*Recent advances in the medical therapy of*

# Inflammatory Bowel Disease

**Medical Grand Rounds**

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## Introduction

The idiopathic inflammatory bowel diseases (IBD's) comprise a collection of diseases of the small and large intestines of unknown etiology and pathogenesis, that are characterized by inflammation and ulceration, frequent recurrences, and multiple gastrointestinal and systemic complications. **Ulcerative colitis** is a diffuse mucosal inflammation limited to the colon. Ulcerative colitis invariably affects the rectum, and may extend proximally in a symmetrical, uninterrupted pattern to involve part or all of the large intestine. In contrast, **Crohn's disease** is a patchy transmural inflammation that may affect any part of the gastrointestinal tract from the mouth to the anus. Its most common distributions are either small bowel alone (regional ileitis or enteritis), colon alone (Crohn's disease of the colon or colitis), or both large and small bowel simultaneously (ileocolitis).

IBD has probably existed for several hundred years (1). Isolated cases consistent with IBD initially appeared in Great Britain and northern Europe and have steadily increased in number and geographic distribution with ulcerative colitis dominating the first half of this century and Crohn's disease the second half. Idiopathic ulcerative colitis, distinct from the then prevailing epidemic dysentery, was recognized in the late 1800s. Infectious causes of colitis were recognized at about the same time — Entameba histolyt*ica* in 1875, *Salmonella typhi* in 1880 and *Shigella dysenteriae* in 1898.

IBD descriptively consistent with Crohn's disease was apparently observed ~300 years ago. In 1932, Crohn, Ginzburg, and Oppenheimer published a paper entitled "Regional ileitis: a pathologic and clinical entity" that included 14 patients characterized by abdominal pain, fever, diarrhea and a hypertrophic and ulcerative stenosis of the distal 2 or 3 ft of the terminal ileum (2). Of note, Crohn's colitis was not recognized as an entity distinct from ulcerative colitis until 1960 (3).

## Epidemiology

The incidence of IBD is highest in "westernized" countries and lowest in "developing" regions of the world (4). The Scandinavian countries, Great Britain and North America have the highest incidence rates while incidence rates are generally lower in Asia, Africa and South America. Recently, however, incidence rates seem to be leveling off in "westernized countries" and increasing in "developing countries". In particular, the incidence of IBD in Japan may be approaching that of North America.

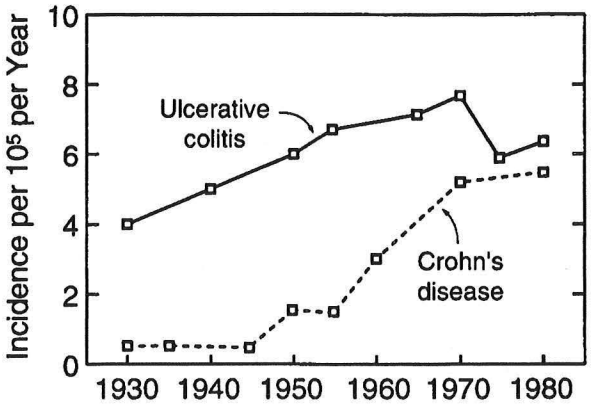



Figure 1. Incidence of IBD by decade.

In North America and Northern Europe, the incidence of ulcerative colitis has remained relatively constant over the last 3 decades while the incidence of Crohn's disease has steadily risen (5). As a result, the incidence Crohn's disease now equals or exceeds that of ulcerative colitis (Figure 1).

A number of early studies demonstrated an increased risk of IBD among Jews. More recent population based studies support a modestly increased risk (2 to 4-fold) among Jews in many countries. In general, the rates for Jews parallel those of the general population. These data appear to support the dual effects of environment and genetics in the pathogenesis of IBD. Interestingly, the incidence of IBD is relatively low in Israel. A number of early reports indicated that the

incidence of IBD in this country was much higher among Caucasians than among Blacks or Asians but these ethnic differences seem to be disappearing as well. IBD has been described in all ethnic groups. No ethnic group is immune.

The age distribution of ulcerative colitis and Crohn's disease is shown in Figure 2. The preponderance of cases have their onset between ages 15 and 40 but the range extends from infancy to old age (6, 7). Men and women are affected about equally with men slightly more likely to have ulcerative colitis and women to have Crohn's disease.

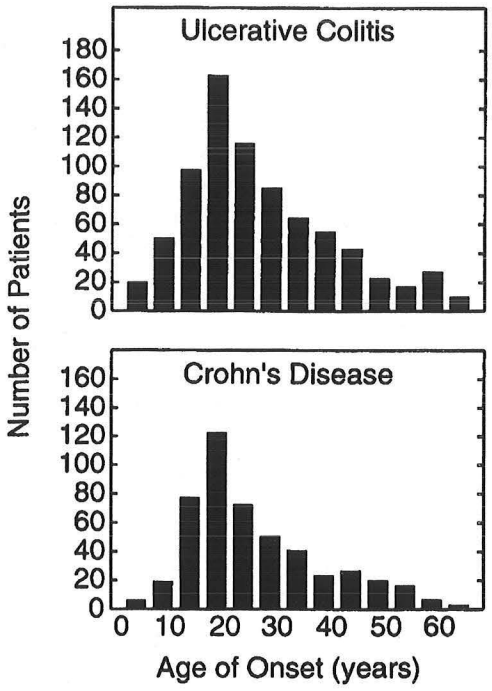



Figure 2. Age distribution of IBD.

## Genetics of IBD

Familial aggregation is clearly increase in IBD, although the data fit no simple mendelian pattern of inheritance. Approximately 10-25% of patients have first degree relatives with the disease and a number of families have been reported with 5-8 members affected over 3 generations. Family members are usually concordant for the same disease; however, the two diseases sometimes coexist in the same family (8).

The results of the two available population-based twin studies are shown in Figure 3 (9, 10). These aggregate data indicate that there is a higher concordance rate for monozygotic than dizygotic twins in both Crohn's disease and ulcerative colitis. The observation that not 100% of monozygotic twins are concordant indicates that there is reduced penetrance for the IBD genotype, presumably due to environmental factors. Indeed, it would appear that environmental factors are likely to play a major role in the genesis of IBD.

Taken together, the data from familial studies seem to rule out simple mendelian and polygenic modes of inheritance. More likely would be a two-locus or oligogenic mode of inheritance in which 2 or a limited number of genes confer susceptibility to IBD (11).

## Etiology and Pathogenesis

Although both genetic and environmental factors are involved, neither the etiology nor pathogenesis of IBD is known despite enormous effort over many decades. IBD would appear to be the result of an unrestrained inflammatory reaction; however, the antigens that induce and perpetuate this chronic immune response and the predisposing genetic factors remain unknown. Although hypotheses abound, most of the attention in recent years has focused on infections and genetically determined defects of immunoregulation.

