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Robert M. Glickman

INFLAMMATORY BOWEL DISEASE: Ulcerative Colitis and Crohn's Disease

DEFINITION *Inflammatory bowel disease* (IBD) is a general term for a group of chronic inflammatory disorders of unknown cause involving the gastrointestinal tract. Since these disorders have no pathognomonic features or specific diagnostic tests, in a strict sense they remain diagnoses of exclusion. Their features are sufficiently characteristic, however, to permit accurate diagnosis in most cases. Chronic IBD may be divided into two major groups, chronic nonspecific *ulcerative colitis* (UC) and *Crohn's disease* (CD). The original description of the latter disease by Crohn, Ginzberg, and Oppenheimer in 1932 localized it to segments of ileum. However, the same process may involve the buccal mucosa, esophagus, stomach, and duodenum, as well as the jejunum and ileum. Crohn's disease of the small bowel is also known as *regional enteritis*. A similar inflammatory picture may occur in the colon, either alone or with accompanying small intestinal involvement. In most instances, this form of colitis can be distinguished clinically and pathologically from ulcerative colitis and may be referred to as *Crohn's disease of the colon. Granulomatous colitis* is a less accurate term because only some cases exhibit granulomas. Clinically these disorders are characterized by recurrent inflammatory involvement of intestinal segments with diverse clinical manifestations, often resulting in a chronic, unpredictable course.

EPIDEMIOLOGY The epidemiology and etiology of UC and CD share many features and will be discussed together. These diseases are more common in whites than in blacks or Asians, and Jews have an incidence three to six times greater than that of non-Jews. The sexes are affected equally.

The incidence and prevalence of the two diseases differ slightly, UC being the more common. When analyzed in western Europe and the United States, UC (including ulcerative proctitis) has an incidence of approximately 6 to 8 cases per 100,000 population and an estimated prevalence of approximately 70 to 150 cases per 100,000 population. Estimates of the incidence of CD (colonic plus small bowel) are approximately 2 cases per 100,000 population; the prevalence is estimated at 20 to 40 per 100,000 population. Many believe the incidence of CD (especially colonic) to be increasing. In western Europe and North America, the incidence and prevalence of CD have been increasing five times faster than those of ulcerative colitis.

While the occurrence of both diseases peaks between the ages of 15 and 35, they have been reported from every decade of life. A familial incidence of IBD has been recorded, with estimates that 2 to 5 percent of persons with CD or UC will have one or more relatives affected. There is no specificity, however, for a given form of IBD within a given family. Such epidemiologic clustering of cases could be due to an effect of either genetic factors or common environmental influences on the development of these diseases (see below). It has been suggested that the pathogenesis of these disorders has both a probable hereditary basis and a strong environmental component.

ETIOLOGY AND PATHOGENESIS While the causes of UC and CD remain unknown, certain features of these diseases have suggested several areas of possible importance. These include familial or genetic, infectious, immunologic, and psychological factors.

As mentioned, the increased incidence of inflammatory bowel disease in whites and in Jews and the occurrence of familial clustering suggest a *genetic* predisposition to the development of the disease. An increased incidence of CD in monozygotic twins also is strong evidence for a genetic component. A search for genetic markers that might be of value in identifying susceptible individuals has not identified any single marker (i.e., a histocompatibility antigen) in patients with IBD.

The chronic inflammatory nature of these diseases has prompted a continuing search for an *infectious* cause. Despite numerous attempts, no bacterial, fungal, or viral agents has thus far been isolated. Preliminary reports of isolates of cell wall variants of *Pseudomonas* or of transmissible agents producing cytopathic effects in tissue culture have yet to be confirmed. As discussed below, many infectious agents can produce *acute* colitis or ileitis; however, there is no evidence that these agents are involved in *chronic* IBD.

The idea that an *immune* mechanism is involved is based on the reasoning that the extraintestinal manifestations that may accompany these disorders (e.g., arthritis and pericholangitis) may represent autoimmune phenomena and that therapeutic agents such as glucocorticoids, azathioprine, and cyclosporine may act via immunosuppressive mechanisms. Patients with IBD may have *humoral antibodies* to colon cells, to bacterial antigens such as *Escherichia coli*, to lipopolysaccharide, and to foreign proteins such as cow's milk protein. In general, the presence and titer of these antibodies do not correlate with disease activity. It is likely that these antigens gain access to immunocompetent cells as a consequence of epithelial damage. In addition, IBD has been described in association with agammaglobulinemia as well as IgA deficiency, casting further doubt on the pathogenetic role of humoral antibodies. *Immune complexes* also have been invoked to explain extraintestinal manifestations of IBD. While there are well-defined examples of tissue injury resulting from immune complexes, studies using specific detection techniques have failed to demonstrate an increased frequency of immune complexes in patients with IBD.

Abnormalities of *cell-mediated immunity* that have been reported in association with IBD include cutaneous anergy, diminished responsiveness to various mitogenic stimuli, and a decreased number of peripheral T cells. Since many of these changes may revert to normal when the disease is quiescent, they are probably secondary phenomena. Many abnormalities of cell-mediated immunity in the mucosa of patients with IBD also have been described. They include an increased concentration of mucosal IgG cells and changes in subsets of T cells, suggesting antigenic stimulation. Activation of mucosal immune cells results in a complex expression of cytokines, which may contribute to the mucosal inflammatory response. In addition, noncytokine inflammatory mediators, such as prostaglandin and thromboxane products, are present in elevated levels in the mucosa of patients with IBD and would further stimulate the inflammatory response. Animal models of IBD, including a transgenic rat model that expresses human HLA-B27, a mouse deficient in interleukin 2, and the spontaneous chronic colitis of the cotton-top tamarin, also may yield important insights into the pathogenesis of IBD. No immunologic alterations specific for either UC or CD have yet been found, however.

The *psychological* features of patients with IBD also have been stressed. It is not uncommon for these diseases to present initially or to flare up in association with major psychological stresses such as the loss of a family member. It has been suggested that patients with IBD have a characteristic personality that renders them susceptible to emotional stresses. While there is little evidence directly relating emotional factors to the etiology of IBD, there is little doubt that a chronic disease of unknown cause, affecting individuals in the prime of life, often results in anger, anxiety, and some degree of depression. These reactions are undoubtedly important factors in modifying the course of these diseases and the response to therapy.

PATHOLOGY In UC, there is an inflammatory reaction primarily involving the colonic mucosa. Grossly, the colon appears ulcerated, hyperemic, and usually hemorrhagic (Fig. 286-1). A striking feature of the inflammation is that it is *uniform* and *continuous*, with no intervening areas of normal mucosa. The rectum is usually involved (95 percent of cases), and the inflammation extends proximally in a continuous fashion for a variable distance. When the entire colon is involved, there may also be minimal involvement of a few centimeters of the terminal ileum, called "backwash ileitis." This involvement never leads to the thickening and narrowing characteristic of Crohn's disease. The surface mucosal cells as well as the crypt epithelium and submucosa are involved in an inflammatory reaction with neutrophilic infiltration (Fig. 286-2*A*). This reaction progresses to epithelial damage with loss of surface epithelial cells, resulting in multiple ulcerations. Infiltration of the crypts by neutrophils results in characteristic (but not specific) small crypt abscesses and eventual crypt destruction. There also may be loss of crypt epithelium, with a loss of goblet cells and submucosal edema. Repetitive cycles of inflammation lead to mild submucosal fibrosis. Regenerative activity is evidenced by crypts with irregular epithelium and often with a basal bifurcation. It is important to stress that, unlike Crohn's disease, deeper layers of the bowel, beneath the submucosa, usually are not involved. In severe UC, as seen with toxic megacolon, the bowel wall may become extremely thin and denuded of mucosa, with inflammation extending to the serosa, leading to dilation and subsequent perforation.

