8 Colon

Colon biopsies are most often performed for one of three reasons:

1. To evaluate a polyp or mass
2. To study a patient with inflammatory bowel disease and monitor dysplasia
3. To look for an explanation for diarrhea

The history is very important; you should not be diagnosing a tubular adenoma when the endoscopist did not see a polyp. You may also be missing a more ominous diagnosis (discussed later). Assuming that you have at least a succinct history or description from the endoscopist, therefore, your approach to the biopsy depends on what you are looking for.

Normal Histology

Normal colonic mucosa should have a flat surface and nicely parallel crypts, like "test tubes in a rack." The crypts are lined with goblet cells, endocrine cells, and precursor cells. Paneth cells, which are red granular cells with basal nuclei, are normal in the ascending and transverse colon but abnormal in the left colon. Immediately under the epithelium is the lamina propria, which is separated from the underlying submucosa by the muscularis mucosa (Figure 8.1). Normal constituents of the lamina propria include lymphocytes, plasma cells, and eosinophils. How many lymphocytes are too many? In general, they are assumed to be physiologic unless there is clinical or histologic evidence of chronic damage to the mucosa (see later discussion). Lymphoid aggregates are common and unremarkable.

Deep to the submucosa is the thick muscularis propria. Beyond this layer lies the serosal fat. In biopsy or polypectomy tissue, seeing adipose tissue below the muscularis propria is *not* normal and means the endoscopist may have taken a full-thickness specimen. In other words, perforated the colon. This should prompt an immediate courtesy call.

Looking for Polyps

Adenomas

An adenoma (at least in the tubular-to-villous family) is defined as a polyp with low-grade dysplasia. Low-grade dysplasia in the colon indicates a cytologic change and stands out from normal colon as looking blue on the slide. The cells lining the crypts and the surface become tall and dark (because of depleted mucin) and have cigar-shaped and/or pseudostratified hyperchromatic nuclei (Figure 8.2). Mitoses may be present but are generally not apical.

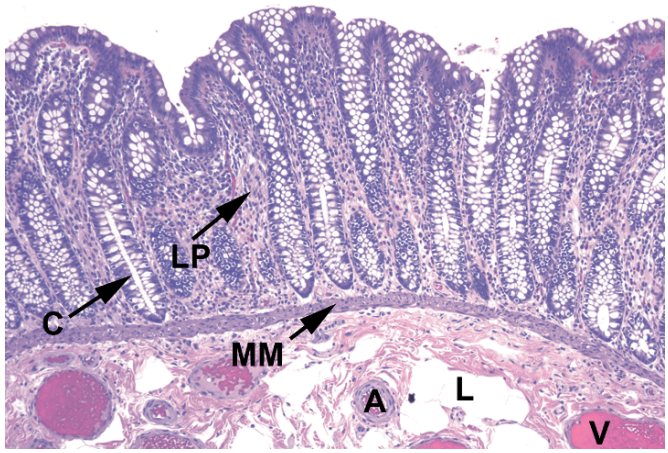

Figure 8.1. Normal colon. Section through colonic mucosa showing parallel crypts (C), lamina propria (LP), muscularis mucosa (MM), and submucosal arteries (A), veins (V), and lymphatics (L).