Infectious agents have always been suspected in the initiation of IBD due to the strong resemblance of IBD to various enterocolonic infections. Although a large number of microbial

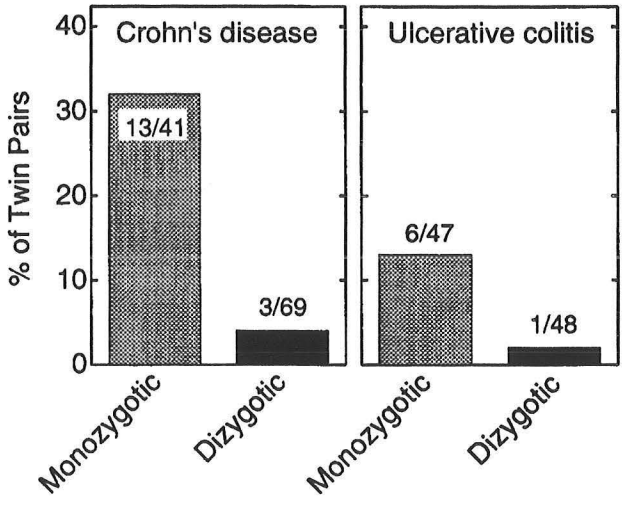



Figure 3. Genetics of IBD: Twin studies.

agents have been implicated, there is no convincing evidence for the etiologic involvement of any (12). At the current time, specific microbial agents being proposed include atypical Mycobacterium (13, 14), measles (15), and Listeria (16).

While there is little compelling evidence to implicate a specific infectious agent in the etiology of IBD, convincing evidence is accumulating that endogenous luminal bacterial constituents can induce and perpetuate chronic intestinal and extraintestinal inflammation in genetically susceptible hosts and that this dysregulated immunmosuppression can lead to an unrestrained inflammatory response to ubiquitous bacterial antigens.

### *New rodent models of intestinal inflammation*

One of the problems in inflammatory bowel disease research has been the lack of a suitable animal model (17). The cotton-top tamarin is unique in that it exhibits spontaneous colitis with associated adenocarcinoma of the colon; however, its endangered species status severely limits its availability for routine investigation. Intestinal inflammation has been induced in experimental animals using a variety of infectious agents, chemical agents, NSAIDs and immunological manipulations. However, the exact relevance of these inducible models to human IBD is uncertain. More recently, overexpression (transgenic) or deletion (knockout) of genes encoding targeted cytokines, T cell receptors, HLA molecules and intracellular messengers by investigators outside of the IBD field have unexpectedly led to spontaneous intestinal inflammation and the creation of a whole new class of rodent models of IBD (18).

Table I. Rodent models of intestinal inflammation.

| |
|---|
| Spontaneous mutation |
| • $C_3H$ HeJ Bir mouse |
| Genetically engineered |
| • HLA-$B_{27}$ transgenic rat |
| • IL-2 deleted mouse |
| • IL-10 deleted mouse |
| • αβ TCR deleted mouse |
| • TGF-$\beta_1$ deleted mouse |
| • Gi2α deleted mouse |
| Reconsitituted |
| • $CD45RB^{high}$ → SCID mouse |

Recently developed rodent models of spontaneous intestinal inflammation are summarized in Table I. The C3H/HeJ Bir is a substrain of mice developed by selective breeding that manifests right-sided colitis. Presumably, colonic inflammation in this substrain is the result of a spontaneous genetic mutation, which remains undetermined.

The clinical and pathologic features of the genetically engineered models of intestinal inflammation are summarized in Table II. These include rats overexpressing human HLA-$B_{27}$ and $\beta_2$-microglobulin, mouse IL-2 knockouts, mouse IL-10 knockouts, mouse T-cell receptor knockouts (TCRα, TCRβ and TCR β x δ), mouse transforming growth factor-β knockouts and mouse Gi2α knockouts. These mouse mutants illustrate that chronic mucosal inflammation can be the result

Table II. Clinical and pathologic features of spontaneous models of intestinal inflammation (adapted from reference 18).

| | Intestinal location | Systemic involvment | Mucosal vs. transmural | Granulomas | AdenoCa | Bacterial influence |
|---|---|---|---|---|---|---|
| HLA-$B_{27}$ TG | Colon, Stomach, duodenum | Joint, skin, testes, anemia | Mucosa | No | Yes | Yes |
| IL-2 KO | Colon, SB (late) | Hemolytic anemia, amyloidosis | Mucosa | No | No | Yes |
| IL-10 KO | Colon, prox. SB | Anemia | Trans. | No | No | Yes |
| αβ TCR KO | Colon | Liver (±) | Mucosa | No | No | ? |
| TGF-$\beta_1$ KO | Colon, Stomach | Lungs, heart, pancrease, liver | Mucosa | No | No | ? |
| Gi2α KO | Colon | ? | Mucosa | No | Yes | ? |
| $CD45RB^{high}$ | Colon, Stomach, duodenum | Liver, lungs, heart | Trans. | Yes | No | Yes |

TG, transgenic; KO, knockout; SB, small bowel; TCR, T cell receptor; $CD45RB^{high}$, reconstitution of SCID mice with $CD4^+$ T lymphocyte subpopulation.

of a primary immunoregulatory defect.

The importance of counterbalancing T lymphocyte subpopulations in intestinal inflammation has been demonstrated by reconstitution studies in immunodeficient Nude rats and SCID mice. These animals readily accept transferred lymphocytes without rejection. Animals receiving specific subpopulations of CD-4$^+$ T-lymphocytes (CD45RB$^{high}$, subset with $T_{H1}$ phenotype) develop chronic colitis whereas animals receiving unfractionated CD4$^+$ T-lymphocytes do not.

A critical role for ubiquitous luminal bacteria in the pathogenesis of chronic intestinal inflammation is demonstrated by the absence of colitis in germ-free HLA-$B_{27}$ transgenic rats and IL-2 knockout mice, attenuated disease in IL-10 and IL-2 knockout mice raised under specific pathogen-free conditions, and amelioration of disease by antibiotic therapy in HLA-$B_{27}$ rats and SCID mice with colitis (repopulated with CD45RB$^{high}$ lymphocytes).

Thus, a single alteration of any of a number of key immunoregulatory cytokines, MHC molecules, signal transducers, or disease susceptibility genes can lead to chronic intestinal inflammation (18). Host genetic susceptibility determines the incidence and aggressiveness of disease as clearly demonstrated when the genetically engineered models discussed above are bred into different genetic backgrounds. Ubiquitous luminal bacteria play a critical role in induction and perpetuation of chronic intestinal and systemic inflammation in genetically susceptible hosts. These observations are consistent with the hypothesis that chronic intestinal (and the related systemic) manifestations are the result of an inappropriately aggressive immune response to ubiquitous luminal bacterial constituents, mediated by genetically determined defective immunosuppression. These observations also suggest that ulcerative colitis and Crohn's may be heterogeneous groups of disorders with multiple etiologies.

## Clinical Manifestations

### Ulcerative colitis

Ulcerative colitis is a diffuse mucosal inflammation of the colon that invariably affects the rectum, and may extend proximally in a symmetrical, uninterrupted pattern to involve part or all of the large intestine. The principal signs and symptoms are rectal bleeding and diarrhea which may progress to the passage of small amounts of mucopus as frequently as every few minutes. Abdominal pain, rectal cramps, fever and weight loss are also common.

### Crohn's disease

Crohn's disease is a transmural inflammation that may develop anywhere along the gastrointestinal tract; consequently, the clinical features of Crohn's disease are diverse and depend on the location of inflammation as well as the individual's reaction to that inflammation. Since Crohn's disease produces transmural inflammation and luminal narrowing in the ileocecal region in 75-80% of cases (Table III), three of the most common clinical presentations are (1) chronic right lower quadrant abdominal pain and diarrhea, (2) partial intestinal obstruction, or (3) an acute attack of right lower quadrant pain that may mimic acute appendicitis. Patients with Crohn's colitis usually present with diarrhea and rectal bleeding.