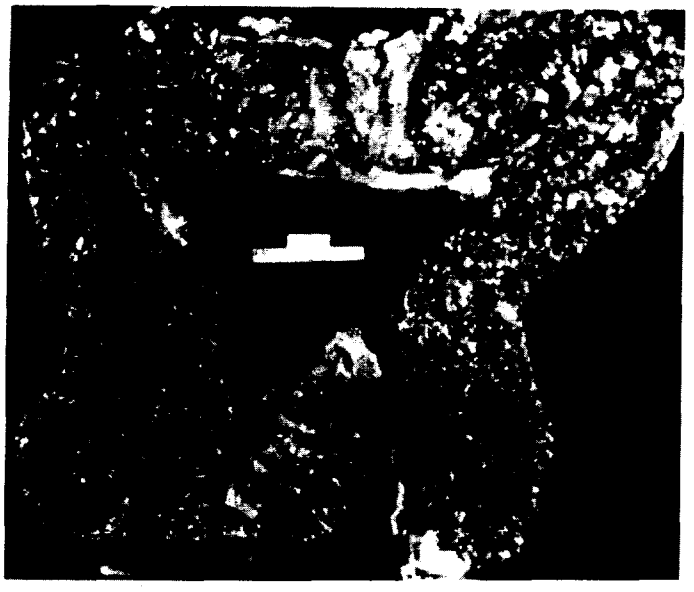

FIGURE 286-1 Ulcerative colitis. Resected colon with portion of terminal ileum. The specimen showed uniform inflammation, erythema, and hemorrhage and a normal terminal ileum.

Recurrent inflammation may lead to characteristic features of chronicity. Fibrosis and longitudinal retraction result in shortening of the colon. Loss of the normal haustral pattern leads radiologically to a smooth, "lead-pipe" appearance of the colon. Regenerating islands of mucosa surrounded by areas of ulceration and denuded mucosa appear as "polyps" protruding into the lumen. However, these protrusions are inflammatory rather than neoplastic and are therefore called *pseudopolyps* (Fig. 286-2*B*).

With long-standing UC, the surface epithelium may show features of *dysplasia*. Nuclear and cellular atypia are thought to represent premalignant changes occurring in the setting of long-standing UC. Marked dysplasia in colonic biopsy samples in the setting of long-standing colitis is associated with a significant risk of a carcinoma elsewhere in the colon and may influence the decision to advise colectomy.

Crohn's disease, in contrast to ulcerative colitis, is characterized by chronic inflammation extending through *all layers of the intestinal wall* and involving the mesentery as well as regional lymph nodes. Whether or not the small bowel or colon is involved, the basic pathologic process is the same for small bowel and colonic involvement.

The earliest pathologic changes in CD are poorly defined, since surgery is usually not undertaken electively early in the course of the disease. At laparotomy, the terminal ileum appears hyperemic and boggy, with mesentery and mesenteric lymph nodes swollen and reddened. At this stage, the bowel wall, although edematous, is usually pliable. While some patients with this initial presentation subsequently develop typical regional enteritis, a significant number recover completely. This acute form of ileitis will undoubtedly be shown to have diverse causes. Indeed, a significant number of patients with this presentation have been shown to be infected with *Yersinia enterocolitica*, an organism capable of producing a self-limited, acute inflammatory ileitis.

As the disease progresses, the gross appearance becomes characteristic. The bowel appears greatly thickened and leathery with a narrowed lumen (Fig. 286-3). This characteristic stenosis can occur in any portion of the intestine and may be associated with some degree of intestinal obstruction. The mesentery appears greatly thickened and fatty and often extends over the serosal surface of the bowel in characteristic finger-like projections. The appearance of the mucosa depends on the severity and stage of the disease, but it may be relatively normal, in sharp contrast to the mucosa in UC. In more advanced cases, the mucosa has a nodular, "cobblestone" look. This appearance is the result of submucosal thickening and mucosal ulceration, often linear in the long axis of the bowel at the base of mucosal folds. These ulcerations may penetrate into the submucosa and muscularis and coalesce to form intramural channels that become manifest as fistulas and fissures.

Other morphologic features also distinguish CD from UC. In CD, the disease is often *discontinuous*; severely involved segments of bowel are separated by "skip areas" of apparently normal bowel. In approximately 50 percent of cases of CD of the colon, the rectum is spared. In sharp contrast, in UC, the involvement is contiguous and the rectum almost always is involved. In addition, in CD, the transmural inflammatory process, involving serosa and mesentery, accounts for the characteristic fistula and abscess formation. As a result of serosal inflammation, adjacent loops of small intestine may become adherent