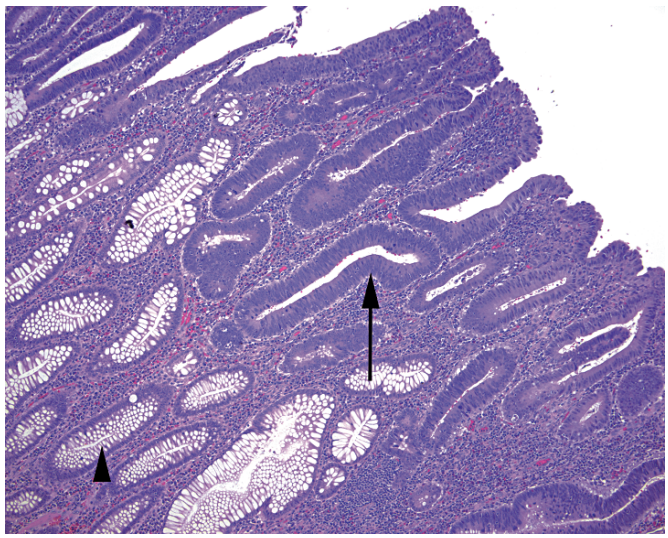

Figure 8.2. Tubular adenoma. This section shows an early tubular adenoma in which low-grade dysplasia is seen in the surface glands (arrow), while the deeper glands are uninvolved (arrowhead). The adenomatous epithelium is dark due to crowded and hyperchromatic nuclei and loss of mucinous goblet cells. Mitotic activity and neutrophils are common in adenomas but may also be seen in benign epithelium.

The dysplasia must extend all the way to the surface epithelium to qualify as an adenoma; if the epithelium shows signs of maturing as it ascends, it is more likely reactive changes.

Adenomas are subdivided by their architecture. The most common type is the *tubular adenoma*, which has a smooth surface and parallel crypts, similar to normal epithelium. A *villous adenoma* is covered in finger-like projections, whereas a tubulovillous adenoma has features of both.

Important considerations for sign out include the following:

- Margins: When an entire polyp is plucked off the colon, ideally it is cross sectioned so that you can see the stalk. Ink on the stalk is helpful, but cautery also identifies your margin. If there are identifiable margins, mention whether or not the dysplasia (adenomatous epithelium) extends to the margin.
- Dysplasia: By definition, low-grade dysplasia is present. However, *high-grade dysplasia* is equivalent to carcinoma in situ and must be noted. The diagnosis of high-grade dysplasia

is made on the basis of architecture rather than cytology. The glands should become cribriform, fused, or back to back (Figure 8.3). Usually the term *high-grade dysplasia* is reserved for areas that look so complex you are worried about carcinoma but cannot prove invasion. High-grade dysplasia is also usually accompanied by ugly cytology: total loss of nuclear polarity, significant pleomorphism, atypical mitoses, and large nucleoli.

- Carcinoma: All adenomas are considered at least premalignant lesions; sometimes you will find carcinoma arising in a polyp on biopsy. To diagnose carcinoma (as opposed to high-grade dysplasia), you must demonstrate cancer crossing the basal lamina, that is, into the lamina propria. Clues to invasion include a jagged interface with the lamina propria, individual infiltrating cells, desmoplastic response, and a pinking up of the invasive cells (Figure 8.4).
- Invasion: Invasion into the lamina propria alone is called *intramucosal carcinoma*. This may happen in a large polyp, and excision is still curative. Within the lamina propria, cancer has no metastatic potential. However, once malignant cells cross the muscularis mucosa into the

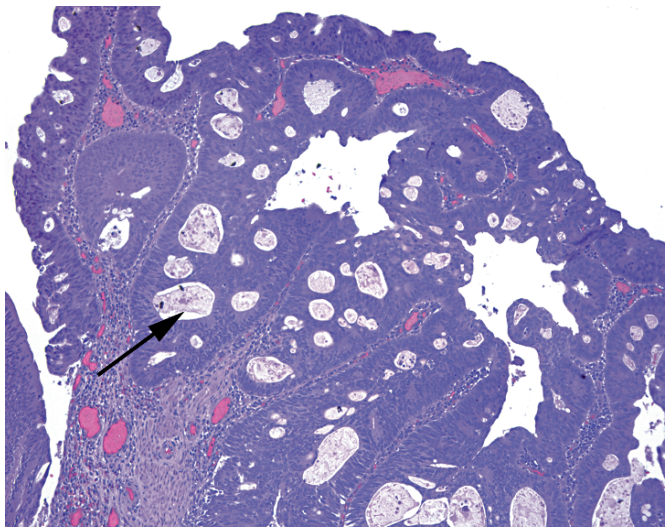

FIGURE 8.3. High-grade dysplasia in an adenoma. The diagnosis is largely based on architectural features, such as cribriform growth (arrow).