Table III. Anatomic location of Crohn's disease

| |
|---|
| • Small bowel only (30%) |
| • Ileocecal (40%) |
| • Colon only (25%) |

The intestinal complications of Crohn's disease follow from its pathology. Inflammatory infiltration, edema and spasm frequently produce marked luminal narrowing and obstruction that frequently improves with medical therapy. With time, fibrostenotic strictures may develop requiring resection or strictureplasty. Fistulas occur when the inflammatory process penetrates into adjacent tissues, adjoining organs or the skin. Fistulas most commonly originate from the terminal ileum. Some fistulas may respond to bowel rest and immunosuppressants (19); however, many eventually require resection of the segment of the bowel from which the fistula originates. Perirectal complications (fissures, fistulas and abscesses) are common in Crohn's disease but rare

in ulcerative colitis.

Some clinical features differentiating ulcerative colitis and Crohn's disease are listed in Table IV. Smoking is probably the most extensively studied exposure that has been linked to IBD (4). The most consistent finding is an apparent 2 to 10-fold increase in the risk of developing ulcerative colitis among nonsmokers and former smokers when compared to current smokers. In contrast to the apparent protective effect of smoking on ulcerative colitis, smoking appears to increase the risk of developing Crohn's disease and may increase the risk of recurrence. Smoking does affect processes that may relate to IBD such as mucus production, gut permeability, vascular responses and even cytokine production by mononuclear cells. Why smoking would decrease the risk of ulcerative colitis and increase the risk of Crohn's disease is unclear.

Table IV. Clinical features distinguishing ulcerative colitis and Crohn's diseaes.

| | Ulcerative colitis | Crohn's disease |
|---|---|---|
| **Clinical** | | |
| Response to antibiotics | No | Yes |
| Response to bowel rest | No | Yes |
| Perianal disease | No | Yes |
| Fistulas | No | Yes |
| Recurrence after surgery | No | Yes |
| **Risk factors** | | |
| Current smoker | Uncommon | Common |
| Former smoker | Common | Uncommon |
| **Lab tests** | | |
| ANCA | Usually | Rarely |

A distinct subset of antineutrophil cytoplasmic antibodies p-ANCA is found in ~75% of patients with ulcerative colitis but in only 5-10% of patients with Crohn's disease (20). ANCA is rare in normal controls (3%). ANCAs appear to be largely independent of disease activity, duration of illness, localization, extent of disease, pervious bowel operations, or medical treatment. The significance of p-ANCA in ulcerative colitis is unknown. Occasionally it may be difficult to differentiate ulcerative colitis from Crohn's colitis. In these situations, the combination of a serum ANCA and smoking history at the time of disease onset should be highly predictive of the type of colitis.

### *Differential diagnosis*

A large number of infectious and noninfectious disorders may mimic IBD. Some of these are listed in Table V. In particular, many enteric infections can lead to a clinical presentation indistinguishable from idiopathic IBD. In addition, apparent exacerbations of IBD may be precipitated by enteric infections in some cases.

Table V. Some infectious and noninfectious disorders that may mimic IBD.

| *Infectious diseases* | *Noninfectious diseases* |
|---|---|
| Salmonella | Diverticulitis |
| Shigella | Ischemic colitis |
| Campylobacter | Radiation enteritis |
| *E. coli* O157:H7 | Vasculitis |
| *C. difficile* | Appendicitis |
| Yersinia | Endometriosis |
| Amebiasis | Eosinophilic gastroenteritis |
| Tuberculosis | Sarcoidosis |
| MAI | Neutropenic colitis |
| Histoplasmosis | Neoplasms |
| STDs | |
| CMV | |

The major extraintestinal manifestations of IBD are listed in Table VI. The activity of some of these tends to parallel the activity of the bowel disease whereas others run an independent course. Primary sclerosing cholangitis is relatively specific for ulcerative colitis (although it occasionally occurs in Crohn's colitis). The other extraintestinal manifestations occur at roughly similar frequencies in the two diseases.

## Medical Therapy of IBD

Despite recent advances and the introduction of several new drugs, there is no cure for IBD. Medical therapy may, however, help control disease and improve quality of life. The goals of therapy are to reduce or reverse bowel inflammation, provide symptomatic relief and to maintain nutritional status. A cure for IBD cannot be expected until the etiology of the disease is understood.

Table VI. Major extraintestinal manifestations of IBD.

| | Frequency (%) | Activity related |
|---|---|---|
| Arthritis | 10 | Yes |
| Skin | 10 | ± |
| Eye | 4 | Yes |
| Ankylosing Spondylitis | 4 | No |
| Sclerosing Cholangitis | 4 | No |

### *Corticosteroids*

Corticosteroids are the mainstay of therapy for the short-term treatment of moderate to severely active IBD. The mechanism of action of corticosteroids is not specific to IBD and relies on binding of the hormone to high-affinity intracellular cytoplasmic receptors present in all human cells leading ultimately to altered transcription of glucocorticoid-regulated genes. Corticosteroids act not only on mediators of the amplified inflammatory reaction but also on immune cells and cytokines down-regulating the immune response.

Corticosteroids are prescribed in doses of 40-60 mg of prednisone/day as short-term therapy and then tapered as soon as clinical remission is achieved. The inability to completely withdraw continuous corticosteroid therapy within 1 year (or at least taper below 20 mg/day prednisone) places the patient at high risk for serious side effects and is a strong indication for steroid-sparing therapy (immunosuppressants in Crohn's disease or surgery in Ulcerative colitis as discussed below).

### *Topical Steroids*

Corticosteroids have a topical activity that can be separated from their systemic properties (21). Efforts are being made to increase the topical steroid potency and to minimize the systemic effects on the hypothalamic-pituitary-adrenal axis by developing analogues that are either poorly absorbed or else rapidly metabolized and inactivated on passage through the liver. Among the newer corticosteroid analogues, budesonide, appears to be the most promising for use in IBD. Budesonide is a very potent water-soluble glucocorticoid derivative (200 times more potent than cortisol) with rapid (~90%) first-pass metabolism by the liver and delayed absorption (prolonged retention in the intestinal mucosa). Budesonide is commercially available in enema form in several European countries. When used in this form for distal colitis it is as effective as other forms of steroid enemas but with minimal effects on plasma cortisol levels.

Of greater potential interest is the development of delayed release formulations of budesonide designed to target the terminal ileum or colon. Two controlled trials recently examined the ability of oral controlled-release budesonide to induce clinical remissions in patients with ileal or ileocolonic Crohn's disease. Budesonide was compared to placebo (Figure 4) in one study (22) and to prednisolone in the other (23). These studies suggest that oral budesonide is better than placebo and nearly as effective as prednisolone in the short-term treatment of active Crohn's disease. Budesonide produced some-

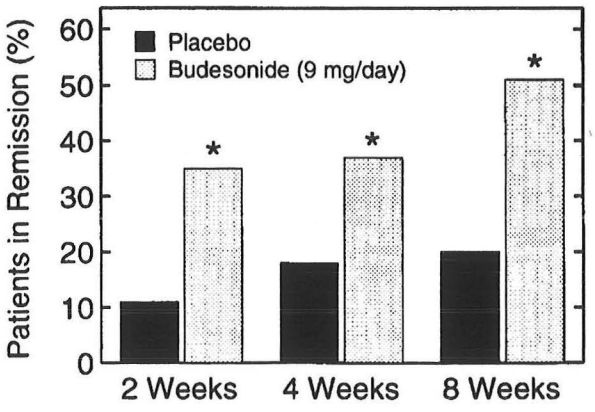



Figure 4. Oral budesonide for active Crohn's disease (from reference 20).

what fewer side effects and less suppression of the hypothalamic-pituitary-adrenal axis than prednisolone although differences in morning cortisol suppression began to wane by 10 weeks.