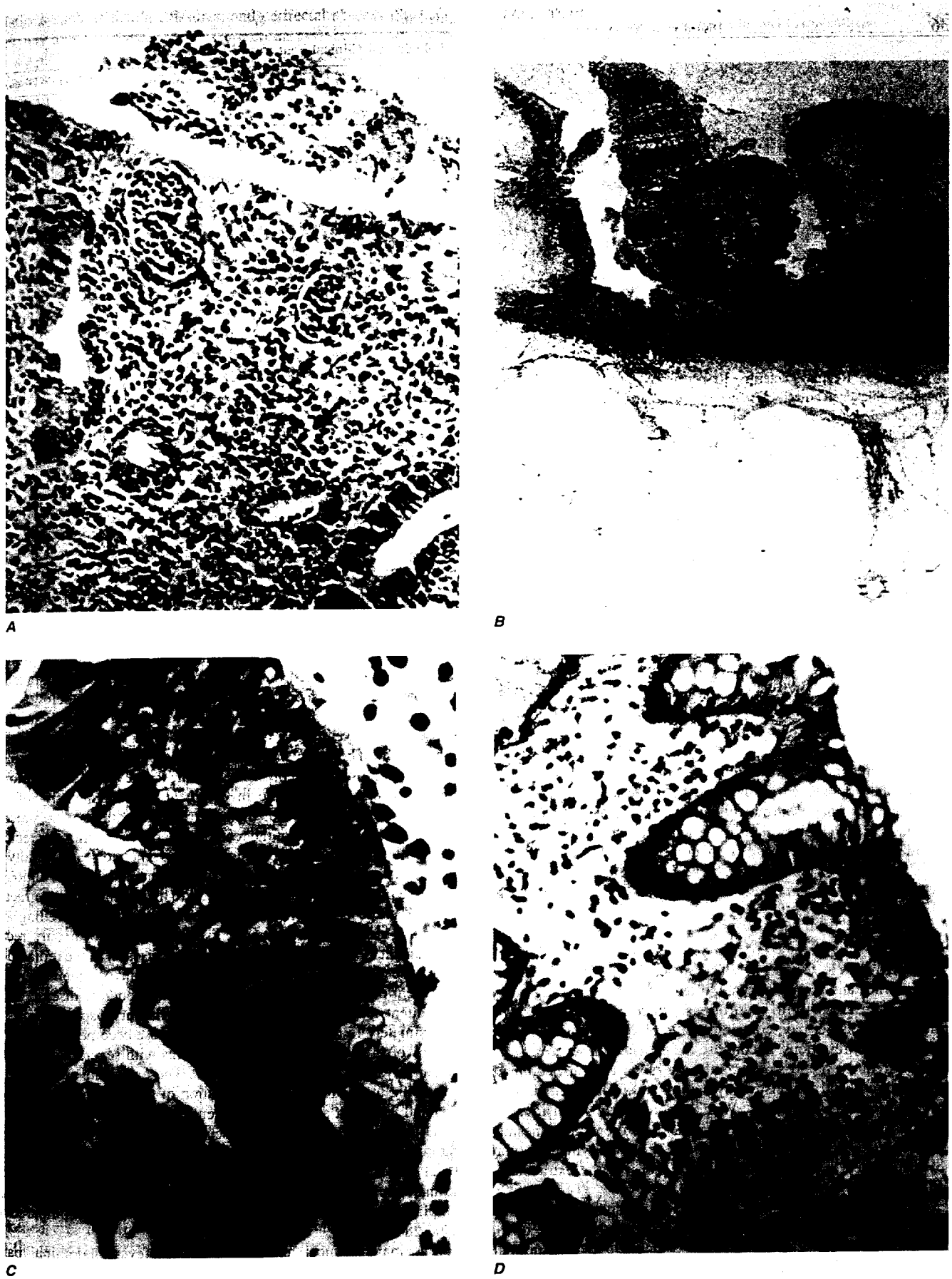

FIGURE 286-2 Colonic biopsy samples in inflammatory bowel disease. *A*. Ulcerative colitis. The surface mucosa is destroyed and the submucosa is diffusely infiltrated with polymorphonuclear leukocytes. Crypt abscesses are also present. *B*. Pseudopolyp. Regenerating island of mucosa with adjacent area of ulceration. *C*. Ulcerative colitis. Severe dysplasia occurring in long-standing chronic ulcerative colitis. Note atypical changes in the nuclei and marked palisading of nuclei of the crypt epithelium. *D*. Crohn's disease of the colon. Note the relatively intact mucosa with a solitary granuloma in the lamina propria.

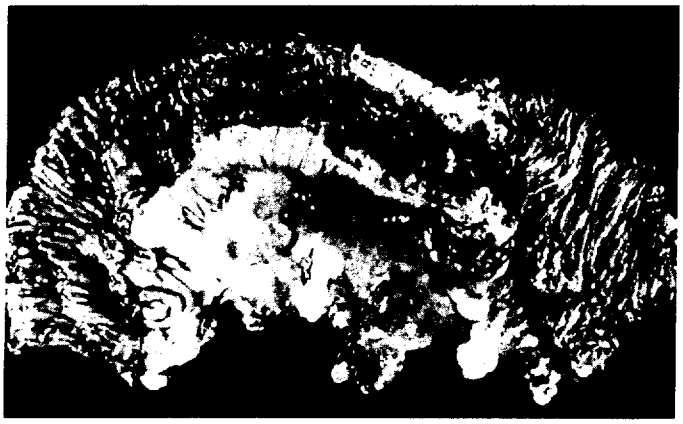

FIGURE 286-3 Regional enteritis. Resected specimen of terminal ileum demonstrates thickened bowel wall and chronically inflamed mucosa. Note the relatively sharp demarcation of the diseased segment, with grossly normal mucosa on either side.

and matted together by a fibrinous peritoneal reaction, leading to a palpable mass, most often in the right lower quadrant. Fistulas may form between adherent structures, including loops of intestine or colon as well as adjacent organs such as the bladder or vagina. Fistulous tracts also may lead to the skin or end blindly in the peritoneum or retroperitoneum, surrounded by adherent loops of bowel and inflammatory tissue. Fistula formation is not seen in UC.

Microscopically, granulomas are most helpful in distinguishing CD from other forms of IBD; they do not occur in UC. They may be seen in rectal or colonoscopic biopsy samples (Fig. 286-2*D*). While granulomas are a helpful finding when present, it is the chronic inflammation involving all layers of the intestinal wall which is most characteristic of CD.

In most series reporting the distribution of CD, approximately 30 percent of cases involve only the small intestine (usually the terminal ileum), 30 percent have only colonic involvement, and 40 percent have ileocolic involvement, usually of the ileum and right colon. In a small number of patients (mostly children and adolescents) there is diffuse and extensive ulceration of the jejunum and ileum.

While there often are sufficient features to permit distinction between UC and CD of the colon (Table 286-1), in 10 to 20 percent of cases this distinction is not possible.

CLINICAL FEATURES

ULCERATIVE COLITIS The major symptoms of UC are bloody diarrhea and abdominal pain, often with fever and weight loss in more severe cases. With mild disease, there may be one or two semiformed stools per day, containing little blood, and there may be no systemic manifestations. In contrast, the patient with severe disease may have frequent liquid stools containing blood and pus, complain of severe cramps, and demonstrate symptoms and signs of dehydration, anemia, fever, and weight loss. With predominantly rectal involvement, constipation rather than diarrhea may be present, and tenesmus may be a major complaint. On occasion, intestinal symptoms may be overshadowed by fever, weight loss, or one of the extracolonic manifestations of the disease (see below).

The physical findings in UC are usually nonspecific; there may be some abdominal distention or tenderness along the course of the colon. In mild cases, the general physical examination will be normal. Extracolonic manifestations include arthritis, skin changes, or evidence of liver disease. Fever, tachycardia, and postural hypotension are usually associated with more severe disease. The laboratory findings are often nonspecific and usually reflect the degree and severity of bleeding and inflammation. There may be anemia, which reflects chronic disease as well as iron deficiency from chronic blood loss. Leukocytosis with a left shift and an elevated erythrocyte sedimentation rate are often seen in the severely ill, febrile patient. Electrolyte abnormalities, especially hypokalemia, reflect the degree of diarrhea. Hypoalbuminemia is common with extensive disease and usually represents luminal protein loss through an ulcerated mucosa. An elevated alkaline phosphatase level may indicate associated hepatobiliary disease (see below).

Table 286-1

Pathologic and Clinical Features of IBD

Features	Ulcerative Colitis	Crohn's Disease
PATHOLOGIC FEATURES		
Segmental	0	+ +
Transmural involvement	+/−	+ +
Granulomas	0	+/+ + (50%)
Fibrosis	+	+ +
Fissuring, fistulas	+/−	+ +
Mesenteric fat, lymph node involvement	0	+ +
CLINICAL FEATURES		
Diarrhea	+ +	+ +
Rectal bleeding	+ +	+
Abdominal pain	+	+ +
Palpable mass	0	+ +
Fistulas	+/−	+ +
Strictures	+	+ +
Small bowel involvement	+/− ("backwash ileitis")	+ +
Rectal involvement	+ + (95%)	+/+ + (50%)
Extraintestinal disease	+ +	+ +
Toxic megacolon	+	+/−
Recurrence after colectomy	0	+
Malignancy (with long-standing disease)	+	+/−

NOTE: 0, never; +/−, rare; +, occasional; + +, frequent, common.

The clinical course of UC is variable. Most patients will suffer a relapse within 1 year of the first attack, reflecting the recurrent nature of the disease. There may, however, be prolonged periods of remission with only minimal symptoms. In general, the severity of symptoms reflects the extent of colonic involvement and the intensity of the inflammation. At one end of the spectrum are patients who present with limited involvement of the rectum (ulcerative proctitis) or rectum and sigmoid (ulcerative proctosigmoiditis). Their disease usually is mild, with minimal systemic or extracolonic manifestations, although ulcerative proctitis is sometimes difficult to treat, exhibiting protracted bleeding and tenesmus. The major symptoms are rectal bleeding and tenesmus. Most of these patients, especially those with only rectal involvement, do not develop more extensive disease. In the remainder, the disease may extend proximally with variable involvement. Perhaps 85 percent of patients with UC have mild to moderate disease of an intermittent nature and can be managed without hospitalization. In approximately 15 percent of patients, the disease becomes more fulminant, involves the entire colon, and presents with severe bloody diarrhea and systemic signs and symptoms. These patients are at risk of developing toxic dilation and perforation of the colon (described below) and represent a medical emergency.

CROHN'S DISEASE As discussed above, the basic pathologic features of CD are the same whether the disease involves the small bowel or the colon. The clinical presentation, however, largely reflects the anatomic location of the disease and to some degree predicts which complications may develop. The clinical features are compared in Table 286-1.