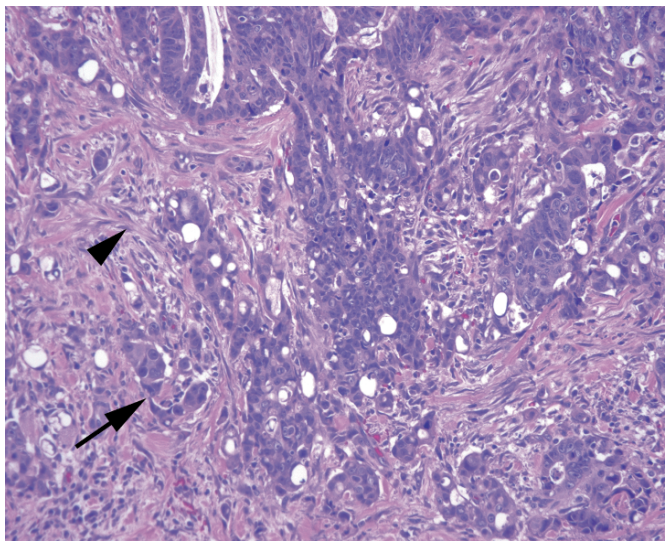

FIGURE 8.4. Invasive adenocarcinoma. Poorly formed glands and single cells (arrow) infiltrate through a desmoplastic stroma (arrowhead). Cells show marked pleomorphism and prominent nucleoli.

submucosa, there is at least theoretical risk of metastasis. The extent of invasion must be noted in the diagnosis.

Hyperplastic Polyps

Hyperplastic polyps are those in which the epithelial cells, although benign, begin to outgrow their available space. The glands have an increased number of goblet cells and therefore look pale or cleared out next to normal epithelium. Furthermore, because the surface area is outgrowing the lamina propria, hyperplastic polyps take on a distinctive frilly (as in a skirt) or lacy appearance (Figure 8.5). Crypts cut in cross section have a distinctive star-shaped lumen.

A polyp with adenomatous-looking cells at the base of the crypts, and frilly hyperplastic cells at the surface, is still a hyperplastic polyp. Remember that surface maturation is not consistent with a tubular adenoma. However, a true adenoma with a serrated surface profile may be a *serrated adenoma* (keep reading).

Serrated Polyps

Serrated is an adjective used to describe the frilly and undulating architecture seen in a classic hyperplastic polyp. Historically, a "serrated adenoma" was a polyp with low-grade dysplasia extending to the surface, as seen in tubular adenoma, but with serrated architecture.

Recently, large (>1 cm) hyperplastic polyps occurring in the right colon were recognized as a distinct subtype of polyp with malignant potential, associated with the microsatellite instability (as in hereditary nonpolyposis colorectal cancer [HNPCC]) cancer pathway. They are called either *sessile serrated adenomas* or *sessile serrated polyps*. The crypts have characteristic dilation and branching at the base ("duck feet"), and the epithelial cells may be more eosinophilic (less mucin) and pseudostratified than the usual hyperplastic polyp (Figure 8.6). However, mature goblet cells and the frilly surface are still evident.

The difference is in the depth of proliferation: hyperplastic polyps show mostly surface hyperplasia and expansion, whereas the sessile serrated group (remember that *sessile* means *flat*) is hyperplastic right down to the base. These are important to recognize, because they should be treated clinically like an adenoma, not just a hyperplastic polyp.

Inflammatory Pseudopolyps

Inflammatory pseudopolyps are polypoid structures that consist either of granulation tissue (when adjacent to an ulcer) or of inflamed lamina propria with distorted crypts. Given the inflammation, there can be severe reactive changes in the crypts (resembling dysplasia).

