Toxic megacolon and perforation can occur.

Treatment falls into three major categories: (1) nonspecific therapy, (2) specific therapy, and (3) therapies aimed at altering the gut flora. Nonspecific treatments include discontinuance of the offending antibiotic, supportive measures, enteric precautions to retard the spread of *C. difficile* outbreaks, and surgery. Surgical excision may occasionally be indicated[327] for patients too sick to take oral antibiotics (the specific therapy), as well as for some patients with relapses and for nonresponders. Toxic megacolon and perforation also require surgical treatment.

Specific therapies include the oral administration of antibiotics such as vancomycin, metronidazole, bacitracin, and the toxin binder cholestyramine. Vancomycin, the preferred treatment, is relatively expensive.[630] Bacitracin and metronidazole appear to be as effective as vancomycin and are less expensive. Theoretical disadvantages to metronidazole therapy include stool levels of the drug that appear far lower than those of vancomycin and the finding that metronidazole has occasionally been implicated as a cause of pseudomembranous colitis.

Treatment or prevention of pseudomembranous colitis by altering the gut flora with the introduction of such agents as *Lactobacillus* and *Saccharomyces boulardii*[630,643,644] has been studied. *Saccharomyces boulardii* was shown to decrease the incidence of antibiotic-associated diarrhea but did not change the rate of *C. difficile* colonization. Another provocative approach to prevention is to restrict the use of newer antibiotics such as third-generation cephalosporins and fluoroquinolones in the hospital setting.[632,638]

Patients with *C. difficile*–associated pseudomembranous colitis who are treated specifically show a 95% to 100% response rate usually with defervescence in 1 to 2 days and resolution of diarrhea in 5 days. However, 5% to 50% of patients have a relapse and relapse treatment can be challenging. Most investigators recommend a second course of the same antibiotic (metronidazole or vancomycin) for 14 days.[645] For a second recurrence, tapered-pulsed vancomycin is advised.[630] For a third or subsequent recurrence, a probiotic or toxin binder is added to tapered-pulsed vancomycin therapy. Newer treatments for recurrences include passive immunoglobulin therapy, toxin receptor decoys (e.g., tolevamer), and active immunization against toxin A.[645]

Stool culture for *C. difficile* is usually not recommended but some investigators report a significantly higher yield of positive results based on fecal culture followed by toxin assay on positive colonies.[646] Cell culture assay for toxin B is not routinely performed. Results of latex agglutination tests have been disappointing.[647] Enzyme-linked immunoassays (EIAs) that detect toxin A (Meridian Diagnostic, Vitec, BD, and Cambridge) or toxin A and toxin B are widely used.[630] These assays have a 90% to 95% positive correlation with cell culture assay. Commercially available tests that detect toxin A and toxin B are preferred because 1% to 2% of *C. difficile* strains produce only toxin B.[629,630] An alternative and more sensitive but slower approach is to perform an EIA for the detection of common antigen (a highly sensitive marker for *C. difficile*) followed by a cytotoxic assay if the results of the EIA are positive.[630] Various gene probes and PCR techniques that detect toxin at the DNA level are available for research purposes.[648]

ENTEROHEMORRHAGIC *ESCHERICHIA COLI*–ASSOCIATED COLITIS (HEMORRHAGIC COLITIS)

The clinical syndrome of *hemorrhagic colitis* is characterized by abdominal cramping, bloody diarrhea, and either no fever or low-grade fever.[346,649] Patients typically demonstrate right-sided colonic edema, erosion, and hemorrhage and the absence of conventional enteric pathogens. In 1983, investigation of hemorrhagic colitis outbreaks occurring in Oregon and Michigan implicated a then-rare serotype of *E. coli*, O157:H7, as the cause of the syndrome.[650] Subsequently, investigations of several additional outbreaks confirmed the association between hemorrhagic colitis and the verocytotoxin-producing *E. coli*, the most important of which is *E. coli* O157:H7.[651]

Patients with hemorrhagic colitis typically present with the sudden onset of crampy abdominal pain occurring 3 to 4 days after ingestion of contaminated food, usually undercooked hamburger. Outbreaks have also been linked to other foods, drinking water, and swimming pools.[652] Watery diarrhea, nausea, and vomiting follow within hours. One to

2 days later, grossly bloody diarrhea replaces the watery diarrhea. In almost all patients, the disease resolves spontaneously, usually within 8 days. Investigation of the epidemic outbreaks of *E. coli* O157:H7 infection revealed that not all patients acquire the full syndrome of hemorrhagic colitis. Rather, a clinical spectrum exists ranging from asymptomatic carrier or self-limited nonbloody diarrhea to severe cases complicated by hemolytic-uremic syndrome and thrombotic thrombocytopenic purpura.[651,653,654]

E. coli O157:H7 produces several toxins active against vero cells (verocytotoxins) and HeLa cells that have been termed *Shiga-like toxins* because their mode of action is similar to that of the toxin produced by *Shigella dysenteriae* type I. The toxins interact with the membrane receptor globotriosyl ceramide, are apparently absorbed into epithelial and endothelial cells, and cause damage or cell death by interfering with protein synthesis.[651,655]

Colonic histologic features in EHEC infection are the best documented of the diarrheogenic *E. coli* organisms because EHEC infection can lead to hospitalization and it clinically mimics ischemia and primary IBD, thus prompting colonoscopy with biopsy.[346,656,657] Colonoscopy typically demonstrates patchy erythema, edema, and surface ulceration of the colon (Fig. 23-96). The cecum and right colon are usually described as markedly abnormal, whereas the descending colon typically has mild or no changes. Histologically, specimens usually show hemorrhage and edema within the lamina propria. Specimens most often show focal necrosis associated with hemorrhage and acute inflammation within the superficial mucosa with preservation of the deep colonic crypts, similar to the pattern of injury described in acute ischemic colitis. Specimens from many patients show neutrophils infiltrating the lamina propria and crypts resembling the focal active colitis pattern of injury seen in infectious colitis or acute self-limited colitis (Fig. 23-97). Rarely patients also demonstrate inflammatory pseudomembranes. This combination of ischemic-like and infectious-like injury with capillary thrombi should at least suggest EHEC-associated colitis in biopsy specimens.

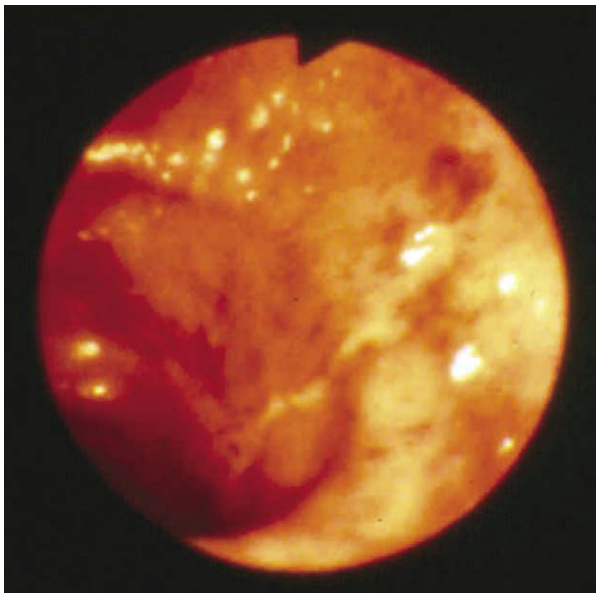

Figure 23-96 ■ Endoscopic view of a patient with culture-proven *Escherichia coli* O157:H7 infection. Patchy erythema and a linear ulcer are visible on the mucosal surface.