The major clinical features of CD are fever, abdominal pain, diarrhea (often without blood), and generalized fatigability. There may be associated weight loss. With *colonic involvement*, diarrhea and pain are the most frequent symptoms. Rectal bleeding is distinctly less common than with UC and reflects (1) sparing of the rectum in many patients and (2) the transmural nature of the disease, with only irregular mucosal involvement. There may be associated severe anorectal com-

countered (usually in the rectum), there are no areas of intervening normal mucosa before the proximal limit of the disease is reached. Ulcers are shallow and may be small or confluent, but ulceration invariably occurs in segments of active colitis. Full colonoscopic examination of the colon in UC is not indicated in the acutely ill patient. Rectal biopsy may corroborate mucosal inflammation. With more chronic disease, the mucosa may appear granular and pseudopolyps may be present.

Endoscopic examination of the colon is also of value in the diagnosis of colonic CD. The salient finding is ulcerations, which may be tiny, aphthous erosions or deep, longitudinal fissures. They usually occur in segments of otherwise normal mucosa. Since the mucosa is not uniformly involved, friability and diffuse granularity—hallmarks of UC—are not characteristic. Rather, a cobblestone appearance—that is, coarse irregularity of the mucosal surface, reflecting submucosal inflammation—is characteristic of CD. Pseudopolyps, edema, and strictures may be seen in CD as well as in UC. Colonic mucosal biopsy reveals granulomas in 30 to 50 percent of specimens taken from involved areas. Features such as crypt abscesses, infiltration with inflammatory cells, or ulcerations are nonspecific but compatible. Since skip areas and rectal sparing are characteristic of CD, colonoscopy may be better than sigmoidoscopy for the evaluation of CD. Colonoscopic examination is also indicated when CD appears only to involve the small bowel. Ileal biopsy may be feasible, and coexisting colonic involvement occurs in a significant number of cases. Perianal inflammatory lesions as well as areas of rectal disease seen at endoscopy often show granulomatous inflammation. In 5 to 15 percent of patients, rectal biopsy samples of seemingly uninvolved areas show microscopic evidence of granulomatous inflammation.

The *radiologic evaluation* of the bowel provides essential information in the diagnosis of IBD. In UC, barium enema may reveal the extent of the disease and help to define associated features such as stricture, pseudopolyposis, or carcinoma. The earliest features seen in UC are irritability and incomplete filling due to associated inflammation. Fine ulcerations may be seen at this time as serrations along the contour of the bowel, producing a hazy margin (Fig. 286-4). The ulcerations may become deeper and, with more fulminant disease, produce a grossly ragged and irregular contour. Polypoid defects appear as a result of edematous mucosa between ulcerations. The diffuse pattern of ulceration is best seen on the evacuation film or on air-contrast barium enema. In the chronic stage of the disease (Fig. 286-5), the characteristic features are shortening of the bowel, depression of the flexures, narrowing of the bowel lumen, and rigidity. The bowel has a symmetric, ahaustral, tubular appearance with a decreased mucosal pattern. Although strictures are uncommon, when they occur, they have a concentric lumen with fusiform tapering margins. Eccentricity should raise the suspicion of an associated carcinoma.

On barium enema examination, CD of the colon usually has features that distinguish it from UC. These features include rectal sparing, the presence of skip lesions, and small ulcerations occurring on small irregular nodules. Small ulcerations often extend to produce longitudinal ulcers (Fig. 286-6) and transverse fissures, which in reality are limited sinus tracts. These may extend into adjacent tissues to produce fistulas. Irregular thickening and fibrosis may lead to stricture formation, which may be multiple. In 10 to 15 percent of cases, the disease involves the entire colon uniformly, making differentiation from UC more difficult. Reflux of barium into the terminal ileum during barium enema may reveal characteristic ileal changes of regional enteritis.

The terminal ileum is the portion of the small intestine most often involved by CD, with features similar to those of colonic involvement. Careful x-ray examination of the small bowel may demonstrate loss of mucosal detail and rigidity of involved segments resulting from submucosal edema or stenosis. The submucosal inflammation may lead to the characteristic radiologic cobblestone appearance of the mucosa (Fig. 286-7), and fistulous tracts may be seen, especially in the ileocecal area (Fig. 286-8). Involvement of the stomach and duodenum usually appears radiologically as stiffening and infiltration of the mucosa and can mimic an infiltrative tumor. If such an appearance is due to regional enteritis, there is almost always coexisting involvement of the jejunum or ileum. In CD, computed tomography (CT) of the abdomen may be of value in the evaluation of thickened, separated bowel loops and may help distinguish thickened, matted loops (phlegmon) from intraabdominal abscess.

While barium studies often provide information on the pattern and extent of IBD, caution must be exercised in performing these studies

FIGURE 286-4 Acute ulcerative colitis, air-contrast study. Note the diffuse fine ulceration of the entire colon, producing serration along the contour of the bowel. *(Courtesy of R. Gold, Columbia Presbyterian Medical Center.)*

FIGURE 286-5 Chronic ulcerative colitis. Note the loss of haustrations and the fusiform stricture in the transverse colon. *(Courtesy of R. Gold, Columbia Presbyterian Medical Center.)*

FIGURE 286-6 Crohn's colitis. Air-contrast study.

FIGURE 286-7 Crohn's ileocolitis. Note the nodularity and ulceration of the terminal ileum and the deformity of the cecum.

FIGURE 286-8 Regional enteritis. X-ray showing fistulas between loops of bowel. Insert is a compression film of this area; note fistulas between adjacent loops of bowel.

in acutely ill patients with severe colitis, as the procedure and the bowel cleansing that precedes it may cause a worsening of the disease and can precipitate toxic dilation of the colon.

Fiberoptic colonoscopy is a powerful tool in the diagnosis of colonic IBD. Areas beyond the reach of the sigmoidoscope can now be directly visualized and biopsied. Early in the course of colonic inflammation, endoscopic examination and biopsy are the most sensitive techniques for demonstrating mucosal involvement. Polypoid lesions, strictures, and unclear x-ray features can usually be defined fully. Periodic colonoscopic examination and biopsy are being used increasingly in cancer surveillance in patients with long-standing IBD (see below).

DIFFERENTIAL DIAGNOSIS

Many entities must be considered in the differential diagnosis of IBD. The focus of the differential diagnosis is determined largely by the presenting features of the disease. When *rectal bleeding* is the presenting complaint, a colonic source should be considered. While *hemorrhoids* are commonly found, they must be considered a tentative source of bleeding until sigmoidoscopy, colonoscopy, and/or barium enema examination have ruled out other colonic lesions. Colonic *neoplasms* (carcinoma, adenomatous polyps) also may present with rectal bleeding and can usually be diagnosed by barium enema with subsequent sigmoidoscopic or colonoscopic biopsy. It should be remembered that carcinoma may complicate long-standing colitis. Rectal bleeding from *colonic diverticula* or *arteriovenous malformations* usually presents no problem in differential diagnosis, since radiologic and endoscopic features of IBD are absent. *Radiation proctitis*, which may present as a localized area of colitis, is usually found in the setting of pelvic irradiation. The onset may be months to years after irradiation. Characteristic features on sigmoidoscopy include mucosal atrophy and telangiectasia along with friability and small ulcerations. A colitis sometimes indistinguishable from ulcerative colitis may occur in Behçet's syndrome and is associated with aphthous oral ulceration, uveitis, and urethritis.

Acute colitis may be caused by a variety of *infectious* agents (Chap. 128). Often presenting with bloody diarrhea, infectious colitis may be difficult to distinguish from IBD at initial presentation, and severe cases may present with colonic dilation mimicking toxic megacolon.

Rectal biopsy in infectious colitis shows marked polymorphonuclear infiltration with pronounced edema and relative sparing of the crypts, features that may distinguish this entity from idiopathic inflammatory bowel disease. A listing of these agents is given in Table 286-2. It should also be noted that an unexplained exacerbation of IBD symptoms may be due to a superimposed infectious colitis. Thus, in all cases of IBD exacerbation, appropriate cultures should be performed to rule out an associated infection.