The much greater problem in the management of IBD is how to maintain clinical remissions in the long term. Whether budesonide will be useful in this regard has yet to be determined. However, studies evaluating the efficacy of oral budesonide in the long-term maintenance of remission of IBD — to date available almost exclusively in abstract form — suggest that doses of budesonide with minimal effects on the hypothalamic-pituitary-adrenal axis are well-tolerated and may delay relapse (24).

***Mesalamine (5-aminosalicylic acid, 5-ASA) preparations***

Sulfasalazine is the original compound from which the subsequent development of alternative, non-sulfa containing derivatives of 5-ASA have evolved. Sulfasalazine, though originally developed for the treatment of rheumatoid arthritis, has come to play a central role in the medical therapy of IBD.

Sulfasalazine consists of a salicylate radical linked to sulphapyridine by an azo bond (Figure 5). The azo bond is split by colonic bacteria, with liberation of 5-ASA and sulphapyridine. The sulphapyridine is almost completely absorbed from the colon, metabolized, and excreted in the urine. Most of the side effects of sulfasalazine have been ascribed to the sulphapyridine moiety and correlate with its serum concentration, while 5-ASA accounts for virtually all of the therapeutic effects (when used in the therapy of IBD). Although sulfasalazine remains the most cost-effective, first-line therapy for mild to moderately active ulcerative colitis and for the maintenance of remission in patients with quiescent ulcerative colitis, the dose-dependent side effects and the isolated colonic delivery has opened the door to alternative 5-ASA preparations with more favorable therapeutic margins and alternative sites of delivery (25, 26).

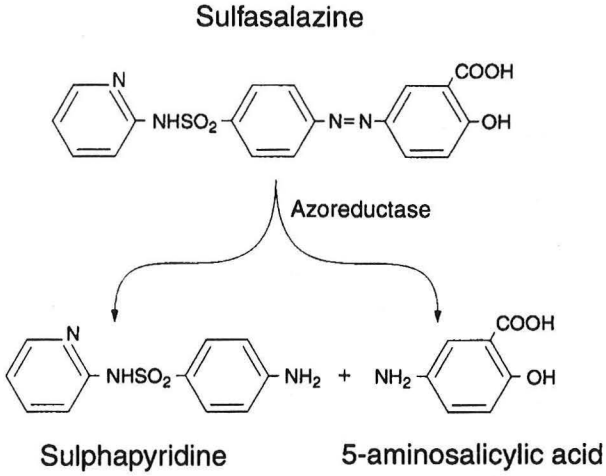


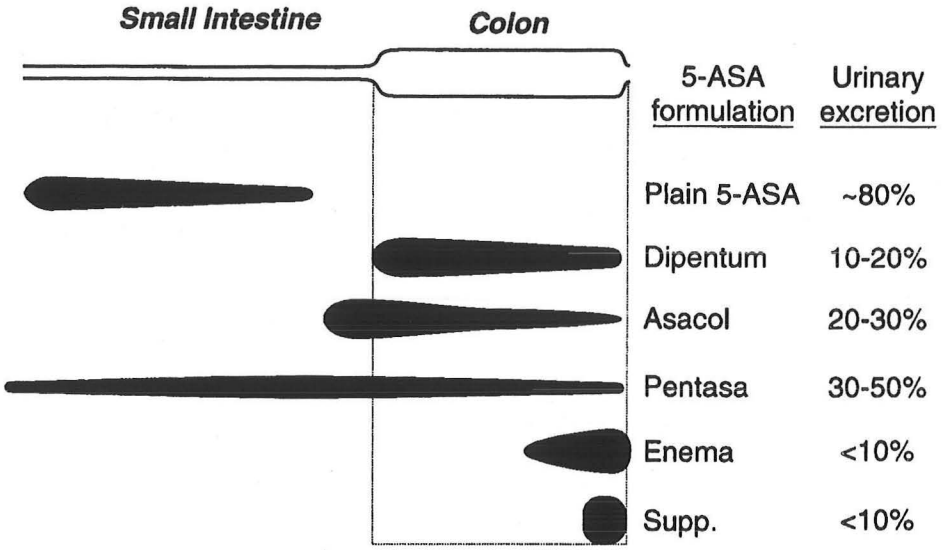

Figure 5. The sulfasalazine molecule consists of 5-aminosalicylic acid (5-ASA) linked by an azo bond to sulfapyridine. The azo bond is split by bacterial azoreductases in the colon.

The development of alternative (sulfa-free) aminosalicylates was based on two premises: (1) 5-ASA is presumed to function topically within the mucosa without significant "systemic"

Table VII. Different 5-ASA preparations

| Preparation | Formulation | Release mechanism | Dose/ day |
|---|---|---|---|
| **Azo-bond** | | | |
| Sulfasalazine (Azulfadine) | | Bacterial azoreductase | 3-6 g (acute), 2-4 g (maint) |
| Olsalazine (Dipentum) | Azodisalicylate | Bacterial azoreductase | 1-3 g (maint) |
| **Delayed release** | | | |
| Asacol | 5-ASA coated with acrylic polymer (Eudragit S) | Release at pH>7 | 2.4-4.8 g (acute), 0.8-4.8 g (maint) |
| **Sustained release** | | | |
| Pentasa | 5-ASA encapsulated in ethyl-cellulose microgranules | Timed release | 2-4 g (acute), 1.5-4 g (maint) |
| **Topical/rectal** | | | |
| Mesalamine enemas | | | bid (acute), q d-bid (maint) |
| Mesalamine supp. | | | bid (acute), q d-bid (maint) |

activity, necessitating delivery of the compound to local sites of intestinal inflammation, and (2) 5-ASA is rapidly and completely absorbed from the proximal gastrointestinal tract but poorly absorbed from the colon. Thus, to provide 5-ASA as a potential "mucosal" therapy, it is necessary to protect the free molecule from proximal absorption. Formulations of sulfa-free 5-ASA delivery systems include alternative azo-bonded carriers, pH-dependent or continuous-release preparations and direct rectal application of 5-ASA (Table VII and Figure 6).




Fiure 6. Distribution of 5-ASA release with different formulations.

Prodrugs linking 5-ASA to alternative carriers or to itself most closely resemble sulfasalazine. Olsalazine (Dipentum), a 5-ASA dimer in which two 5-ASA molecules are linked together via an azo bond, is chemically the most logical alternative to sulfasalazine. As with sulfasalazine, colonic bacteria are required to split the azo bond and release free 5-ASA, thus minimizing small bowel absorption and urinary excretion of 5-ASA. Of the new azo compounds, Dipentum is the only one currently available in this country.

Asacol is a tablet of mesalamine covered with an 80-130 μm cover of the acrylic polymer Eudragit S that dissolves at pH 7 and above. Pharmacokinetic studies have demonstrated that Asacol begins to release 5-ASA in the terminal ileum allowing most of the 5-ASA to enter the colon as a bolus. Because of inter- and intra-individual differences in transit time and intestinal pH (27), the systemic availability is variable but averages ~30%.

The Pentasa formulation incorporates 5-ASA into microgranules of ethycellulose that act as semipermeable membranes and when hydrated, gradually release 5-ASA in a pH-dependent manner. The current formulation of Pentasa is designed to release approximately 50% of 5-ASA into the small intestine and the remainder in the colon.