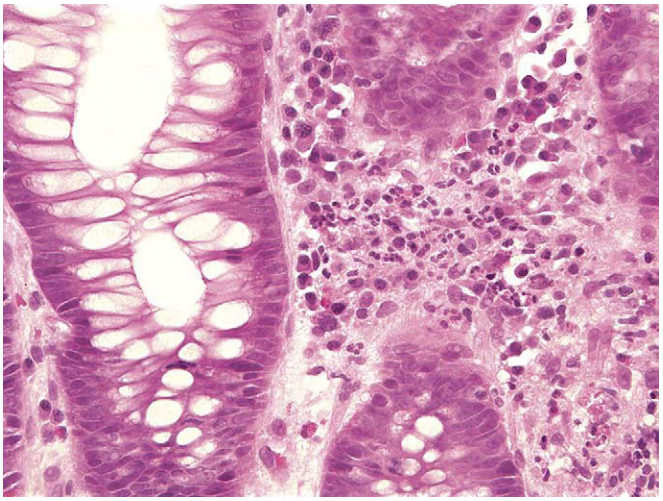

Figure 23-97 ■ Enterohemorrhagic *Escherichia coli* infection showing the infectious-type colitis pattern of injury with focal active colitis and neutrophils infiltrating the lamina propria.

Routine stool culture media do not enable one to distinguish *E. coli* O157:H7 from other strains of *E. coli* normally found in the stool. Physicians suspecting hemorrhagic colitis caused by *E. coli* O157:H7 should specifically request that stools be screened for this organism. Specimens may be examined using sorbitol fermentation as a strain marker; unlike most *E. coli* organisms, *E. coli* O157:H7 strains test negative for sorbitol or have delayed positive results.[658] Colonies that test negative for sorbitol at 24 hours can be screened with commercial O157 antisera. Additional biochemical tests and H-antigen determinations can be performed later.[346] DNA hybridization techniques, PCR, direct immunofluorescence, and latex agglutination techniques have also been described for identification. Procedures for detection of free fecal verocytotoxin and more sensitive methods for screening stool cultures for verotoxin-producing *E. coli* using polymyxin B on colony sweeps have been reported.[651,652]

OTHER *ESCHERICHIA COLI* PATHOGENS

E. coli organisms are the predominant components of the gut microflora. Although most of these organisms are harmless or even beneficial, at least six categories of *E. coli* intestinal pathogens are recognized (Table 23-9).[659,660]

Much is known about the microbiology, pathogenic mechanisms, virulence factors, molecular genetics, and epidemiology of intestinal *E. coli* infections. However, surprisingly little is known about the histopathologic features of the human gut infection. Information remains scant because most infectious diarrheas, being self-limited, do not require specific treatment even when an infectious organism is identified. Therefore, sophisticated diagnostic tests such as organism identification, virulence factor determination, and endoscopy with biopsy are reserved for outbreaks or for cases with unusual features (e.g., severe or protracted diarrhea, systemic symptoms, need for hospitalization, or a

TABLE 23-9
***Escherichia coli* Intestinal Pathogens**

Category	Virulence Mechanisms	Clinical Features
Enterotoxigenic (ETEC)	Heat-labile or heat-stable toxins Adherence	Watery diarrhea in travelers and children
Enteroinvasive (EIEC)	Adherence and invasion	Dysentery
Enterohemorrhagic (EHEC)	Shiga-like toxins Adherence	Bloody diarrhea HUS/TTP
Enteropathogenic (EPEC)	Attachment and effacement	Watery diarrhea in children
Enteroaggregative (EAEC)	Adherence, ? cytotoxin	Watery or persistent diarrhea Children/developing countries, traveler's diarrhea, diarrhea in HIV-infected patients
Diffusely adherent (DAEC)	Adherence	Acute or persistent diarrhea Children/developing countries

HIV, human immunodeficiency virus; HUS/TTP, hemolytic-uremic syndrome/thrombotic thrombocytopenic purpura.

differential diagnosis including serious diseases such as primary IBD or ischemia).

Analysis of the information available yields limited numbers of reaction patterns in *E. coli*–associated infection that have been described in the human gut or inferred from in vitro models or from human infection with other organisms having similar virulence factors. These include the following: no histologic change (enterotoxigenic *E. coli* [ETEC]); observation of surface adherent organisms (enteropathogenic *E. coli* [EPEC], enteroaggregative *E. coli* [EAEC], possibly diffusely adherent *E. coli* [DAEC]; Fig. 23-98); mild, nonspecific inflammation (possibly all subtypes); ischemic-like change (EHEC); and acute infectious (self-limited) colitis (EHEC, enteroinvasive *E. coli* [EIEC], possibly ETEC).

ETEC organisms are thought to adhere to and colonize the surface of the small bowel where they elaborate their toxins.[659] It is possible that a serendipitously obtained small bowel biopsy specimen may contain adherent surface bacteria. Histologic appearances of the small bowel and colon are inferred from ETEC's close relationship with *Vibrio cholerae,* which does not cause histologically recognizable lesions in the small bowel or the colon. Therefore, normal colon would be expected in ETEC-associated diarrhea. It is possible that ETEC could cause some acute self-limited colitis. Recognizing the difficulty in identifying pathogenic *E. coli* in routine stool culture, it is possible that EIEC and EHEC could otherwise be responsible for some cases of acute self-limited colitis.

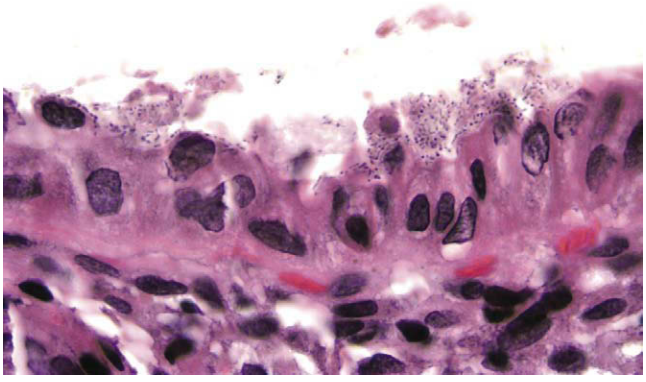

Figure 23-98 ■ Adherent rod-shaped bacteria presumed to be *Escherichia coli* from a patient with human immunodeficiency virus infection/acquired immunodeficiency syndrome and bacterial enterocolitis.

As stated earlier, diffuse active colitis was also seen in some examples of documented cases of infectious colitis. These infectious colitis cases were associated with an epidemic outbreak of *Shigella* dysentery. Because the pathogenic features of *Shigella* species are virtually identical to those of EIEC, it is possible that EIEC may on rare occasions cause the diffuse active colitis pattern of injury. That said, EIEC infection with this pattern of injury may represent an infectious exacerbation of underlying primary IBD.