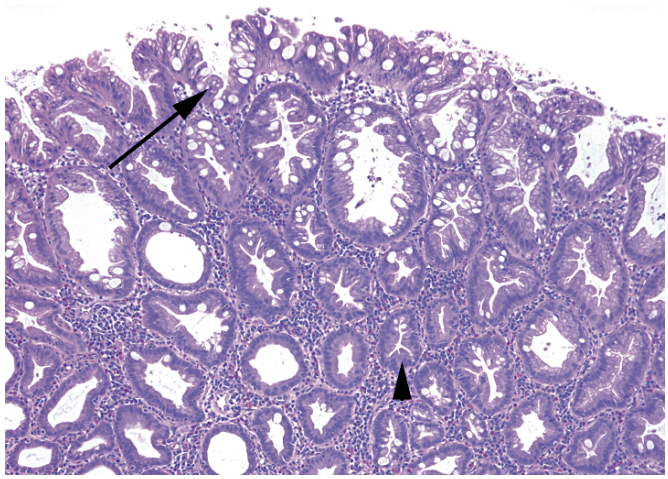

Figure 8.5. Hyperplastic polyp. The surface of the polyp shows a characteristic "frilly" appearance (arrow), with hyperplastic mucinous epithelium and prominent goblet cells. Deeper crypts (arrowhead) show star-shaped lumens.

However, surface maturation should be visible. These are common in inflammatory bowel disease. A polyp that looks like an inflammatory polyp but occurs without background inflammatory disease may be a *juvenile polyp*, a diagnosis that can be made in a patient of any age.

Prolapse-Type Lesions

Mucosal prolapse is like a tiny focus of intussusception; a protruding bulge of mucosa gets pulled, twisted, generally battered in the breeze, suffers ischemia and trauma, and begins to look fairly weird as it tries to repair itself. Features include extension of the muscularis mucosa into the lamina propria, as disorganized fibers; crypt distortion and dilation with diamond-shaped crypts; hemosiderin; and edema and inflammation with reactive atypia (Figure 8.7). This lesion may be called a *polypoid prolapsing mucosal fold* in the colon, *solitary rectal ulcer syndrome* in the rectum, or *inflammatory cloacogenic polyp* at the anorectal junction.

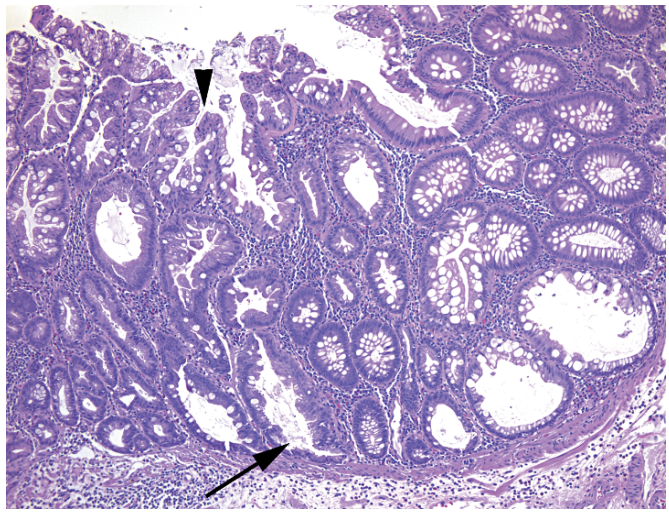

Figure 8.6. Sessile serrated adenoma. The surface looks similar to a hyperplastic polyp (arrowhead), but the base shows sideways branching of crypts (arrow) caused by proliferation at the base of the lesion.