***Mechanisms of 5-ASA activity*** — The therapeutic benefits of 5-ASA are likely related to multiple effects including inhibition of lipoxygenase activity (and thus $LTB_4$ production), platelet activating factor synthetase, thromboxane synthetase, mucosal immunoglobulin production, cytokine signaling, and adhesion molecule expression (25, 26, 28). In addition, 5-ASA scavenges free oxygen radicals and inhibits reactive oxygen metabolite production at concentrations attainable in mucosa. Thus, most, if not all,

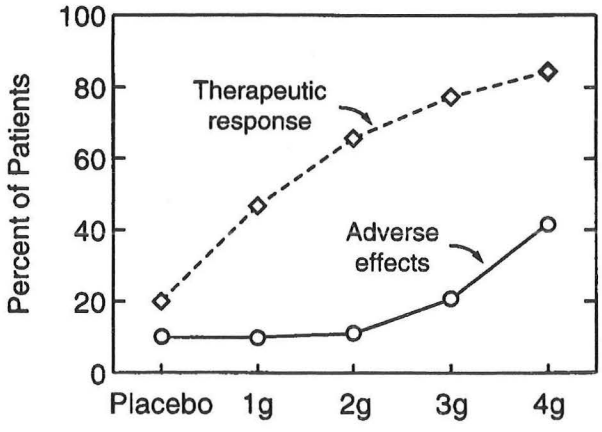



Figure 7. Sulfasalazine: Efficacy and toxicity as a function of dose.

elements of the immune and inflammatory cascades implicated in the pathogenesis of IBD are inhibited to some extent by aminosalicylates.

***Toxicity of sulfasalazine and 5-ASA analogues*** — Due to cost, Sulphasalazine is still the most commonly prescribed aminosalicylate in the United States. Up to one-third of patients will be intolerant of sulfasalazine (25, 26, 29). The most common dose-related side effects include headache and GI intolerance related to the sulfapyridine moiety (Figure 7). These can be minimized by gradual upward titration of the drug and administration with food. Hematologic effects, including bone marrow suppression, hemolytic anemia, and megaloblastic anemia, are also uniformly related to the sulfapyridine moiety. Abnormalities of sperm counts and function are probably related to the sulfa moiety and appear to resolve when a sulfa-free 5-ASA analogue is substituted for sulfasalazine. More severe "allergic type" reactions include skin eruptions, pancreatitis, pulmonitis, hepatotoxicity, colitis and neurotoxicity (Table VIII). Patients who have experienced worsening colitis, pancreatitis, hepatitis or pulmonitis associated with sulfasalazine therapy should not be exposed to 5-ASA since many of these "allergic type" reactions have also been observed with 5-ASA. Overall, about 80% of patients intolerant of sulphasalazine will tolerate one of the new sulfa-free 5-ASA preparations (30). Conversely, 20% may experience similar side effects with either type of drug.

Table VIII. Sulfasalazine toxicity.

- Common dose-related
  GI, headache
- Allegic
  Rash, fever, arthralgia
- Hematologic
  Hemolysis, BM suppression
- Sperm abnormalities
- Severe toxic (rare)
  lung, liver, pancreas, skin, colon

While long-term use of sulfasalazine has never been considered to give rise to renal damage, the 5-ASA in sulphasalazine is released in the colon where it is poorly absorbed. Some of the new 5-ASA preparations, on the other hand, set free considerable amounts of 5-ASA in the small bowel, where it is rapidly absorbed and excreted in the urine. The generally higher doses used and greater renal excretion of Asacol and Pentasa has produced some concern about potential nephrotoxicity by extrapolation from animal studies which suggest that the kidney is the principal target for 5-ASA toxicity. That 5-ASA may affect renal function in humans is indicated by reports of increases in serum creatinine, proteinuria and even full-blown nephrotic syndrome with 5-ASA preparations targeted to the small bowel (29, 31). Overall, nephrotoxicity appears to be rare; nevertheless, renal function should be monitored with high-dose therapy, in patients with preexisting renal disease or in combination with other nephrotoxic therapies (29).

Dipentum has the unique property of stimulating net small bowel secretion. In subjects with an ileostomy, Dipentum increases output by ~250 ml/day. This increased fluid load to the colon may induce looser bowel movements or diarrhea, especially in the setting of active colonic inflammation (26).

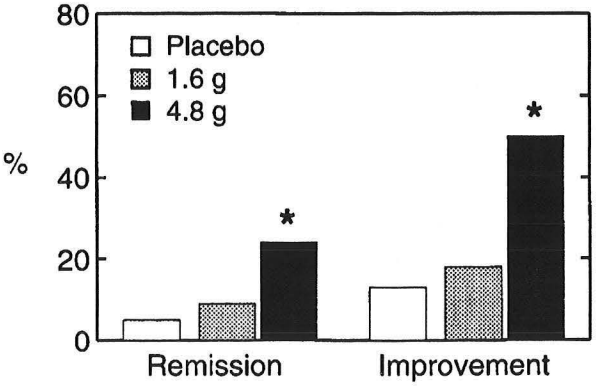



Figure 8. Oral 5-ASA (Asacol) in mild to moderately active Ulcerative colitis. A dose of 4.8 g/day significantly increased the likelyhood of improvement or complete remission at 6 weeks (reference 34).

***Clinical Experience*** — Sulfasalazine has been effective in the treatment of mild to moderately active ulcerative colitis and for preventing the relapse of quiescent ulcerative colitis. Between 2 and 6 g per day in divided doses is commonly used for the treatment of active disease and 1.5 to 4 g per day for maintaining remission. The dose response

in both situations is offset by dose-related intolerance that often limits compliance and has led to the lower doses for maintenance.

All of the currently available 5-ASA analogues (Dipentum, Asacol, Pentasa) have been shown to be effective in the treatment of mild to moderate ulcerative colitis (28, 32-34) and in the maintenance of remission in patients with quiescent disease. Dipentum would appear to most reliably deliver 5-ASA to the colon but should be used with caution (if at all) in active disease due to its unique tendency to induce diarrhea. Overall, the sulfa-free 5-ASA analogues appear to share the efficacy of sulfasalazine without many of the side effects.

The utility of sulfasalazine in Crohn's disease is controversial, although clinical trials and clinical experience support the use when the colon is involved and to prevent symptomatic recurrences in patients who have responded to sulfasalazine initiated for active disease. The ability to target 5-ASA release to more proximal sites in the GI tract has significantly expanded the role of 5-ASA in Crohn's disease. As noted above, Pentasa releases 5-ASA throughout the small intestine while Asacol usually begins to release 5-ASA in the distal small intestine. Placebo-controlled trials suggest that both preparations will be useful in the management of Crohn's disease. Thus, 3.2 g/day of Asacol (35) and 4 g/day of Pentasa (Figure 9)(36) were both superior to placebo in the treatment of mild to moderately symptomatic Crohn's disease. Lower doses of 5-ASA were clearly ineffective. Asacol 2.4 g/day showed a benefit in preventing relapse in patients with quiescent Crohn's disease (37) and Pentasa 2 g/day (Figure 10) was effective in reducing the relapse rate in high risk patients with inactive Crohn's disease — defined as remission of less than 3 months duration prior to therapy (38).