The ability to adhere to and colonize host enterocytes or colonocytes is requisite for human infection for all six recognized categories of diarrheogenic *E. coli*. However, EPEC, EAEC, and DAEC, which are traditionally referred to as the *enteroadherent E. coli,* are best differentiated on the basis of their adherence patterns to HEp-2 cells in culture. These patterns include localized adherence (EPEC), aggregative adherence (EAEC), and diffuse adherence (DAEC).[659]

The human gut histopathologic features in EPEC in vivo have been described[661,662] and are similar to those seen in experimental animal models.[663] Jejunal biopsy specimens have demonstrated variable villous abnormalities without acute inflammation.[661,662] Adherent bacteria could be identified on routine H&E-stained sections on the luminal surface. Adherent surface bacteria have also been seen in colorectal biopsy specimens.[661] The characteristic attaching and effacing lesion can be recognized only by the use of electron microscopy.[659,661,662] The bacteria intimately adhere to the host cell by an attachment pedestal and cause effacement of the adjacent microvilli.

Human histopathologic features associated with EAEC and DAEC infection can be inferred only from animal models and in vitro studies.[659,664-666] Presumably, bacteria adhere to the surface epithelium of the small intestine and the colon.[667] EAEC and DAEC infection may be associated with variable villous abnormalities. Electron microscopic study has shown adherent bacteria in cell culture with a normal microvillous structure. In the colon, EAEC produces cytotoxic effects ultrastructurally (microvillous vesic-

ulation, enlarged crypt openings, creation of intercrypt crevices, and mucosal epithelial cell extrusion).[667]

The most detailed description of human ileal and colorectal infection with EPEC, EAEC, and possibly DAEC probably is found in a published review of patients with AIDS.[668] Unfortunately, the exquisite light and electron microscopic descriptions of these diarrheogenic bacterial enterocolitides were not complemented by microbiologic studies. Therefore, identification of these organisms as *E. coli* rests on the pathologic similarity to other reported cases and preliminary isolation studies that have shown that at least some of these cases were caused by EAEC and DAEC.[668]

The colonic histologic pattern showed surface epithelial degeneration with adherent bacteria (some extremely subtle) without colonic architectural distortion or significant inflammation. Electron microscopic examination demonstrated three patterns: (1) typical adhering and effacing lesions (as with EPEC), (2) a loosely adherent pattern with effacement (as with EAEC), and (3) an intercalated pattern with effacement in which vertically oriented bacteria were seen burrowing between intact microvilli. The intercalated pattern could be DAEC in vivo because it is similar to the pictures and descriptions of DAEC in other in vitro and animal models.[666]

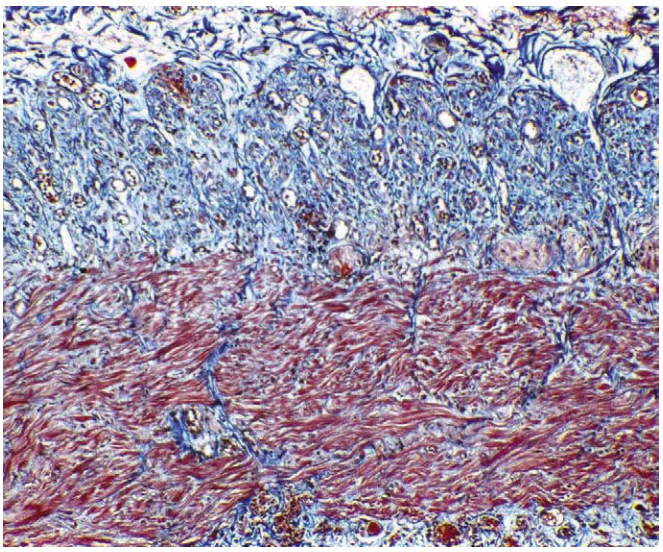

Figure 23-99 ■ Progressive systemic sclerosis showing atrophy and fibrosis of the inner circular layer of the muscularis externa (trichrome stain).

MOTILITY DISORDERS

Intestinal Pseudo-obstruction and Visceral Myopathy

The term *intestinal pseudo-obstruction* describes a disorder in which patients present with signs and symptoms of intestinal obstruction and in whom no mechanical obstructive lesion can be demonstrated.[669] Intestinal pseudo-obstruction can be associated with a heterogeneous group of conditions some of which can affect the colon.[669-671]

Systemic lupus erythematosus, dermatomyositis, and scleroderma can cause fibrosis of the muscularis externa.[669,671] Amyloid deposits can also affect colonic motility.[672]

Visceral myopathies can occasionally be identified in the colon. Recognized variants of familial visceral myopathy demonstrate differences in the mode of inheritance (autosomal dominant versus recessive), site of gut involvement, clinical symptoms, and extraintestinal manifestations. Visceral myopathies also occur in sporadic form.[673]

The intestinal pathologic changes of many familial and sporadic visceral myopathies are identical and consist of muscle cell degeneration, muscle cell loss, and fibrosis of the muscularis externa. The degenerative fibers appear swollen and rarified. Collagen may encircle the residual muscle fibers in areas of muscle fiber dropout and impart a vacuolated appearance.[671,673,674] These changes are often limited to, or are more severe in, the external layer of the muscularis externa.

The differential diagnosis of these forms of visceral myopathy includes other entities that cause fibrosis of the muscularis externa and encompasses ischemia, tuberculosis, and scleroderma. Ischemia usually is associated with a fibrous stricture and hemosiderin deposits. Tuberculosis typically causes strictures and granulomas, often with central necrosis. Progressive systemic sclerosis is associated with more patchy bowel involvement than are the visceral myopathies. The fibrosis is often denser and replaces all the muscle layers of the muscularis externa or is accentuated in the inner layer (Fig. 23-99). Vacuolar change is usually not seen with progressive systemic sclerosis.[671]

Visceral Neuropathy

The visceral neuropathies[675-681] form a complex group of unusual entities that vary in their pattern of inheritance, the extent of intestinal and extraintestinal involvement, and the nature of the histologic changes in the neural plexuses of the gut. Many of the neuronal and axonal changes are subtle; with the exception of inflammatory neuropathies[675] and some neuropathies associated with intranuclear or intracytoplasmic inclusions (e.g., red cytoplasmic inclusions in ganglion cells of mitochondrial neurogastrointestinal encephalomyopathy),[677] they cannot be recognized in routine H&E-stained sections. Difficult and unusual cases should probably be referred for consultation to pathology departments with particular expertise in the evaluation of visceral neuropathies. That said, referral is rarely indicated clinically. Some sporadic cases demonstrate mononuclear inflammation in the myenteric plexuses, and these cases can be identified by routine light microscopy.[678,679] Some of these cases are manifestations of paraneoplastic syndromes often linked to small cell carcinoma of the lung.[680] Others are postinfectious.[675] The inflammatory neuropathies can sometimes cause acquired aganglionosis and can be associated with circulating antibodies, such as anti-Hu, (ANNA-1, antineuronal nuclear antibody-1), anti-Ri, and anti-Yo (Purkinje cell cytoplasmic autoantibody).[680,681] An acquired form of hypoganglionosis associated with buserelin-induced formation of anti-GnRH (anti–gonadotropin-releasing hormone) antibodies has been reported.[682]

Investigators now recognize the role interstitial cells of Cajal (ICCs) play as gut pacemakers and as mediators of neurotransmission.[683,684] ICCs stain specifically with the tyrosine kinase receptor c-*kit*.[685] Immunohistochemical analysis for c-*kit* (CD117) and for CD34 (which reacts with many c-*kit* receptors) represents a relatively easy way to study severe constipation and intestinal pseudo-obstruction. Streutker and colleagues[685] described completely absent or markedly reduced numbers of ICCs in some cases of intestinal pseudo-obstruction. Reduced volumes of ICCs have also been described in some patients with slow-transit constipation.[685-689] Although the observations could be an epiphenomenon, they could form the basis of an alternate classification system for these cases.