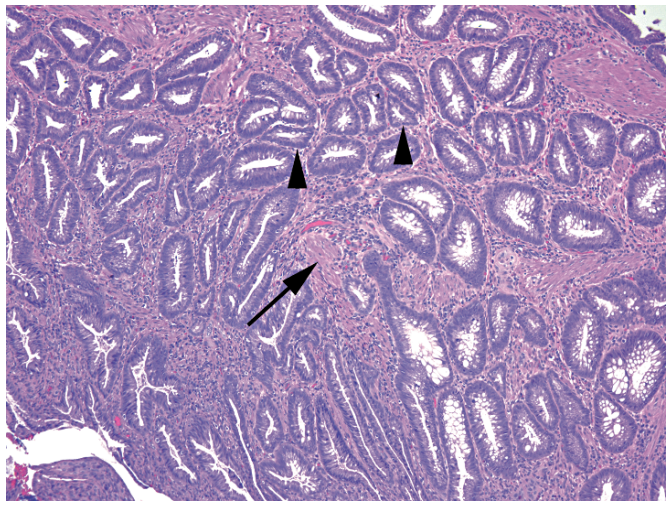

Figure 8.7. Prolapse lesion. The center of this prolapse-related polyp shows typical features, including angulated or diamond-shaped crypts (arrowheads) and smooth muscle growing between crypts (arrow).

Adenocarcinoma

Adenocarcinoma of the colon seems to follow principally two lines of tumorigenesis, highlighted by two familial cancer syndromes. Familial adenomatous polyposis (very rare) is a mutation in the *APC* gene, a tumor suppressor gene, such that the second allele is vulnerable to somatic mutations. Knockout of both genes leads to adenoma formation. These patients have thousands of tubular adenomas and inevitably progress to adenocarcinoma. *p53* is involved in this same pathway, but as a late event in the progression from adenoma to carcinoma. The resulting adenocarcinoma is of the garden variety, indistinguishable from sporadic adenocarcinoma. Approximately 85% of all colon cancers arise from this pathway (most of them sporadic, not familial, hits to these genes).

The second major pathway is seen in HNPCC patients (less rare), who have defective DNA mismatch repair genes (such as *hMLH1* and *hMSH2*). As above, these are tumor suppressor genes that are vulnerable to the "second hit" somatic mutation. The double hit leads to microsatellite instability. However, instead of tubular adenomas, these tumors tend to arise in the sessile serrated adenomas and mature into medullary, mucinous, or signet-ring cancers, usually right sided. Approximately 15% of all colon cancers fall along this pathway, most of them sporadic.

Medullary carcinoma of the colon is a distinct and rare variant with a dense associated lymphoid population (like medullary carcinoma of the breast) but a bland, almost neuroendocrine cytology (like medullary carcinoma of the thyroid), although there is probably no connection. It is worthy of mention in the colon, as medullary carcinoma in the right colon of a young person suggests HNPCC.

Carcinoid (Neuroendocrine) Tumors

The most common locations for gastrointestinal carcinoids are the appendix and small bowel, with rectum and colon further down the list. Often submucosal, carcinoid tumors may present as a mass on endoscopy or cause obstruction. The carcinoid syndrome (flushing, etc.) does not occur until and unless the tumor metastasizes to the liver. Carcinoid tumors are characterized by uniform neuroendocrine-type cytology and trabecular, spindly, or rosette-like architecture (Figure 8.8). As in other sites, the histologic features are not predictive of behavior, and a very bland-looking tumor may still metastasize. Neuroendocrine tumors are covered in more depth in Chapter 24.

Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) is an idiopathic relapsing inflammatory disease affecting the colon and consists primarily of ulcerative colitis and Crohn's disease. A definitive diagnosis of IBD must include changes of chronicity. A simple acute colitis without chronic changes may be due to infection, ischemia, drugs, or bowel preparation, as well as IBD. There is a long list of descriptive diagnoses used for the colon, depending on whether there are acute or chronic changes, whether the changes are focal or diffuse, and whether the patient has a history of IBD. The changes should be pretty compelling to make a first-time diagnosis of IBD, as the patient will carry the label for life.

Features of activity (Figure 8.9) include the following:

- Polys, polys, spot the polys: neutrophils in the crypt epithelium = cryptitis.
- Neutrophils in the crypt lumen = crypt abscesses.
- Erosions and ulcers and pus are also consistent with active lesions.