Amebiasis may present with bloody diarrhea and may be indistinguishable by sigmoidoscopy from idiopathic ulcerative colitis. A history of recent foreign travel or homosexual exposure would be important. Serologic testing may be of value, although initial positive titers may indicate prior amebic infection at an indeterminate time in the past. Since specific amebicidal therapy is necessary to eradicate this infection and corticosteroids may be detrimental, every effort should be made to exclude this diagnosis in appropriate individuals via serologic titers and careful examination of colonic secretions and biopsy samples. Acute *bacillary dysentery* may be caused by *Shigella* and *Salmonella* or *Campylobacter*, all easily diagnosed by stool culture. *Yersinia enterocolitis* infection, which may present as acute ileitis, also can produce a self-limited colitis, sometimes with granulomatous reaction. Infectious agents may cause acute proctitis indistinguishable from idiopathic ulcerative proctitis. Such infections, often seen in homosexuals, may represent herpes simplex virus infection, *gonorrhea*, *lymphogranuloma venereum* (LGV), cytomegalovirus infection, *Isospora* infection, or *Treponema pallidum* infection, as well as *amebiasis*. In homosexual men, non-LGV strains of *Chlamydia* have been shown to produce a granulomatous proctitis closely resembling Crohn's disease of the rectum.

Pseudomembranous colitis (antibiotic-associated colitis) is caused by a necrolytic toxin elaborated by *Clostridium difficile*, which proliferates the bowel under certain circumstances (see Chap. 148). Most often the disease is a result of antibiotic therapy, which presumably upsets the normal ecologic balance of the bowel flora and permits *C. difficile* to proliferate. Almost every antibiotic has been implicated, although cases related to the use of vancomycin or aminoglycosides are rare. Most often diarrhea is profuse and watery, although bloody diarrhea occurs in 5 percent of cases. Characteristic multiple, discrete yellowish plaques are seen on sigmoidoscopy, which on biopsy show features of acute inflammation and ulceration with a pseudomembrane of fibrin and necrotic material. On occasion, lesions may be beyond the reach of the sigmoidoscope and require colonoscopy. Diagnosis is best made by detecting *C. difficile* toxin in the stool. Treatment is initially directed at eradicating *C. difficile* from the stool. Vancomycin (250 mg orally qid for 7 to 14 days) is the treatment of choice for more severely ill patients and should produce clinical improvement within 5 days. Since vancomycin therapy is expensive, alternative therapies have been proposed. The use of metronidazole (500 mg orally qid for 7 to 14 days) has been shown to be as effective as vancomycin. Bacitracin (20,000 units qid for 7 to 14 days) is also quite effective. With all forms of therapy, relapse rates of 15 to 30 percent have been observed, and a second course of therapy may be required to eradicate the organism.

Occasionally, infectious colitis is superimposed on an unsuspected case of UC or CD. In this situation, once the acute infection has subsided, symptoms and inflammatory mucosal changes may persist, raising the possibility of associated idiopathic IBD. Similar considerations apply to the rare patient with IBD who develops associated *pseudomembranous colitis*. The finding of *C. difficile* toxin in the stool and subsequent treatment will serve to clarify this presentation.

Abdominal pain in association with rectal bleeding, especially in older patients, may be due to *ischemic colitis*; this condition may be most difficult to distinguish from IBD, especially CD. Because of an excellent collateral circulation, the rectum is usually spared. Radiologic features are often characteristic, showing submucosal edema or hemorrhage (thumb-printing) which typically resolves spontaneously over several weeks.

IBD may be difficult to distinguish from functional diarrhea early in the course of disease. The presence of constitutional symptoms such as fatigue, fever, weight loss, and nocturnal diarrhea, coupled with laboratory findings of anemia, an elevated erythrocyte sedimentation rate, or occult blood in the stool, should alert the clinician to the possibility of IBD. Similarly, the presence of leukocytes in a stained stool specimen points to an inflammatory basis for the diarrhea. In all cases, stool cultures and parasitologic examination of the stool are required to rule out enteric bacterial pathogens or amebiasis. In the *irritable bowel syndrome*, sigmoidoscopy, rectal biopsy, and barium enema examination all give normal results (see Chap. 287).

Once the diagnosis of idiopathic IBD has been established, it is usually possible to distinguish between UC and CD of the colon (see Table 286-1).

With small-intestinal involvement (regional enteritis), the differential diagnosis should include disorders presenting with intraabdominal abscesses, fistulas, intestinal obstruction, and malabsorption. The finding of associated colonic involvement in patients with ileal disease will often serve to distinguish CD from other ileal disorders. With diffuse involvement of the jejunum and ileum, regional enteritis must be distinguished from *nongranulomatous ulcerative jejunoileitis*. Abdominal pain and diarrhea are prominent features of the latter disorder, and weight loss, malabsorption, and hypoproteinemia tend to be more prominent than in regional enteritis. Small-bowel biopsy shows a more diffuse lesion with flattened villi (similar to celiac sprue), infiltration of the lamina propria, and mucosal ulceration. *Abdominal lymphoma* likewise may present with clinical and radiologic features difficult to distinguish from those of regional enteritis. Hepatosplenomegaly and peripheral adenopathy, when present, are helpful clues, but often disease is confined to the intestine. In such cases, laparotomy is usually required to make the definitive histologic diagnosis.

The advanced presentation of regional enteritis with areas of stenosis and draining fistulas also may be confused with *chronic fungal infection of the bowel*, including actinomycosis, aspergillosis, and blastomycosis. These infections often are seen in debilitated patients with impaired host defenses. Fungal skin tests and examination of fistula drainage and biopsy material for characteristic granules and fungi are helpful in making the diagnosis.

Intestinal tuberculosis characteristically produces stenotic lesions, usually in the terminal ileum and often also involving the contiguous cecum and ascending colon. Unlike regional enteritis, skip areas are unusual. Histologically, the granulomatous inflammation seen with *Mycobacterium tuberculosis* infection may be indistinguishable from regional enteritis; acid-fast stains and cultures are required for diagnosis. Fortunately, in western countries, primary intestinal tuberculosis is now rare.

Table 286-2

Microbiologic Causes of Colitis

Shigella infection
Salmonella infection
Amebiasis (infection with *Entamoeba histolytica*)
Yersinia enterocolitica infection
Campylobacter jejuni infection
Lymphogranuloma venereum (LGV)
"Non-LGV" *Chlamydia* infection
Neisseria gonorrhoeae infection
Pseudomembranous colitis (caused by *Clostridium difficile* toxin)
Tuberculosis (*Mycobacterium tuberculosis* infection)
Infection with enteropathogenic *Escherichia coli* O157:H7
Aeromonas hydrophila infection
Plesiomonas shigelloides infection

COMPLICATIONS OF INFLAMMATORY BOWEL DISEASE

The complications of IBD may be classified as local or systemic, the former being direct consequences of inflammation or its extension

the underlying bowel disease, they sometimes pose difficult diagnostic problems. Their cause is currently unknown.

Joint manifestations occur in 25 percent of patients with IBD. They range from arthralgia to an acute arthritis with painful, swollen joints. The nondeforming arthritis is mono- or polyarticular and often migratory. Knees, ankles, and wrists are most commonly involved, but any joint may be affected. Joint fluid, if aspirated, reveals findings of an acute arthritis without crystals or evidence of infection. Tests for markers of specific forms of arthritis (rheumatoid factor, antinuclear antibody, and lupus erythematosus factor) are negative. Typically, the severity of arthritis varies with the activity of the underlying bowel disease. Rarely, peripheral arthritis truly predates clinical bowel symptoms. Arthritis is more common in patients with colonic than with only small-bowel involvement (regional enteritis).