Ceroidosis: The Brown Bowel Syndrome

Severe intestinal malabsorption for whatever reason (e.g., celiac sprue, cystic fibrosis) can be associated with dark brown or orange-brown discoloration of the bowel wall,[690,691] owing to deposits of a granular material that has the characteristics of lipofuscin in the smooth muscle of the muscularis externa and to a lesser degree the muscularis mucosae (Fig. 23-100). This excessive accumulation of lipofuscin is termed *ceroidosis* or the *brown bowel syndrome*. Whether this pigment deposition adversely affects muscle function is debated; however, damage to smooth muscle mitochondria has been described, and several reports have linked ceroidosis to intestinal pseudo-obstruction.[692] Because of the name *brown bowel syndrome*, ceroidosis may be confused with melanosis coli (discussed in the next section).

Melanosis Coli, Cathartic Colon, and Severe Idiopathic Constipation

Melanosis coli is a condition in which macrophages filled with lipofuscin-like pigment are found within the lamina propria or deeper in the wall of the colon (Fig. 23-101).[693,694] These macrophages may be of such numbers as to impart a brown or black color to the colonic mucosa (Fig. 23-102). Melanosis coli has been associated with increased apoptosis, which is often linked to ingestion of purgatives of the anthracene group (*Cascara sagrada,* aloe, rhubarb, senna, frangula).[695-697]

One group of patients has severe and persistent constipation with no apparent cause (idiopathic constipation or morbid obstipation). These patients, usually women, can have as little as one bowel movement every 1 to 4 weeks,[673] and many of these patients are so uncomfortable that they require colectomy for relief.[698-701] Because these patients almost invariably take laxatives, melanosis coli is usually

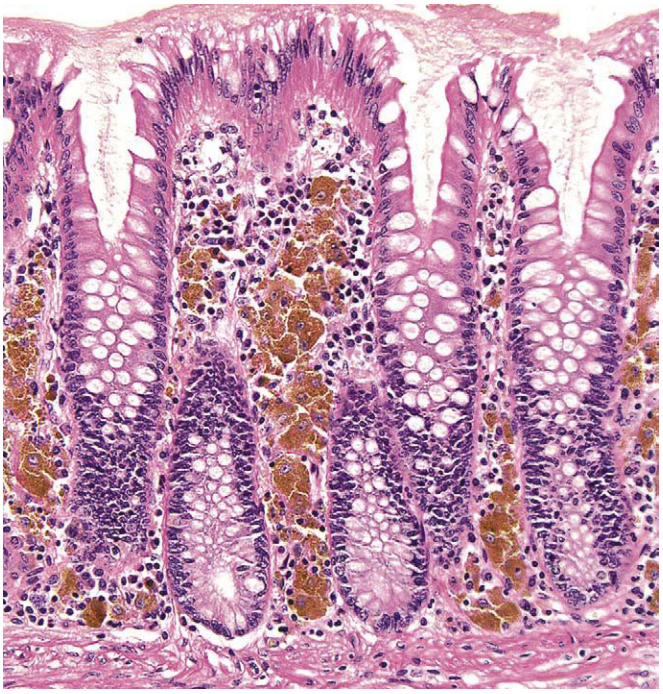

Figure 23-101 ■ Melanosis coli. Macrophages laden with lipofuscin-like pigment are present within the lamina propria.

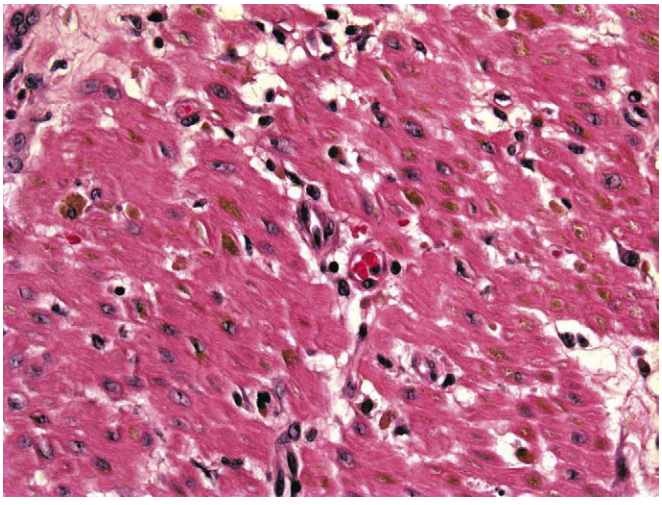

Figure 23-100 ■ Ceroidosis. Note the deposits of brown-staining lipofuscin-like granules in the smooth muscle of the muscularis externa.

Figure 23-102 ■ Specimen of resection performed for constipation shows severe melanosis coli imparting a black color to the mucosa.

found. What is so frustrating to the pathologist is that by H&E staining, the neuronal plexus and smooth muscle in these patients appear normal. Distinctive abnormalities of the myenteric plexuses (e.g., loss of "argyrophilic" neurons) have been reported using special silver staining techniques.[673,693,701,702] These tests are best performed by pathology departments with expertise in this area. Reduced volumes of ICCs have been described in some patients with severe constipation.[685,689] *Cathartic colon* is the name given to end-stage idiopathic constipation in which the bowel can no longer contract effectively. The mucosa has the gross appearance of snakeskin and histologically shows melanosis coli. The muscularis propria is thin and atrophic, and neurons are decreased in Auerbach's plexus.

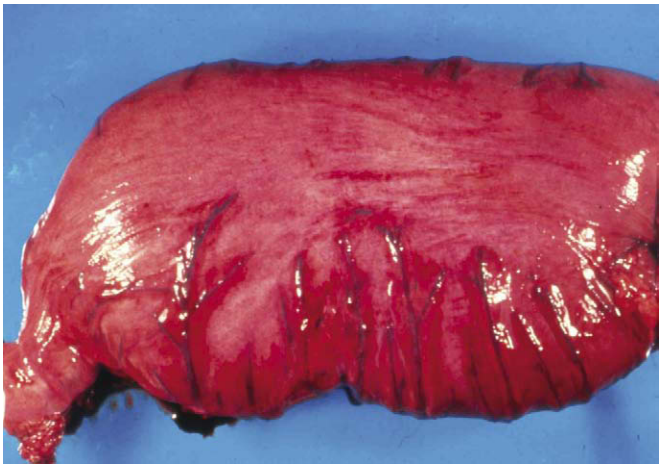

Figure 23-103 ■ Hirschsprung's disease, resection specimen. The unexpanded aganglionic segment *(left)* merges with the cone-shaped hypoganglionated region that extends into the dilated ganglionated zone *(right)*.