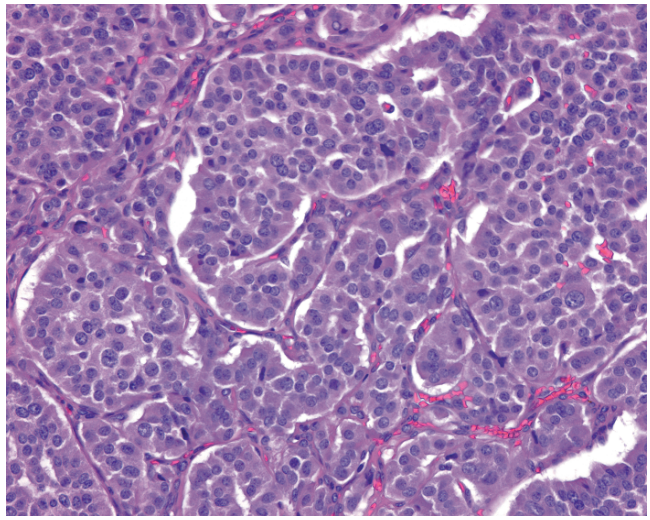

Figure 8.8. Carcinoid tumor. Nests and ribbons of cells separated by delicate fibrovascular septa are classic, as are the round and regular nuclei with finely speckled chromatin.

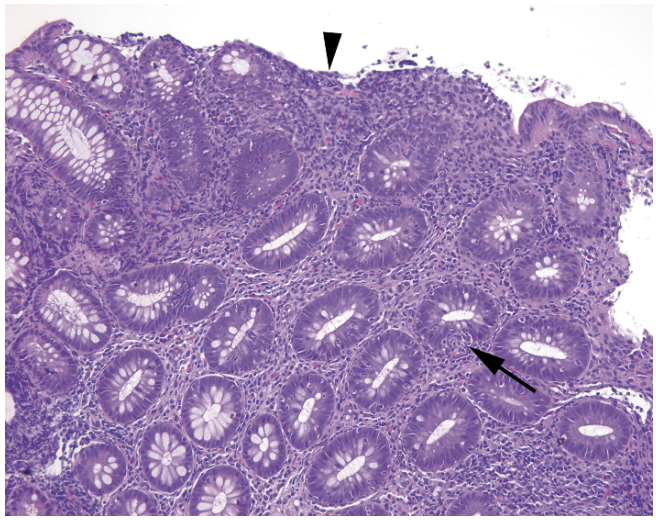

Figure 8.9. Active colitis. Neutrophils are seen in the epithelium of the crypts (arrow), and the surface is ulcerated (arrowhead).

Features of chronicity (Figure 8.10) include the following:

- Crypt distortion (branching, tortuous, or sideways crypts; test tubes warped)
- Crypt loss (test tubes missing)
- Crypt atrophy (test tubes too short)
- Basal plasmacytosis (test tubes pushed up by a dense layer of chronic inflammation)
- Paneth cell metaplasia (Paneth cells in the left colon)

Chronic inflammatory disease is usually qualified as either active (having neutrophils) or inactive. The differentiation between Crohn's disease and ulcerative colitis is difficult on biopsy; a more definitive diagnosis is made on colectomy (should it come to that). However, there are features that suggest one or the other. Remember that you must first see chronic changes to consider making the diagnosis of IBD (at least at the time of initial diagnosis).

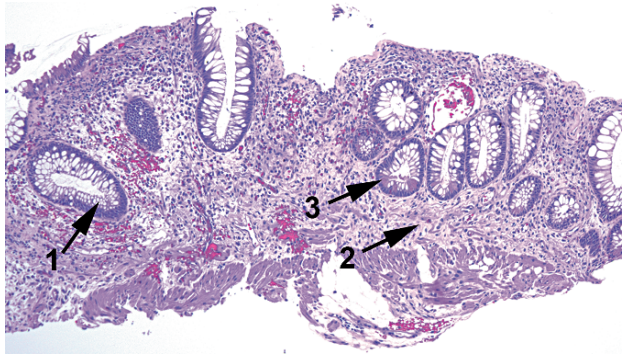

Figure 8.10. Chronic inflammatory disease. This biopsy specimen shows a loss of crypt density (atrophy); crypt distortion (1); elevation of crypts off of the muscularis mucosa (2), often accompanied by a dense basal lymphocytic infiltrate (not seen here); and Paneth cell metaplasia (3).