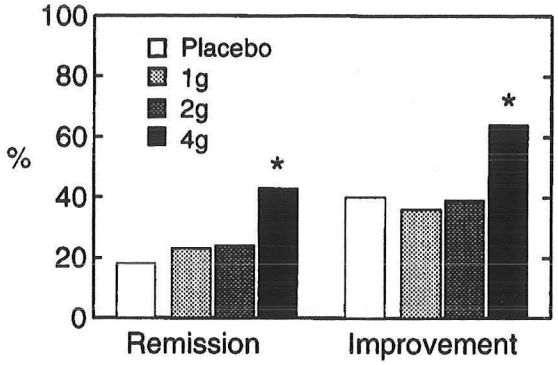



Figure 9. Oral 5-ASA (Pentasa) in active Crohn's disease. Patients taking 4 g/day were significantly more likely to be in remission or to have improved at 16 weeks (reference 36).

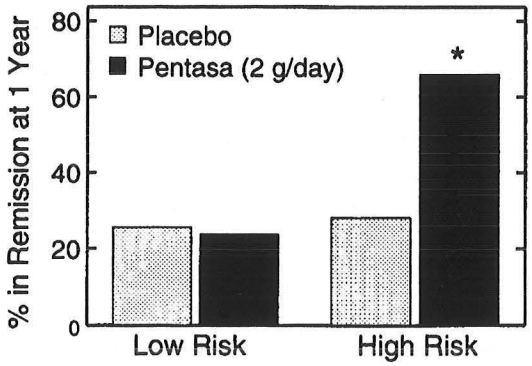



Figure 10. Oral 5-ASA as maintenance therapy in Crohn's disease. Pentasa at 2 g/day was effective maintenance therapy in high risk (recent exacerbation) but not low risk (no recent exacerbation) patients (reference 38).

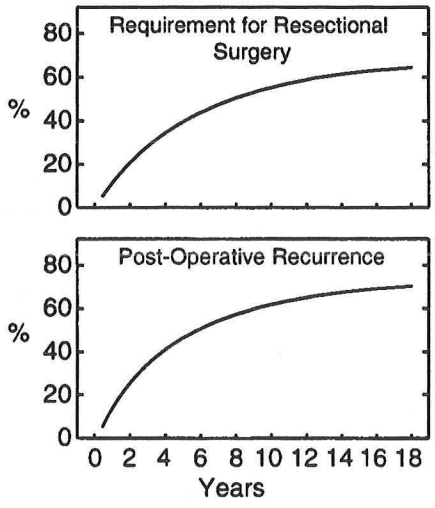



Figure 11. Post-operative recurrence in Crohn's disease.

Up to 80% of patients with Crohn's disease will eventually require resectional surgery. Of these, the vast majority will relapse and about half will require a second operation (Figure 11). To date, no drugs have been shown to significantly decrease the recurrence rate after surgery. However, controlled data were recently published indicating that oral 5-ASA is effective in decreasing the risk of clinical and endoscopic recurrence after resectional surgery (Figure 12) (39).

The question of which 5-ASA preparation to use in a particular situation should take into account the following factors: (1) efficacy, (2) site of disease, (3) toxicity and (4) cost. In ulcerative colitis, all preparations deliver 5-ASA to colon and appear to be equally effective in mild to moderate disease and in

the maintenance of remission at the suggested doses. Although sulfasalazine has a higher incidence of dose-related intolerance, severe allergic reactions can occur with any 5-ASA preparation. Since cost greatly favors sulfasalazine, it is generally used first with gradual upward titration of dose to minimize side effects. Patients intolerant of sulfasalazine can be switched to a sulfa-free 5-ASA preparation. The same approach can be used in patients with Crohn's disease of the colon.

In Crohn's disease involving the terminal ileum, either Asacol or Pentasa would be appropriate based on their sites of 5-ASA release and the clinical data reviewed above. Pentasa should be used with more extensive small bowel disease.

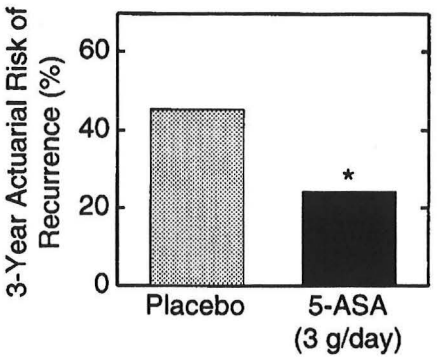



Figure 12. Oral 5-ASA after resectional surgery for Crohn's disease (reference 39).

***Immunomodulators***

The benefit of steroid therapy in Crohn's disease is limited to short-term treatment since maintenance trials have failed to demonstrate any long-term efficacy. In addition, once initiated, up to 50% of patients become either steroid-refractory or steroid-dependent, and thus susceptible to the chronic sequelae of corticosteroids (osteoporosis, osteonecrosis, cataracts, glucose-intolerance, hypertension, etc.). The clinician is therefore forced to consider various steroid-sparing techniques. In the past decade, there has been a major change in physicians attitudes toward the use of immune-modifying agents in IBD (40). Accumulating evidence suggests an immune component in the pathogenesis of IBD and expanding clinical experience with immunosuppressive agents has documented clinical benefits without the previously anticipated complications (ie., neoplasia, teratogenicity).

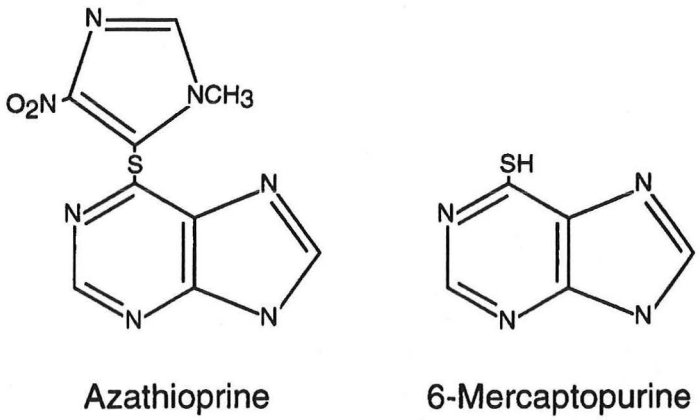



Figure 13. Purine analogues

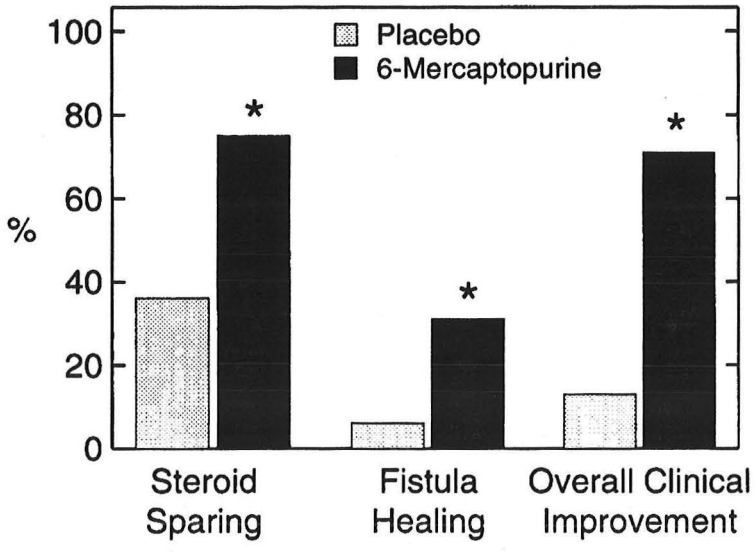



Figure 14. 6-Mercaptopurine in active steroid-dependent Crohn's disease (reference 41).

***Purine analogues*** — Azathioprine and 6-mercaptopurine (6-MP) are purine analogs that competitively inhibit the synthesis of purine ribonucleotides resulting in inhibition of cell proliferation (Figure 13). Azathioprine is metabolized in vivo to 6-MP. These agents are known to have selective effects on T cells and T-cell-dependent responses. They also possess an antiinflammatory effect that may play a role in their therapeutic efficacy.