Hirschsprung's Disease and Allied Conditions

Hirschsprung's Disease

Hirschsprung's disease (aganglionic megacolon) has a predilection for boys and men. Approximately 90% of patients present in infancy with constipation, abdominal distention, vomiting, and delay of meconium stool; diarrhea may occur[703] and some patients may even be affected by life-threatening enterocolitis. Reports suggest that many cases of Hirschsprung's disease have a genetic basis. Both Hirschsprung's disease and MEN2 are associated with mutations of the *RET* proto-oncogene.[704-706] In cases of MEN2, the mutations are activating and enhance the function of the coded protein, whereas in Hirschsprung's disease the mutations are inactivating. Several cases of familial Hirschsprung's disease have been linked to mutations of the endothelin receptor-B *(ENDRB)* gene.[707] At least nine additional genes have been implicated in the pathogenesis of Hirschsprung's disease: *NTN* (seen only with *RET* mutations), *GDNF, EDN3, ECE-1, SOX10, PHOX2B, ZFHX1B, L1CAM,* and *7DHCR*.[706] Despite this progress, mutations of one or more of the known genes are detected in only half the patients with Hirschsprung's disease.

In the typical clinical picture of Hirschsprung's disease, the anus is normal. The anal canal and rectum are usually small and devoid of stool. In classic cases, these physical findings are confirmed by barium enema study. The contrast material flows into an unexpanded distal segment, then passes through a cone-shaped area, and finally passes into the dilated proximal bowel (Fig. 23-103).

The pathologic change is aganglionosis. The narrowed distal segment shows loss of ganglion cells in both the submucosa and myenteric plexuses, usually accompanied by hypertrophy of the muscularis mucosae and muscularis externa and increased numbers of nerve fibers in the submucosa and between the muscle layers of the muscularis externa.[708] Hypertrophied nerve fibers (>40 μm) derived from the extrinsic and sensory fibers are observed in many but not all cases of Hirschsprung's disease. In the tapered or cone-shaped region, the number of ganglion cells may be decreased (hypoganglionosis).

Historically, histologic diagnosis was based on full-thickness rectal biopsy specimens. However, this procedure requires general anesthesia and risks the development of stricture and perforation. Because the submucosal and myenteric plexuses stop at about the same level in Hirschsprung's disease,[708,709] suction biopsy that samples the mucosa and submucosa is now considered the method of choice for the diagnosis. All rectal biopsy specimens for suspected Hirschsprung's disease should be serially sectioned throughout the block and each section examined.[708,710] If no ganglion cells are found, then some comment should be made concerning the adequacy of the specimen. Biopsy specimens devoid of ganglion cells, but in which the amount of submucosa is less than the thickness of the mucosa, should be considered insufficient to diagnose Hirschsprung's disease.[708] If the biopsy specimen contains epithelium of the anal canal, this specimen should also be considered inadequate, because the anal canal and distal 2 cm of rectum are normally hypoganglionated or aganglionated.

Many pathologists prefer to examine frozen section slides stained for acetylcholinesterase in addition to standard H&E-stained sections. In Hirschsprung's disease, examination using the acetylcholinesterase stain demonstrates increased acetylcholinesterase-positive nerve fibers in the lamina propria and muscularis mucosae. The utility of this technique as an adjunct to diagnosis is debated. False-positive and false-negative reactions have been reported, and the use of this method is a matter of personal preference.[711-713]

Occasionally, ganglion cells may be difficult to identify using light microscopy alone, especially in the neonate.[708] In such cases, a positive immunohistochemical reaction for neuron-specific enolase can be valuable in documenting ganglion cells.[714] We have been successful in performing immunohistochemical analysis for neuron-specific enolase on sections after they have been stained with H&E and examined. Other immunostains such as cathepsin D, PGP 9.5 (protein gene product 9.5), RET, BMPR1A (bone morphogenetic protein receptor type 1A), and bcl-2 decorate ganglion cells.[710,715]

Frozen section is often used as an adjunct to visual inspection to select the site for colostomy. However, use of

the frozen section to establish a primary diagnosis of Hirschsprung's disease is best avoided because of the high rate of incorrect interpretations.[716]

LONG-SEGMENT HIRSCHSPRUNG'S DISEASE

In 90% of patients with Hirschsprung's disease, the aganglionic segment of colon is less than 40 cm in length. The remaining patients have longer aganglionic segments that may extend even into the small intestine.[673] Microscopically, the hypertrophied nerve trunks of short-segment Hirschsprung's disease are absent, but increased numbers of acetylcholinesterase-positive mucosal nerve fibers are usually but not always seen.[717]

ULTRASHORT-SEGMENT HIRSCHSPRUNG'S DISEASE

Ultrashort-segment Hirschsprung's disease (segments <2 cm) reportedly exists but is impossible for a pathologist to document by routine H&E stains of the rectal mucosa and submucosa alone because this segment of the colon is relatively hypoganglionated or aganglionated even in physiologically normal individuals. Rectal manometry may be used in the diagnosis of this lesion. Recognition of acetylcholinesterase nerve abnormalities similar to those seen in Hirschsprung's disease may complement that study. Some patients may have internal sphincter achalasia with abnormalities of nitric oxide–induced sphincter relaxation. Regardless of pathogenesis, some patients benefit from sphincterotomy.

Hypoganglionosis

Hypoganglionosis is regularly observed in the cone-shaped transition zone between normal and aganglionic bowel in Hirschsprung's disease.[673] Some authors believe that diffuse hypoganglionosis of the colon may give rise to megacolon similar to that observed in Hirschsprung's disease.[708,718] No accepted definition of hypoganglionosis exists; however, guidelines were offered by Meier-Ruge.[717] This study suggested that a decrease by a factor of 10 in the number of ganglion cells per centimeter of bowel as compared with normal (40 to 80 myenteric plexus neurons/cm bowel) is diagnostic of hypoganglionosis.[717] Other investigators have accepted much higher numbers of ganglion cells as evidence of hypoganglionosis.[719] In general, the condition has not been well characterized and many reports lack quantitation.[673] Diverse abnormalities have been described by special silver staining in cases that would have been called *hypoganglionosis* by H&E staining results,[720] and some cases of "hypoganglionosis" may be similar to those cases reported as severe idiopathic constipation or cathartic colon.