Features of Crohn's Disease

- Patchy mucosal involvement with skip areas
- Granulomas and/or histiocytes (Figure 8.11)
- On colectomy, transmural inflammation, cobblestoning, fissures, fistulas, and creeping fat

Features of Ulcerative Colitis

- Predominantly distal involvement or pancolonic (no skip areas)
- Diffuse mucosal inflammation, many polys

Note, however, that once a patient has begun treatment ulcerative colitis may appear patchy in activity.

Dysplasia in Inflammatory Bowel Disease

Once diagnosed, IBD must be followed both to monitor activity (response to therapy) and to look for dysplasia. The constant inflammation puts the patient at high risk for developing cancer. Therefore, the presence or absence of dysplasia should be noted in every IBD surveillance biopsy specimen.

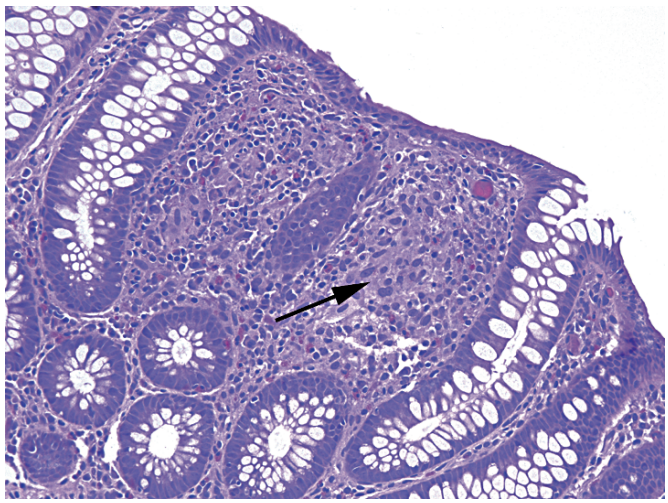

Figure 8.11. Granuloma in Crohn's disease. The granulomas in Crohn's are small and subtle. This image, taken at 40×, shows a small collection of histiocytes (arrow) between crypts.

The tricky part is that often areas of dysplasia may arise in a polypoid irregularity or fold, and it is difficult to tell a *dysplasia-associated lesion or mass* (DALM) from a sporadic and unrelated tubular adenoma. Both show the typical adenomatous epithelium. Does it matter? In fact, the DALM may be at higher risk of transforming to cancer and is usually p53 positive on immunostain (unlike an adenoma). It is managed more aggressively than a sporadic adenoma.

Flat dysplasia (not associated with a mass) can be a subtle and subjective call. Intense inflammation causes reactive changes that can look much like dysplasia. However, remember that true dysplasia does not mature at the surface. Also, be very wary of calling dysplasia in a sea of neutrophils.

Microscopic Colidities

Microscopic colidities are defined by having no abnormal endoscopic findings; they are only diagnosable under the microscope. The symptoms include chronic watery diarrhea, abdominal pain, fatigue, and weight loss. The two types are *lymphocytic colitis* and *collagenous colitis*. Both are characterized by the following:

- A lack of chronic changes (no crypt distortion, no basal plasmacytosis)
- A predominantly top-heavy lymphocytic infiltrate
- Intraepithelial lymphocytes
- Evidence of damage to the epithelium (loss of cells)

Collagenous colitis affects predominantly women and has a distinct thickened collagen band along the basement membrane. This band must be irregular and blurred into the lamina propria, not just thick. A trichrome stain confirms the diagnosis (Figure 8.12).