The role of purine analogs in IBD is now well established. The first major randomized, double-blind trial was carried out by Present et al. (41) and demonstrated the usefulness of 6-MP

in the treatment of patients with Crohn's disease (Figure 14). This study showed that 6-MP was more effective than placebo in allowing discontinuation or reduction of steroid dosage (75 vs. 36%). Nine of 20 fistulas (31%) closed completely during treatment with 6-MP compared with 1 of 17 (6%) treated with placebo. Overall, 71% of patients on 6-MP showed clinical improvement (despite the reduced steroid usage) compared to 13% on placebo. These findings have subsequently been corroborated by others (40). In addition, these agents have been shown to be beneficial at sustaining remission in patients with Crohn's disease. Purine analogs are also effective in the induction and maintenance of remission in patients with UC (42).

The purine analogs are slow-acting drugs that require 1-6 months (mean ~3 months) before clinical efficacy becomes apparent. The delay in clinical effects is consistent with the measured decline of natural killer cell cytotoxicity in patients with IBD (43).

The usual starting dose for 6-MP is 50-75 mg/day titrated up to 2 mg/kg per day. As a large experience with 6-MP in patients with IBD develops, concerns about toxicity have been somewhat allayed (44). Significant bone marrow suppression is uncommon with the doses currently used in IBD. Pancreatitis has been a troublesome complication but almost always rapidly resolves with discontinuation of the drug. Drug-induced hepatitis has been reported. Of greatest concern, however, is the risk of developing neoplasm. The potential risk for neoplasia has been the primary concern based on the reported increase in malignancies (especially lymphoproliferative) arising in the transplant population. However, no increase in the risk for neoplasm has been observed to date in IBD populations (44). Nevertheless, long-term immunosuppression should be avoided in patients at increased risk for developing neoplasms, particularly patients with ulcerative colitis who have the option of a surgical cure.

***Cyclosporine*** — Cyclosporine A has been proposed as a rapid-acting alternative or adjunct to 6-MP for refractory IBD (45). Cyclosporine is a highly lipid-soluble neutral cyclic polypeptide consisting of 11 amino acids. Cyclosporine affects the induction and amplification of the immune response by inhibiting the T-cell production of cytokines including IL-2. These actions result in the inhibition of helper T-cell functions such as recruitment of effector cells and amplification of T-cell-dependent immunological events. In addition to its direct inhibition of T-cell proliferation, cyclosporine also indirectly inhibits B-cell activating factors and interferong by T-helper cells. The functions of other leukocytes, including granulocytes, monocytes, and macrophages, are relatively spared.

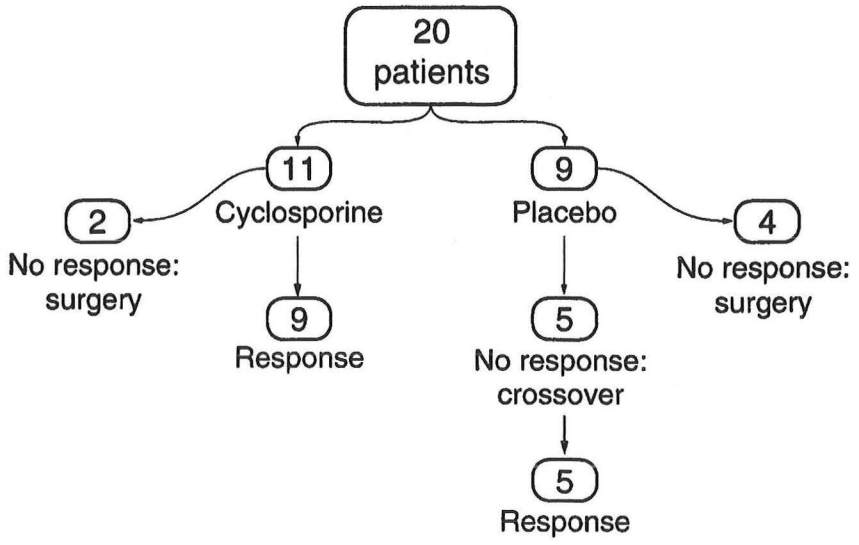



Figure 15. Intravenous cyclosporine (4 mg/kg/day) in fulminant steroid-refractory ulcerative colitis. This randomized, double-blind study showed cyclosporine to be rapidly effective in the majority of patients (reference 46).

*Results in severe ulcerative colitis.* Over the past decade, uncontrolled studies reported a high rate of response to i.v. cyclosporine in patients with severe ulcerative colitis who had failed high-dose i.v. steroids and who were otherwise candidates for colectomy (45). In those patients who responded, the onset of action was rapid, with improvement occurring within 1-2 weeks.

This uncontrolled experience was confirmed by a controlled trial published in 1994 (46). In this trial, 20 patients with severe ulcerative colitis unresponsive to i.v steroids were randomized to receive cyclosporine 4 mg/kg/day by continuous i.v. infusion or placebo for up to 14 days (Figure 15). After 14 days, 9 of 11 (82%) of patients receiving cyclosporine had improved compared to 0 of 9 patients receiving placebo. The mean time to improvement was 7 days. Five of the patients receiving placebo crossed over after failing the study and all responded to i.v. cyclosporine. Despite the initial high response rate, most of the responders discharged on oral cyclosporine (doses up to 8 mg/kg/day) had relapsed by 6 months. Subsequent experience suggests that about half to two-thirds of patients with severe/fulminant ulcerative colitis will respond to i.v. cyclosporine but that most patients relapse as cyclosporine is tapered.

There has been one study evaluating Cyclosporine enemas in the treatment of active left-sided colitis that showed no benefit (47).

*Results in Crohn's disease.* There have been four placebo controlled studies of oral Cyclosporine in Crohn's disease. Three studies using 5 mg/kg/day were unequivocally negative (48-50). This is in contrast to rheumatoid arthritis and psoriasis where low doses of cyclosporine are effective. One study using 7.5 mg/kg/day showed modest efficacy (51). Uncontrolled studies suggest a high initial response to i.v. (4 mg/kg/day) cyclosporine in Crohn's disease but the frequency of sustained remission has been quite low.

The major issue that prevents long-term use of cyclosporine at doses > 5 mg/kg/day is the potential for permanent renal damage. A recent retrospective analysis with renal biopsy data from 192 patients with autoimmune diseases without associated renal insufficiency treated with oral Cyclosporine A (mean dose 7.1 mg/kg/day) showed that 21% had histologic evidence of cyclosporine-induced nephropathy (52). It was recommended that patients receiving cyclosporine for autoimmune diseases should never be treated with >5 mg/kg/day and that the dose should be adjusted downward whenever the baseline serum creatinine increased by >30%.

Thus, relatively high and potentially toxic doses of cyclosporine are required in IBD. These findings necessarily direct the use of cyclosporine in IBD away from long-term low-dose therapy (which is ineffective) and long-term high-dose therapy (which is not safe). In severe ulcerative colitis, acute i.v. cyclosporine appears to be useful as rescue or temporizing therapy to allow nutritional and psychological preparation for surgery. Uncontrolled data suggest that acute i.v. cyclosporine is also useful as temporizing therapy in severe steroid-refractory Crohn's disease while awaiting safer more effective immunosuppressants to take effect.

***Methotrexate*** — Methotrexate is an inhibitor of dihydrofolate reductase, an enzyme important in the synthesis of DNA. Despite decades of use in inflammatory diseases, the molecular mechanisms by which methotrexate suppresses inflammation is uncertain.