In contrast, the central arthritis or ankylosing spondylitis associated with IBD is unrelated to the activity of the underlying bowel disease. It may antedate the bowel disease by years and persist after surgical or medical remission of the disease has been achieved. Symptoms consist of low backache and stiffness with eventual limitation of motion. Sacroileitis may be present as well. X-rays usually reveal characteristic changes. In contrast to the peripheral arthritis, there is a strong association of HLA-B27 with ankylosing spondylitis, whether or not IBD is present.

Like the peripheral arthritis, *skin manifestations* are more common with colonic disease. They occur in about 15 percent of patients, and their severity correlates with activity of the bowel disease. *Erythema nodosum* may be seen and heals without scarring. *Pyoderma gangrenosum*, an ulcerating lesion often occurring on the trunk, is relatively painless and may heal with scarring. In rare patients, the lesion persists even after colectomy for UC. *Aphthous ulcers* resemble "canker sores" of the mouth, and in approximately 5 to 10 percent of patients they are present during periods of active disease and then resolve. Their cause is unknown, and they are treated symptomatically. *Ocular manifestations* such as episcleritis, recurrent iritis, and uveitis occur in approximately 5 percent of patients and may represent a severe manifestation of the disease. In general, their activity parallels the course of the bowel disease, and they may respond dramatically when colectomy is done for other indications.

Abnormalities of *liver function* are common in IBD. In the severely ill, malnourished patient, mild abnormalities of serum levels of aminotransferases and alkaline phosphatase are often seen and represent nonspecific focal hepatitis or fatty infiltration. Factors favoring hepatosteatosis in the severely ill patient are poor nutrition and, often, concomitant steroid therapy. The lesion is not progressive and resolves with disease remission. *Pericholangitis* is characterized histologically by portal tract inflammation, some bile ductular proliferation, and concentric fibrosis around bile ductules. Some workers think that this lesion represents the intrahepatic form of sclerosing cholangitis. Most often, the lesion is clinically insignificant, and its sole manifestation is an elevated serum alkaline phosphatase level. It is usually nonprogressive and requires no therapy. Rarely, there is apparent progression to cirrhosis of either the postnecrotic or biliary type. Uncommonly, patients with IBD develop *sclerosing cholangitis* (Chap. 302), a chronic inflammation of unknown cause involving the extrahepatic and intrahepatic bile ducts, which may produce various degrees of extrahepatic biliary obstruction. Corticosteroids and immunosuppressive therapy are not beneficial. The disease only sometimes reverses after colectomy and should not be the sole indication for colectomy. Cholangiocarcinoma, arising in the extrahepatic biliary tree, has an increased incidence in patients with chronic UC, especially patients with sclerosing cholangitis. Such patients will present with extrahepatic biliary obstruction, which must be distinguished from sclerosing cholangitis. Finally, *autoimmune chronic active hepatitis*, which may progress to *cirrhosis*, may be seen in IBD, although the exact relationship between these disorders is unknown. There is no clear evidence that colectomy influences the course of this form of liver disease.

TREATMENT

Certain common principles govern the treatment of UC and CD. Initial treatment of all forms of uncomplicated IBD is primarily medical, and the principles of medical therapy are similar for the two types of disease. Surgery is reserved for (1) specific complications and (2) intractable disease. There are important differences between the treatment of UC and CD however: the response to drug therapy may differ, complications often differ, and the prognosis after surgical therapy is not the same.

Ulcerative Colitis ***MEDICAL THERAPY*** Once the diagnosis is established, the severity of the disease must be assessed. Mild UC, including ulcerative proctitis, can usually be treated on an ambulatory basis. It should be noted that the disease is occasionally severe, even though it is limited to the rectum. The disease can worsen rapidly, and the course of a given attack cannot be predicted at the outset. The aims of therapy are to control the inflammatory process and to replace nutritional losses. A degree of improvement usually follows intravenous correction of fluid and electrolyte disturbances. Blood transfusions may be required, especially when there is continued active bleeding. Agents to control diarrhea (diphenoxylate, loperamide, codeine, anticholinergics) should be used with extreme caution for fear of precipitating colonic dilation and toxic megacolon. The decision to institute specific nutritional replacement therapy is determined by the patient's nutritional status and by whether the clinical course is expected to be protracted. In the severely ill patient, even clear liquids taken orally may stimulate colonic activity, and it is often wise to give the patients nothing by mouth. In this setting, intravenous alimentation, either peripheral or central, has been used as interim nutritional replacement therapy (see Chap. 78). While there is no evidence that intravenous alimentation is effective as primary therapy, it is an important component of a treatment program. In less severely ill patients able to tolerate fluids by mouth, the use of elemental oral diets may be beneficial, providing supplemental nutrition with low fecal volume.

The principal drugs used in the therapy of ulcerative colitis are the anti-inflammatory agents *sulfasalazine* (Azulfidine) and *glucocorticoids*. Sulfasalazine consists of a sulfonamide (sulfapyridine) moiety chemically bound to a salicylate (5-aminosalicylate); it undergoes bacterial cleavage in the colon. The liberated sulfapyridine is efficiently absorbed and largely excreted in the urine; the liberated 5-aminosalicylate, believed to be the active component, remains largely in the colon and is excreted in the stool. The salicylate moiety is thought to exert its action through inhibition of prostaglandin synthesis. While most physicians are familiar with the use of sulfasalazine to prevent recurrences of UC, it is less well appreciated that this agent is effective in the therapy of acute UC of mild to moderate severity. Therapeutic doses of 4 to 6 g/d are required. The drug is usually started at a dose of 500 mg bid and then increased daily or every other day by 1 g until the therapeutic dose is achieved. Topical preparations of 5-aminosalicylate (mesalamine) given as an enema are effective in the control of distal proctocolitis. Some of the oral and rectal 5-aminosalicylic acid products and their uses are listed in Table 286-4.

In the severely ill patient who may not tolerate oral medication, and for whom more rapid therapy is often desired, initial therapy is begun with glucocorticoids. While adrenocorticotropic hormone is as effective as glucocorticoids when given in equivalent dosages and by comparable routes of administration, most physicians seldom use it. The choice is one of individual preference; oral prednisone (45 to 60 mg/d) is usually employed initially. In the severely ill patient, parenteral administration of corticosteroids (i.e., intravenous prednisolone, 45 to 60 mg/d) is preferable to avoid the uncertainty of oral absorption. Improvement is usually noted after 7 to 10 days of such therapy by a reduction in fever, a decrease in bloody diarrhea, and improvement in appetite.

After initial improvement, low-roughage oral feedings can be resumed. At this point, the dose of steroids can be tapered. While there is no specific tapering schedule, the guiding principle is that,

once clinical remission is achieved, there is no evidence that chronic glucocorticoid administration improves the long-term outlook or helps to prevent recurrences. In practice, steroid therapy can be tapered and discontinued over a 2- to 3-month period after discharge. In some patients (10 to 15 percent), efforts to completely eliminate steroids may be associated with a flare-up of the disease, and low to moderate steroid doses (10 to 15 mg prednisone daily) may be required to suppress disease activity. This regimen should not be confused with prophylactic administration of steroids to patients in remission but rather represents treatment of incompletely responsive disease. Once the acutely ill patient is taking oral feedings, sulfasalazine should be added as described above in a daily dose of 2 g. Controlled trials have shown that this dose of sulfasalazine, when administered chronically to patients with UC, is effective in decreasing the frequency of relapses and should be continued chronically after glucocorticoids have been discontinued. Patients with glucose phosphate dehydrogenase deficiency and those exhibiting severe allergic reactions to the sulfa moiety of the drug unfortunately cannot be maintained on it. Patients who exhibit intolerance for the drug (headache, nausea) or allergic reactions can be treated with one of the oral preparations of 5-aminosalicylate listed in Table 286-4. Mesalamine enemas are effective topical therapy for distal UC and are necessary to maintain remission.