Intestinal Neuronal Dysplasia (Hyperganglionosis)

Intestinal neuronal dysplasia is characterized by hyperplasia of the myenteric plexuses, increased acetylcholinesterase activity in nerves of the lamina propria and submucosa, and increased numbers of ganglion cells with the formation of giant ganglia.[719,721-723] These giant ganglia, typically containing more than 7 to 10 neurons (normal ganglia contain 3 to 5), make up only 3% to 5% of all ganglia seen in a given case and are usually not seen in the distal 7 cm of the rectum.[724] Occasionally, ganglion cells may be found within the lamina propria but this feature should not be considered diagnostic for intestinal neuronal dysplasia because it can be seen in physiologically normal individuals.[725,726] The condition may give rise to signs and symptoms similar to those seen in Hirschsprung's disease. Intestinal neuronal dysplasia may occur in a localized or disseminated form. Similar lesions sometimes referred to as *ganglioneuromatosis* can be observed in patients with von Recklinghausen's disease or MEN2B.[673,722,723] Although some clinicians diagnose intestinal neuronal dysplasia based on abnormal acetylcholinesterase staining in specimens containing ganglion cells, others believe that one cannot rely on acetylcholinesterase staining alone for the diagnosis.[727] Diagnostic criteria for intestinal neuronal dysplasia and even its very existence are challenged[727,728] because 95% of infants so diagnosed experience normalization of gut motility within 1 year. Therefore, many of the observed "abnormalities" could be within normal range and in general the diagnosis should be reserved for florid pathologic cases.[729]

Other Related Conditions

In *zonal aganglionosis* or skip-segment Hirschsprung's disease, ganglion cells are found distal to one or more aganglionic segments.[729-731] Evidence suggests that zonal aganglionosis is rare and is likely to be acquired by ischemia (e.g., necrotizing enterocolitis), viral infection, or some other (e.g., immunologic) injury. The problem is that a rectal biopsy specimen may yield ganglion cells in spite of an authentic Hirschsprung's disease–like aganglionic lesion. Immaturity of ganglion cells[673,717] and hypogenesis of myenteric plexuses[717,718] have been reported to cause signs and symptoms similar to those seen in Hirschsprung's disease. Immunostains for bcl-2 may be helpful in detecting immature ganglion cells.[719]

MISCELLANEOUS CONDITIONS OF THE COLON AND RECTUM

Amyloidosis

The GI tract is a common site for amyloid deposits; such deposition has been documented in 70% of primary amyloidosis cases and in half of secondary cases.[672,732,733] Occasionally the deposition is symptomatic and causes ischemic manifestations such as bleeding diarrhea or infarct, sometimes referred to as *amyloid colitis*. On rare occasions, the deposits can be localized and form a tumor.[734] The AA (secondary) type of amyloid primarily deposits in the lamina propria and walls of blood vessels; the AL (primary or myeloma-associated) type tends to accumulate preferentially in blood vessel walls and in the muscularis externa.[672,735] Amyloid can be subtyped using immunohistochemical analysis.[736] Although subcutaneous biopsy or aspiration is an easy way to obtain tissue for diagnosis, rectal biopsy is still widely used to diagnose amyloidosis.[735,737]

Pneumatosis Cystoides Intestinalis

The term *pneumatosis cystoides intestinalis (PCI)* describes the occurrence of gas-filled cysts within the bowel wall. The large intestine is a common site of involvement; benign and fulminant forms have been described.[738,739] The fulminant form of PCI is most often seen in infants as a complication of ischemia. PCI in this setting is caused by mural invasion by gas-forming bacteria and subsequent formation of cysts (see Fig. 23-84). The fulminant form can be seen in adults sometimes in association with drugs such as antineoplastic chemotherapeutic agents or in pseudomembranous colitis.[739] Histologically, one sees ischemic change, bacterial overgrowth, and gas cysts predominantly within the submucosa. It is easy to dismiss the gas cysts as cutting artifact because an endothelial or histiocytic lining is rarely seen in this form of PCI.

The benign form of PCI is most often seen in adults and is usually asymptomatic,[738] although diarrhea, constipation, and rectal bleeding have been documented.[738,740] Benign PCI is often seen with comorbid conditions that either increase intraluminal pressure or provide a breach in mucosal integrity by which the gas can enter the bowel wall. These conditions include chronic obstructive pulmonary disease, emphysema, diverticular disease, appendicitis, cholelithiasis, peptic ulcer disease, abdominal trauma, Crohn's disease, and GI tract surgery.[738,739] At endoscopy, mucosal broad-based elevations that are sometimes semitranslucent have been described. Resection specimens often show crepitance. Microscopic analysis demonstrates occasional tears in the submucosal connective tissues, but more often one sees dilated spaces lined totally or partially by endothelium, inflammatory cells, histiocytes, and marked foreign body giant cell reaction (Fig. 23-104).[741]

The principal differential diagnostic consideration is the entity referred to as *pseudolipomatosis*.[742,743] Pseudolipomatosis resembles fatty infiltration of the lamina propria but ultrastructural study convincingly demonstrates that the spaces are, in fact, gas cysts (Fig. 23-105). Pseudolipomatosis has been associated with air inflation used to distend the bowel during colonoscopy. Some investigators have implicated cleaning agents used to disinfect colonoscopes.

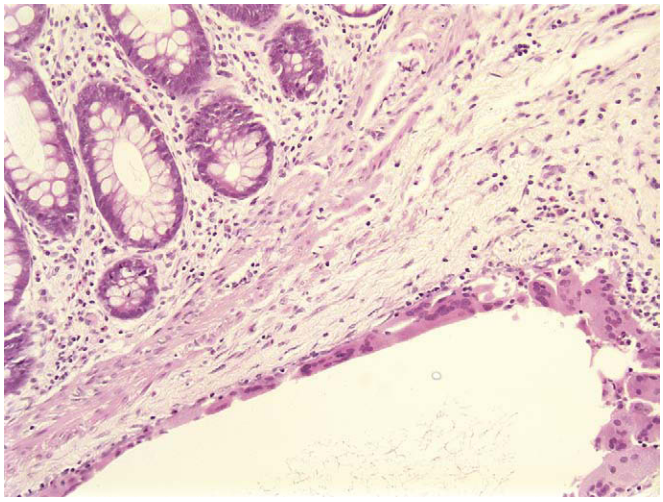

Figure 23-104 ■ The benign form of pneumatosis cystoides intestinalis showing a submucosal dilated space lined by histiocytes and a foreign body giant cell reaction.

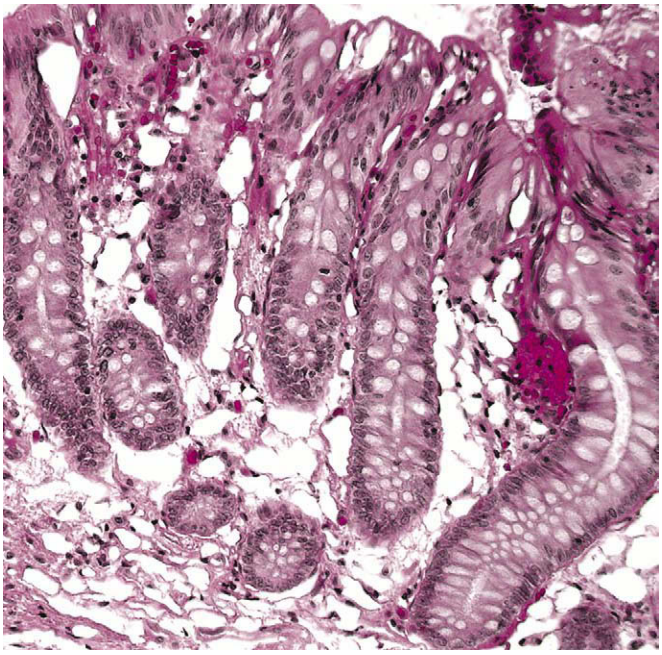

Figure 23-105 ■ Pseudolipomatosis. The lamina propria contains small gas cysts that resemble adipose tissue.

