and organisms from nonharmful ones. As a result, a large and well-maintained network of many different mucosal immune cells exists, including cells involved in reducing immune responses (regulatory cells) and those involved in activating immune responses. In IBD, this homeostatic balance, or immune tolerance, is dysregulated, resulting in overactivation of the immune system.

In Crohn's disease, there is an excessive and persistent CD4-positive helper T lymphocyte subtype 1 (T_H1) immune response to components of commensal bacterial flora. The T_H1 cytokine profile, which includes interferon-γ, IL-2, IL-12, and tumor necrosis factor-α (TNF-α), is elevated in patients with Crohn's disease. Patients with UC demonstrate greater expression of IL-5 and IL-13, cytokines characteristically associated with a T_H2 response. In addition, non-T_H1/T_H2 pathways have been identified as being potentially important in the pathogenesis of IBD. IL-23, for example, has been recognized as an inducer of a subset of proinflammatory T cells (T_H17) that secrete high levels of IL-17 and play an important role in mediating inflammation in murine models of colitis. IL-17 expression has been shown to be upregulated in active IBD, both Crohn's disease and UC.

Environmental factors also are believed to play a role in the pathogenesis of IBD, because the disease is more common in industrialized countries. Moreover, the frequency has tended to increase in countries as they become more industrialized. It has been postulated that poor sanitation, food contamination, and crowded living conditions are associated with helminthic infection, which leads to regulatory T-cell conditioning and stimulation of IL-10 and transforming growth factor-β production by mononuclear cells, thereby preventing intestinal inflammation. However, the only environmental factor clearly associated with IBD is tobacco smoking. Smoking seems to be protective against UC, whereas smoking in Crohn's disease causes a more aggressive disease. No dietary triggers have been found to cause IBD, but elemental diets and diversion of the fecal stream can reduce inflammation in Crohn's disease.

PATHOLOGY

Mucosal biopsies in IBD reveal acute and chronic inflammation with infiltration by plasma cells, neutrophils, lymphocytes, and eosinophils; focal ulcerations; crypt architectural distortion; and crypt abscesses (Figs. 37-1 and 37-2). In Crohn's disease, the inflammation is transmural and more commonly focal. Granulomas are found in 25% to 30% of histologic specimens in Crohn's disease, but not in UC. The presence of granulomas is not required but can assist in making the diagnosis of Crohn's disease in the right clinical setting (Fig. 37-3). Granulomas are not diagnostic because they can be found in many other diseases, such as Beçhet's disease, tuberculosis, *Yersinia* infection, and lymphoma.

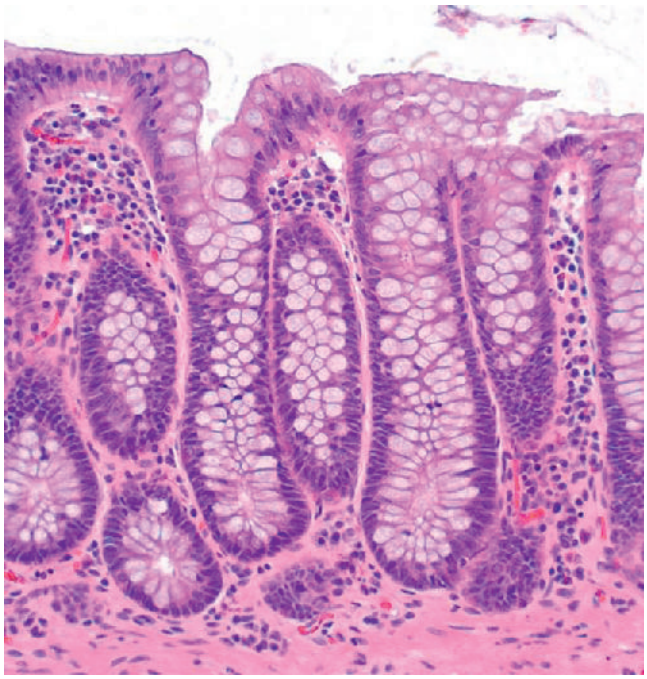

FIGURE 37-1 Normal colonic mucosa (hematoxylin and eosin stain).

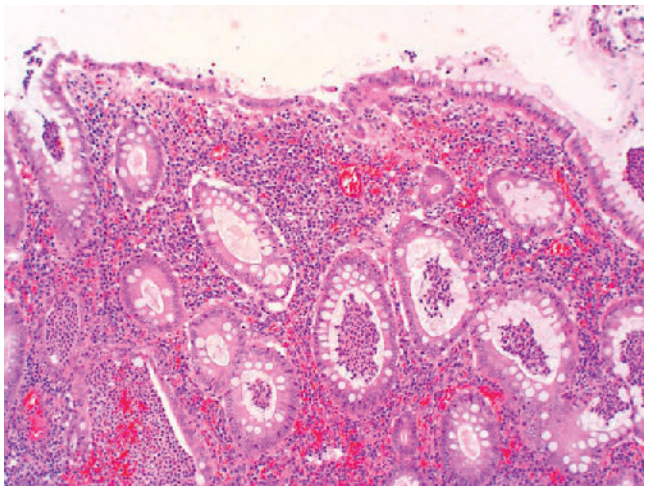

FIGURE 37-2 Mucosal biopsy specimen demonstrates crypt branching and a crypt abscess characteristic of ulcerative colitis (hematoxylin and eosin stain).

CLINICAL PRESENTATION

Intestinal Manifestations

UC is characterized by chronic inflammation of the mucosal surface that involves the rectum and extends proximally through the colon in a continuous manner. The extent and severity of the colonic inflammation determine prognosis and presentation (insidious versus acute onset). Most patients initially exhibit diarrhea, abdominal pain, urgency to defecate, rectal bleeding, and the passage of mucus per rectum. At presentation, approximately 40% to 50% of patients have proctitis or proctosigmoiditis, 30% to 40% have left-sided colitis (disease extending to the splenic flexure), and the remaining 20% to 25% have pancolitis. Of the patients who initially present with proctitis or proctosigmoiditis, about 15% develop more extensive disease over time.

The typical clinical course of UC is one of chronic intermittent exacerbations followed by periods of remission. Signs of a worsening clinical course include the development of abdominal pain, dehydration, fever, and tachycardia. Clinical features that have been used to assess severity of UC include bowel frequency, fever, increased heart rate, and hematochezia (blood in the stool), as well as the presence of anemia and an elevated erythrocyte