The use of immunosuppressive therapy with drugs such as azathioprine is less well established in UC. As a single agent in the therapy of acute UC, the drug is ineffective. However, it may be added to the regimen at a dose of 1.5 to 2.0 mg/kg when glucocorticoids fail or when the steroid dose needed to reduce inflammation is too high. It is desirable to monitor the blood count and observe the patient carefully for infection. Azathioprine also may have a limited role as a "steroid-sparing agent" in the patient with chronic UC who must be maintained on glucocorticoids to control disease activity. Cyclosporine (4 mg/kg per day), a potent immunosuppressive agent, is also beneficial in severely ill patients, producing marked improvement in patients who otherwise would require colectomy.

Toxic megacolon is a major complication of severe UC that requires rapid, intensive management, best carried out jointly by the internist or gastroenterologist and the surgeon. Once the diagnosis is established, prompt and vigorous use of intravenous fluids, electrolyte replacement therapy, and blood transfusions are indicated. Because of the fear of perforation and high likelihood that bacteremia and occult perforation have occurred, many physicians institute broad-spectrum antibiotic coverage after appropriate cultures have been obtained. The patient is given nothing by mouth and nasogastric suction is instituted. Full intravenous glucocorticoid therapy is also begun. Most workers favor an initial period of medical stabilization for the first 24 to 48 h. If significant objective improvement has not occurred, and if perforation seems imminent, emergency colectomy should be carried out. While some patients slowly improve under maximal medical therapy and thus avoid colectomy, this approach is risky, because mortality rates rise sharply if perforation occurs, approaching 50 percent in patients who subsequently undergo colectomy.

At the other end of the spectrum is the patient with mild UC limited to the rectum or rectosigmoid. Therapy is started with sulfasalazine, 0.5 to 1.0 g four times a day with meals. Alternatively, in the sulfa-allergic patient, 5-aminosalicylate enemas or oral 5-aminosalicylate preparations can be given. If rectal symptoms such as tenesmus are prominent, topical steroid enemas may produce marked improvement. The equivalent of 100 mg of hydrocortisone (20 mg of prednisone) in 60 to 100 mL of saline is used as a bedtime enema. On occasion, steroid foam preparations may be better tolerated in patients with severe tenesmus. Retention enemas have been shown to deliver medication as far as the descending colon, and absorption of steroid is slight (10 to 20 percent). If large doses of rectal steroids are required for control, it is preferable to use oral prednisone at a moderate dosage (20 mg/d).

PSYCHOTHERAPY The elements of trust and mutual understanding combined with the compassion and expertise of the physician are essential in the therapy of any chronic disease and are particularly important in the long-term management of patients with IBD. Often these patients are intelligent young adults, who frequently are resentful of a disease that affects them during their most productive years. However, through the vigorous participation of the physician, many patients are able to lead reasonably stable and productive lives. More formal psychiatric assistance may be required in chronically ill patients, in particular children or adolescents, and in the elderly, in whom severe depressive reactions are common. This is particularly true when colectomy is being advised and for the emotional adjustment that must be made after colectomy.

PREGNANCY AND ULCERATIVE COLITIS While many physicians are apprehensive about the management and prognosis of UC in the pregnant patient, the outcome for the patient and fetus is excellent. In general, the pregnancy is not threatened by coexisting colitis, with no increase in stillbirths or premature deliveries when compared with the general population. When patients with inactive colitis become pregnant, approximately 50 percent have an exacerbation of their disease, with some clustering of these flare-ups during the first trimester and in the postpartum period. The therapy of UC during pregnancy is largely the same as in the nonpregnant patient. Sulfasalazine is used to treat mild to moderate disease, since there is no evidence that the drug is harmful to the fetus or leads to fetal malformations. Women with inactive colitis who enter a pregnancy on maintenance sulfasalazine should be continued on the drug to protect the mother during the postpartum period from a relapse of disease. Both sulfasalazine and 5-aminosalicylate preparations may be taken during breast feeding. Corticosteroids should be used in the same dosage and for the same indications as in the nonpregnant patient. However, other immunosuppressive agents should not be

Table 286-4

5-Aminosalicylic Acid Products and Their Uses

Drug	Delivery Method	Dose	Use in Ulcerative Colitis	Use in Crohn's Disease
Sulfasalazine (Azulfidine)	Colonic bacterial azo reductases	2–4 g	Active colitis Maintenance	Active colonic disease
Olsalazine (Dipentum)	Colonic bacterial azo reductases	1 g	Active colitis Maintenance	Active colonic disease
Mesalamine (Asacol)	Eudragit-S Release at pH > 7	800–2400 mg	Active colitis Maintenance	Active colonic disease
Mesalamine (Pentasa)	Ethylcellulose microgranules Time-release	1500–4000 mg	Active colitis Maintenance	Active disease Maintenance
Mesalamine enemas (Rowasa)	Directly available	4 g	Active left-sided disease Maintenance	Distal colonic disease
Mesalamine suppositories (Rowasa)	Directly available	500 mg	Active proctitis Maintenance	Crohn's proctitis

SOURCE: Modified from Griffin and Miner.

used during pregnancy. Similar therapeutic approaches apply to the management of CD during pregnancy.

SURGICAL THERAPY Approximately 20 to 25 percent of patients with UC require colectomy during the course of their disease. A major indication for colectomy is failure to respond to intensive medical management. This group includes patients who do not improve after 7 to 10 days of optimal medical therapy, even if they do not show signs of colonic dilation. Fever, persistent bloody diarrhea, and severe fatigue may persist, and consideration should be given to semielective colectomy. Elective colectomy may be performed in patients whose disease remains chronically active and who require continuous glucocorticoid administration. Such patients are at risk of developing the complications of chronic steroid therapy. After colectomy, these patients often feel more energetic and usually gain weight to their preillness level. As discussed above, the patient with long-standing colitis is at high risk for colonic cancer. While most authorities do not advise "prophylactic" colectomy in patients with quiescent disease, the finding of marked dysplasia on colonoscopic biopsies performed as a part of a surveillance program should make the physician think seriously about advising colectomy.

The decision to advise colectomy in other than emergency circumstances is difficult for both patient and physician. Many patients have an understandable reluctance to undergo colectomy and have difficulty in viewing life with an ileostomy. In most metropolitan centers there are ileostomy groups who visit patients preoperatively and can provide answers to many practical questions. It is also desirable for the patient to be visited by a nurse familiar with stoma care to instruct the patient on the practical aspects of handling the ileostomy.

While total proctocolectomy with permanent ileostomy has been the standard surgical procedure for almost all patients undergoing colectomy, several alternative approaches are available. The *continent ileostomy* is an ileal loop reservoir fashioned under the skin with a nipple valve to prevent spilling of ileal contents. Ileal effluent collects in this reservoir, which must be emptied with a soft rubber catheter. Only a small stoma is externally visible, thus eliminating an external ileostomy appliance. Problems with leakage and frequent revisions have made this procedure less attractive. There is great enthusiasm for *ileal-rectal anastomosis* with an internal ileal pouch created to act as a reservoir. This often produces a highly satisfactory result, with continence and five to seven stools per day. Complications such as pouchitis or the need for surgical revision seem less frequent than with the continent ileostomy. Refinement in technique has permitted an *ileoanal anastomosis* with an internal pouch fashioned from small intestine anastomosed to the anal canal. When the procedure is performed by experienced surgeons, continence is excellent; however, nocturnal leakage occurs in about 20 percent of patients. Since some residual rectal mucosa may remain after these anastomotic procedures, surveillance proctoscopy for dysplasia should be performed.