Fibrosing Colopathy

The term *fibrosing colopathy* has been applied to colonic strictures seen in some patients with cystic fibrosis.[744,745] The pathologic change is submucosal fibrosis, which can sometimes extend into the muscularis externa. Fibrosing colopathy has been linked to administration of high-dose pancreatic replacement therapy.

Developmental Abnormalities

Agenesis, Atresia, and Stenosis

Large bowel agenesis and atresia are extremely rare.[746,747] Congenital atresia and stenosis are associated with failure to pass meconium, abdominal distention, and vomiting. These conditions are often seen on a background of other congenital anomalies. Pathologically, one can see an imperforate septum, a portion of the colon replaced by fibrous cord, or the absence of a segment of colon and associated mesentery.

Malrotation

Colonic malrotation occurs with malrotation of the small bowel and is associated with abnormal anatomic relationships and fibrous bands; it may predispose patients to volvulus.[747,748] Mispositioning of the cecum and appendix may lead to delayed diagnosis of acute appendicitis.

Congenital Duplications, Diverticula, and Developmental Cysts

Congenital duplications and diverticula are located within the mesentery and often occur in combination with other congenital malformations.[749,750] Sometimes, the duplications are tubular, represent doubling of the bowel, and run parallel to the colon and rectum. Other duplications can become cystic and are often referred to as *enterogenous cysts*. Patients may have associated spine abnormalities. We classify tubular duplications that communicate with the lumen at one end as *congenital diverticula*. Small duplications and diverticula are usually asymptomatic. Larger ones may cause mass lesions, abdominal pain, constipation, or bleeding. Hindgut duplications may be associated with complex genital and urinary tract abnormalities.

Duplications and congenital diverticula usually have organized layers of smooth muscle sometimes with a nerve plexus within their walls. Mucosal linings if present resemble colon, respiratory epithelium, or gastric mucosa. As lesions enlarge to become cystic, the lining and the wall can become atrophic.[751]

The retrorectal space is a relatively common location for developmental cysts that can become symptomatic in adults.[752-754] Epidermoid or dermoid cysts are unilocular, are lined by squamous epithelium, and may contain adnexal structures (dermoid cyst) and lack smooth muscle in the wall. Rectal duplications can become cystic. Rectal duplications are also unilocular, are lined by colonic, gastric, or respiratory epithelium, and have an organized muscular wall that recapitulates the muscularis externa. The retrorectal cystic hamartoma is often referred to as a *tailgut cyst*. This lesion manifests as a multilocular cystic and solid tumor (Fig. 23-106). The variably sized cysts can be lined by squamous, transitional, or glandular epithelium. Disorganized bundles of smooth muscle are found within the wall. Inflammatory changes such as a foreign body giant cell reaction are quite common. Developmental cysts in the retrorectal space are susceptible to infection and fistula, and associated malignancy has been reported.[754] Therefore, total excision is recommended.

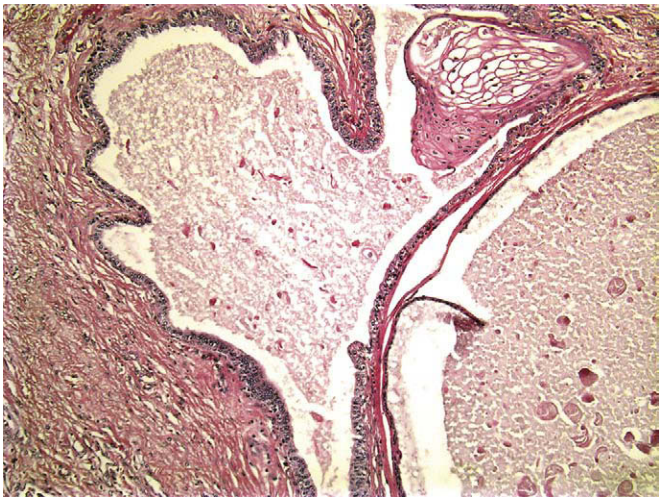

Figure 23-106 ■ Tailgut cyst. These retrorectal cystic lesions are typically multilocular. The cysts can be lined by squamous, transitional, or glandular epithelium.

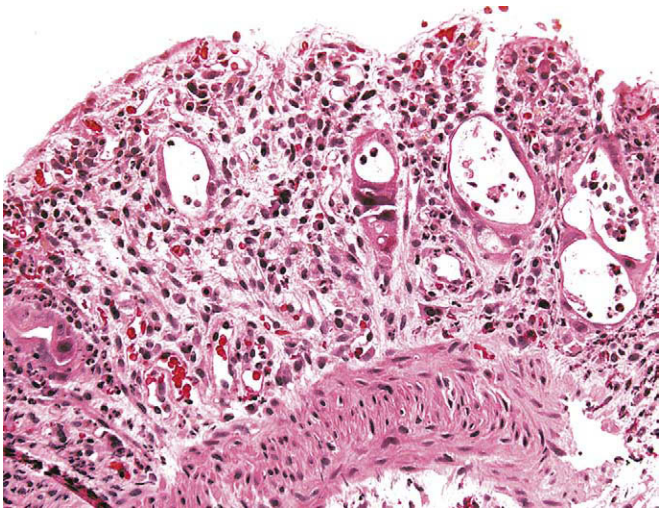

Figure 23-107 ■ Acute irradiation change. Sections show marked epithelial atypia. Features that favor radiation effect include the bizarre atypia, the maintenance of tubular structures, the relatively low nuclear-to-cytoplasmic size ratio despite the cellular gigantism, and the paucity of mitotic figures.

Antineoplastic Chemotherapy and Radiation Effect

Acute Changes

The histologic changes associated with acute chemotherapy- or radiation-induced colitis are similar. Necrosis, ulcer, and inflammation occur usually within 2 weeks of the cessation of therapy.[593,755,756] Epithelium lining the colonic tubules often shows marked enlargement with large atypical nuclei and loss of intracellular mucin (Fig. 23-107). Apoptotic bodies similar to those seen with grade 1 GVHD may be prominent.[757] Typically, the acute changes subside in 1 to 2 months.[755,758]

The epithelial atypia seen as a result of acute irradiation and chemotherapy can be alarming and may mimic the appearance of glandular dysplasia and carcinoma. Features favoring chemotherapy or radiation effect over dysplasia or carcinoma include (1) overall preservation of mucosal architecture, (2) bizarre atypia, (3) maintenance of a relatively low nuclear-to-cytoplasmic size ratio despite cellular enlargement and nuclear atypia, (4) a paucity of mitotic figures, (5) recognition of similar atypia in nearby fibroblast and endothelial cells, and (6) lack of an infiltration pattern in tumor desmoplasia.[759] The taxanes can cause epithelial changes that can mimic high-grade glandular dysplasia[760] similar to the changes seen with colchicine toxicity.[761] The histologic changes include increased apoptosis, increased mitotic figures, and "ringed" mitotic figures that correlate with metaphase arrest (Fig 23-108). The nuclear stratification and loss of polarity can mimic dysplasia.[760,761]