In the setting of a dense lymphoplasmacytic infiltrate, pay attention to whether the blueness is top heavy (more prominent under the surface) or bottom-heavy (more prominent at the base of

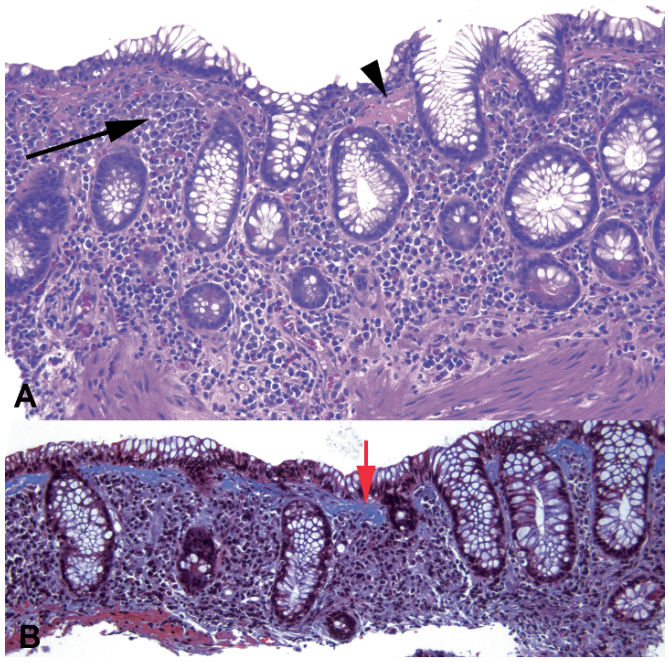

Figure 8.12. Collagenous colitis. **(A)** The hematoxylin and eosin stain shows a top-heavy lymphoplasmacytic infiltrate (arrow) accompanied by a dense pink material just under the surface epithelium (arrowhead). **(B)** A trichrome stain confirms the thickened collagen table (blue on this stain, red arrow), which has an irregular border and entraps nuclei within the lamina propria.

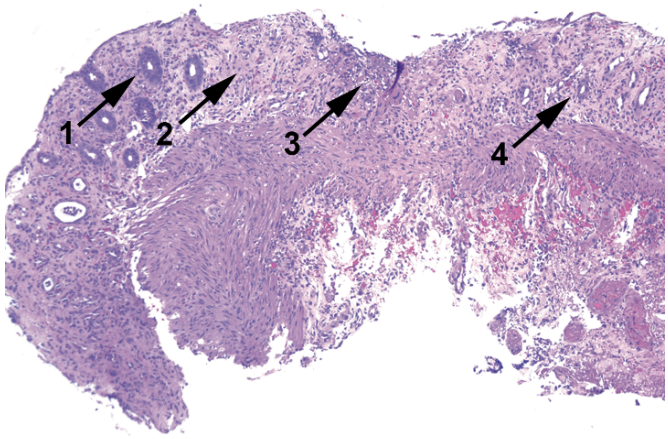

Figure 8.13. Ischemic colitis. Features include small dark regenerative crypts (1), hyalinization and fibrosis of the lamina propria (2), ulceration (3), and crypt dropout (4).

the crypts). Inflammatory bowel disease tends to be bottom-heavy and the microscopic colidities more top-heavy. This is a soft feature rather than a rule.

Other Colidities

Ischemic colitis may have many appearances, from focal active colitis to diffuse pseudomembranous colitis. Acute or transient ischemia appears as damage to the superficial surface of the mucosa, with hemorrhage and coagulative necrosis. Prolonged ischemia causes fibrosis of the lamina propria and a top-down atrophy of the crypts: they appear collapsed at the surface and regenerative at the base (Figure 8.13).

Infectious colitis is not often biopsied because of its usually self-limited course. It may range from no pathologic findings to a severe active colitis.

Diversion colitis is a special entity associated with a Hartmann pouch, which is a blind-ended rectal cavity disconnected from the fecal stream. The loss of normal colonizing flora causes a nonspecific colitis, which may be mistaken for inflammatory bowel disease.

Both drugs and the bowel preparation process may cause transient acute colitis. Acute inflammation in the absence of chronic changes is non-speficic, and should not be overinterpreted.