Crohn's Disease The medical management of colonic CD is similar in most respects to that of UC. In a multicenter study (National Cooperative Crohn's Disease Study), sulfasalazine was shown to be effective in the therapy of active colonic disease. Glucocorticoids also were efficacious, but less so than with small-bowel involvement. The indications and dosages for these medications are similar to those for UC. Since, in CD, intraabdominal sepsis can result from fistula or abscess formation, glucocorticoids must be used with caution, and constant attention is required to detect sepsis, which can be masked by these agents. In general, the disease is less explosive in onset, and toxic dilation and perforation are less common than in UC. The principles of management are the same. Because of the indolent nature of the disease, the response to therapy is often less complete than in UC, and the disease tends to progress despite apparent clinical inactivity. It may be more difficult to achieve a clinical remission and to withdraw steroids completely. As in UC, controlled studies have shown no benefit to continuing steroids after remission, since the frequency of recurrence is not altered by prophylactic steroid therapy. Disappointingly, sulfasalazine has not decreased recurrence rates in CD.

While response to treatment of the initial attack of Crohn's colitis may be satisfactory, many patients continue to have persistently active disease. This may express itself as progressive weight loss, diarrhea, and deterioration of general health. Perianal disease with predominantly left-sided colonic involvement (fistula formation and perirectal abscesses) may be a recurrent problem. In one controlled study, *metronidazole* (20 mg/kg per day in divided doses) resulted in marked improvement in some patients with chronic perineal fistulas associated with CD. It is not clear whether the drug is active because of its antibacterial properties or through another mechanism. It is possible that metronidazole may be of value in treating the perineal complications of CD before surgical therapy is attempted. In patients taking these doses of metronidazole on a chronic basis, peripheral sensory neuropathy is a significant side effect and may necessitate reducing the dose or discontinuing the drug if symptoms persist. The role of immunosuppressive therapy in the treatment of CD has become better established in recent years. The use of 6-mercaptopurine or azathioprine (1.5 to 2.0 mg/kg) has been shown to decrease disease activity, cause fistulas to close or become less active, and exert a steroid-sparing effect; it may decrease the relapse rate if used as maintenance therapy. Often, adding these drugs to a maximal program in a nonresponding patient produces beneficial results. However, a positive response may take 3 to 4 months to appear.

The management of CD of the small intestine (regional enteritis) is similar to that for colonic CD, and, as noted, many patients have both small- and large-bowel disease. Several additional considerations are pertinent, however. *Intestinal obstruction* is not uncommonly a presenting feature with ileal involvement. Initially, this problem may be secondary to acute inflammation and will respond to glucocorticoids. With recurrent involvement and the development of fibrosis, steroid therapy is less effective, and surgical decompression is required. *Nutritional problems* often are more severe with involvement of the small intestine than with colonic involvement alone. Added to the general catabolic nature of the disease may be loss of absorptive surface, either from progressive involvement or because of surgical resection. Refinements in the technique of parenteral alimentation have made it possible to provide a patient's total daily caloric intake intravenously for a period of weeks or even months (see Chap. 78). Parenteral alimentation has been employed with increasing frequency in severely ill patients as a means of "resting" the gastrointestinal tract and in preparing the malnourished patient for surgery. However, disease activity frequently recurs when oral feedings are resumed. On occasion, prolonged intravenous alimentation, administered at home, may be required when oral feedings are not effective or in children exhibiting severe growth failure associated with CD. Most often it is possible to design a dietary program of oral supplementation to nourish the patient adequately.

In patients with extensive small-bowel involvement and in those with a short bowel resulting from extensive intestinal resection, supplementation of electrolytes, minerals, and vitamins will be necessary. Extensive ileal disease or resection often results in diarrhea induced by impaired bile salt absorption; cholestyramine may be needed to control the diarrhea, and medium-chain triglycerides may need to be added to reduce fat malabsorption (see Chap. 285). In patients with stenotic segments of intestine, a low-residue (low-fiber) diet should be recommended. A lactose-free diet should be instituted if there is an associated lactase deficiency. Other dietary modifications have not been shown to have any beneficial effect on the primary disease process. Patients should be encouraged to eat a nutritious, appealing diet of their own choosing.

Surgical therapy in general should be reserved for the complications of CD rather than used as a primary form of therapy. More patients with CD than with UC require surgery in the chronic management of the disease. Approximately 70 percent of patients require

at least one operation during the course of their disease. Although each case must be assessed individually, surgery may be required (1) for persistent or fixed bowel narrowing or obstruction, (2) for symptomatic fistula formation to the bladder, vagina, or skin, (3) for persistent anal fistulas or abscesses, and (4) for intraabdominal abscesses, toxic dilation of the colon, or perforation. In contrast to UC, where colectomy is curative, in CD surgical resection of the small or large intestine is followed by a high rate of recurrence. With resection of segments of small bowel or ileum and reanastomosis, a recurrence rate of 50 to 75 percent over a 5-year period is not unusual. The site of recurrence invariably is proximal to the created anastomosis. When total colectomy and ileostomy are performed for CD of the colon without significant small-intestinal involvement, recurrence rates are lower, varying from 10 to 30 percent. Despite these recurrences, most patients do not develop a short bowel syndrome, and most can expect significant improvement. Faced with the possibility of recurrent disease, many physicians are reluctant to advise surgery in CD, except for the clear-cut complications described above. Alternatively, surgery may be indicated for patients with persistently active disease that requires chronic maintenance therapy with unacceptably high levels of corticosteroids. While patients with Crohn's colitis without major small-bowel involvement also have a definite rate of recurrence, such recurrences often are not disabling. When extensive small-bowel disease is present, surgical therapy often is not feasible and should only be reserved for specific disease complications.

The therapy of CD in children presents special problems, since active disease may retard normal growth and development. In addition to conventional drug therapy, intensive nutritional therapy or the judicious use of surgery may be required.

PROGNOSIS

The overall prognosis of IBD has been improved by the use of glucocorticoids and sulfasalazine, as well as supportive measures such as intravenous alimentation. In *acute* UC, these therapeutic modalities can produce a remission in almost 90 percent of patients. The mortality rate from an initial acute attack is less than 5 percent. The prognosis is poorer and the mortality rate higher when there is total colonic involvement, when disease onset is after age 60, and when toxic megacolon develops.

The long-term prognosis of *chronic* UC is more difficult to assess owing to the variable and intermittent nature of the disease and improvements in therapy. Left-sided colitis and ulcerative proctitis have a very favorable prognosis and probably cause no increase in mortality rate; similarly, the long-term prognosis for extensive colitis has improved greatly. Previous studies suggested a poor prognosis for extensive colitis, with less than 50 percent of patients surviving 15 years after onset. However, more recent observations (longest follow-up, 11 years) show 10-year mortality rates of 5 and 10 percent for severe first attacks (excluding toxic megacolon). Approximately 75 percent of patients will experience relapses, and 20 to 25 percent will require colectomy. The problem of carcinoma developing in the setting of long-standing chronic UC is important in determining the long-term prognosis of UC. As discussed above, periodic colonoscopic surveillance with multiple biopsies to detect dysplastic changes is indicated to detect a high-risk group in whom to advise colectomy.

The prognosis for CD is not as favorable as for UC. An exception is *acute regional enteritis*, often discovered during laparotomy for suspected appendicitis; this condition has an excellent prognosis. More than two-thirds of such patients may show no subsequent evidence of regional enteritis, and this form of acute ileitis may well be due to *Yersinia* infection (see above). Surgical opinion favors a conservative approach in this situation, and in general operative resection is not advised.

In most patients with CD, the course is chronic and intermittent regardless of the site of involvement. The disease responds less well to medical therapy with time, and over two-thirds of patients develop complications requiring surgery at some point in their disease. In contrast to UC, where mortality appears greatest early in the disease, in CD the mortality rate increases with the duration of the disease and probably ranges from 5 to 10 percent. Most deaths are caused by peritonitis and sepsis. As indicated above, patients with CD often have recurrence and relapses after surgery. Nevertheless, therapy results in reasonably stable and productive lives for most CD patients.

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14TH EDITION

VOLUME 2

Harrison's PRINCIPLES of INTERNAL MEDICINE

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