Chronic Effects

Late complications of radiation-induced change are better documented than are antineoplastic chemotherapy effects and may occur weeks to years after therapy.[593] These late complications of radiation include chronic colitis, stricture,

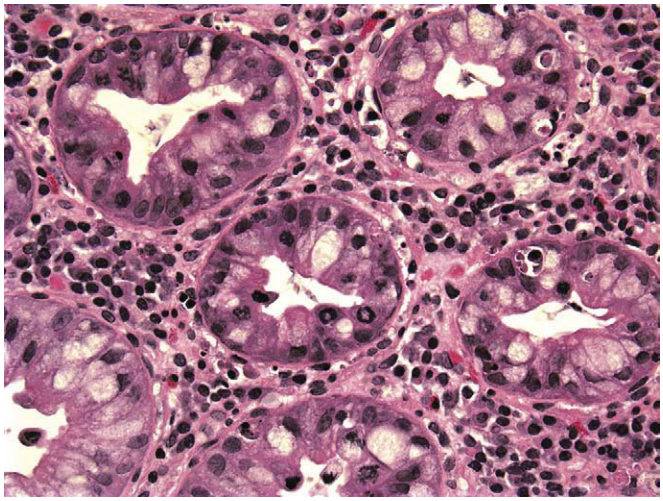

Figure 23-108 ■ Colchicine effect within a colonic hyperplastic polyp. Note the numerous apoptotic bodies and the "ringed" mitoses. The nuclear stratification can mimic dysplasia.

ulcers, and fistula.[594] The histologic pattern resembles that of ischemic damage with mucosal atrophy and architectural change. Mucosal and submucosal blood vessels can become ectatic. Fibrosis occurs and often resembles hyalin. Fibrosis can affect any bowel layer, including the muscularis externa. Atypical radiation-type fibroblasts can persist for years. Other vascular changes include intimal fibroplasia, accumulation of foamy macrophages in blood vessel walls, and luminal stenosis.

Infarcted Epiploic Appendices

Epiploic appendices are pedunculated, serosa-covered accumulations of adipose tissue seen on the lateral aspects of the colon. They can become very large in obese individuals. The pedicles of epiploic appendices are thin and prone to torsion, a feature that can cause infarct and even amputation. Infarcted epiploic appendices can appear as fine, gray-white nodules attached to the bowel or even can be found loose within the abdomen at surgery. These appearances can mimic metastatic carcinoma or foreign body. The subsequent biopsy specimen can be confusing to the pathologist who is asked to identify the frozen section. Microscopically, these lesions show a central zone of infarct with mummification of the adipose tissue surrounded by a variable amount of fat necrosis and calcification. The outermost portion usually shows fibrosis.[762]

Hyperplastic Pacinian Corpuscle

Pacinian corpuscles occur in many areas of the body. Although most are noted in the skin, they occur in the base of the mesentery. For unknown reasons, these intra-abdominal pacinian corpuscles can enlarge up to 1.0 cm or more and thus can mimic tumor implants or carcinomatosis.[763,764] They also may be a source of confusion to the surgical pathologist asked to identify them at frozen section and are often misinterpreted as nematodes. Histologically, this specialized end organ resembles its cutaneous counterpart. A central blood vessel and nerve are surrounded by tortuous, roughly concentric lamellae (Fig. 23-109).

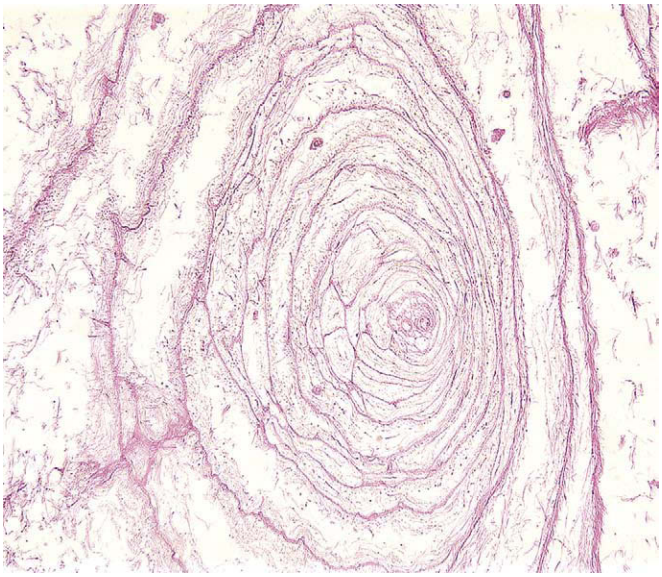

Figure 23-109 ■ Hyperplastic pacinian corpuscle. Microscopically, hyperplastic pacinian corpuscles can mimic a parasite. The histologic pattern, however, shows a central blood vessel surrounded by edematous concentric lamellae.

Barium Granuloma

Extravasation of barium sulfate used in radiologic examination outside the lumen of the colon and rectum may elicit an inflammatory response often referred to as a *barium granuloma*. These lesions are usually encountered coincidentally in resection specimens in biopsies performed for IBD. Rarely, this inflammatory reaction can produce a polypoid mass or ulcerated lesion that mimics neoplasm.[765] Microscopically, barium sulfate appears olive green and is refractile, especially with the microscopic condenser lowered (Fig. 23-110). The small granular crystals do not

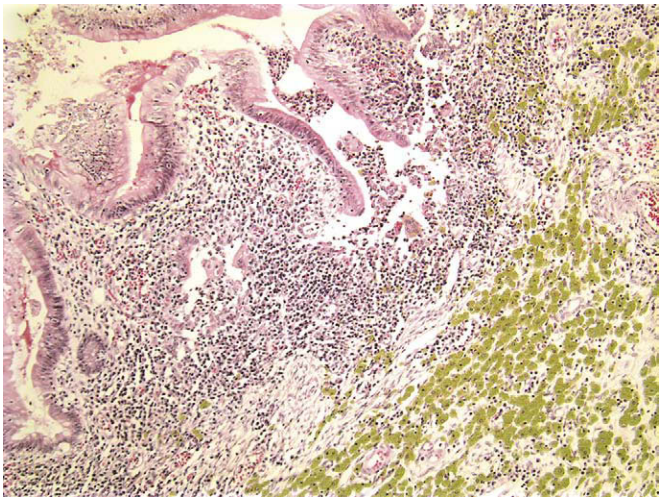

Figure 23-110 ■ Barium granuloma. Macrophages are present that contain olive green refractile extravasated barium sulfate.

bend polarized light and coalesce within connective tissue and macrophages. Water-soluble contrast media such as Gastrografin (sodium amidotrizoate and meglumine amidotrizoate) tend not to cause an exuberant inflammatory response. Gastrografin morphologically is composed of larger rectangular or rhomboidal light tan to pale yellow crystals.

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