A recent double-blind, placebo-controlled trial showed that i.m. methotrexate (25 mg/week) was more effective than placebo in improving symptoms and reducing requirements for prednisone in patients with chroni-

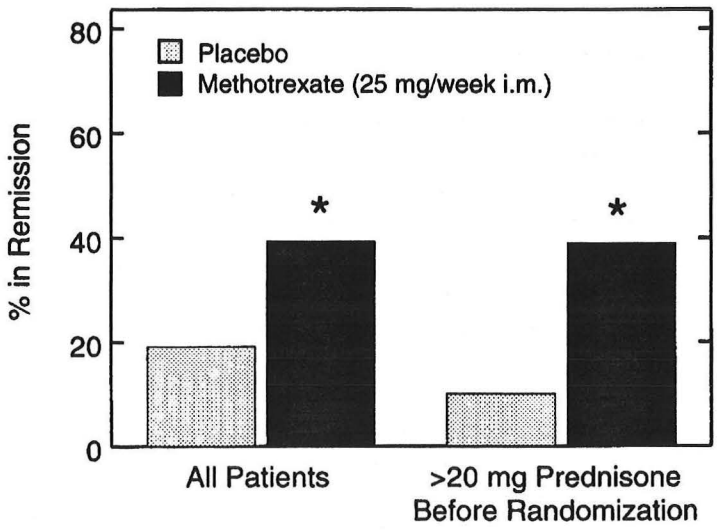



Figure 16. Methotrexate for chronically active steroid-dependent Crohn's disease. Methotrexate was more effective than placebo in improving symptoms and reducing steroid requirements (reference 48)

cally active Crohn's disease (Figure 16)(48). This trial enrolled 141 patients who had been receiving >12.5 mg/day prednisone (mean 20 mg/day), had failed at least one previous attempt at withdrawing from this drug, and had continued to exhibit active disease. The daily prednisone dose was maintained at 20 mg/day during the first 2 weeks of the study, than lowered by 2.5 mg/day each week if patients were stable or showing improvement. Response was defined as clinical remission (normalization of the Crohn's activity index) plus successful discontinuation of prednisone at week 16. The response rate was significantly higher in the methotrexate-treated group than in the placebo group (39% vs. 19%). Among patients who had required more than 20 mg/day of prednisone before study entry, 39% of the methotrexate-treated group responded vs. 10% of the placebo group. Overall, 17% of patients in the methotrexate group (compared to 2% in the placebo group) withdrew because of adverse events — primarily asymptomatic elevations of serum AST and GI intolerance. As with 6-mercaptopurine, onset of response is delayed with methotrexate therapy.

A randomized trial to evaluate long-term methotrexate as maintenance therapy for Crohn's disease is currently underway. Methotrexate may become an alternative to 6-MP as a steroid sparing agent in the management of Crohn's disease.

***Modulation of Specific Cytokines*** — Cytokines are intercellular peptide messengers that facilitate interaction among various immune effector cells. These peptides collectively regulate a wide variety of processes that are central to the pathophysiology of IBD. It seems unlikely that altered expression of any single cytokine can be implicated as a primary initiating factor in the pathogenesis of IBD; nevertheless, it is apparent that several may play important roles in the amplification and persistence of inflammation and may be directly involved in many of the clinical manifestations of IBD.

Cytokines thought to be important in the pathogenesis of IBD include IL-1, -2, -4, -6, -8, -10, IFNγ and TNFα (40). Several of these have predominantly proinflammatory effects and their expression and secretion by mononuclear cells in inflamed intestine is generally increased (IL-1, -6, -8, and TNFα). Others, such as IL-10, appear to function predominantly as inhibitors of the immune system. There have been no controlled studies relating to the modulation of specific cytokines in IBD. The limited uncontrolled experience is briefly summarized below.

*TNF neutralization.* The availability of a mouse-human chimeric anti-TNFα antibody (53) has made it possible to investigate the role of this cytokine in the pathogenesis of IBD. Although a controlled study has yet to be performed, a recent open-label study showed that a single infusion of an anti-TNF monoclonal antibody resulted in remarkable clinical improvement in 8 of 10 patients with active steroid-resistant Crohn's disease (54). The mean duration of response after a single infusion was 4 months and was accompanied by healing of endoscopic ulcerations and reductions in C-reactive protein and, to a lesser extent, ESR.

IL-10 administration. Based on the ability of IL-10 to down-regulate production of the proinflammatory cytokines IL-1, -6, -8, and TNFα, and the observation that inactivation of the IL-10 gene leads to intestinal inflammation in mice, topical IL-10 enema treatment was evaluated in 3 patients with steroid-refractory left-sided ulcerative colitis (55). IL-10 enema administration down-regulated the enhanced expression and secretion of the proinflammatory cytokines IL-1 and TNFα in rectal biopsies and apparently resulted in clinical and endoscopic improvement.

Humanized rodent antibodies directed against T-cell subsets, adhesion molecules and proinflammatory cytokines have shown promise in animal models and are currently being evaluated for efficacy in human IBD.

## *Enteral and Parenteral Nutrition*

***Adjunctive nutritional support*** — Malnutrition is common in IBD even in patients with relatively quiescent disease. When severe anorexia, nausea, or vomiting preclude adequate oral intake, enteral or parenteral nutrition must be considered (56-58). Enteral feeding is the preferred

method of nutrition if the GI tract is able to absorb and utilize nutrients without aggravating symptoms such as abdominal pain and diarrhea. If this is not the case, parenteral feeding is the only alternative. The most common indications for nutritional support as adjunctive therapy include growth retardation, short bowel syndrome, perioperative support of the severely malnourished patient and nutritional support during severe exacerbations of IBD accompanied by ileus (Table IX).

Table IX. Enteral or parenteral nutrition is used as adjuntive therapy in malnourished IBD patients who cannot eat a regular diet. Enteral and parenteral nutrition, along with bowel rest, may be effective primary therapy in some patients with Crohn's disease. Neither nutritional therapy nor bowel rest is useful as primary therapy for ulcerative colitis.

**Adjunctive for malnutrition**

- Short bowel syndrome
- Growth failure
- Perioperative
- Bowel obstruction
- Ileus

**Primary therapy**

- With bowel rest in Crohn's
- No role in UC

***Primary nutritional therapy*** — In addition to its use as adjunctive therapy in patients unable to tolerate a regular diet, a second — and more controversial — issue relates to the use of nutritional support as primary therapy for IBD. Although there are no controlled data, it would appear that about half of patients with Crohn's disease refractory to standard medical therapy will improve when placed on bowel rest/TPN. Patients with fistulas may also benefit from bowel rest/TPN. In contrast to ulcerative colitis, Crohn's disease is known to improve with bowel rest so that the precise contributions of nutritional therapy and bowel rest to any outcome are frequently difficult to sort out.

Several studies have compared elemental diets to corticosteroids as primary therapy for mild to moderately active Crohn's disease. Some of these conclude that elemental diets are as effective as corticosteroids in inducing remission; however, taken together, these studies suggest that elemental diets are significantly inferior to corticosteroids (59), especially when the data are analyzed on an intention-to-treat basis (many patients cannot tolerate elemental formulations).

In ulcerative colitis, neither bowel rest nor specific nutritional therapy are beneficial as primary therapy, in terms of achieving remission or any other clinical outcome. Nutritional support should be used only as an adjunct in those who are malnourished and cannot tolerate a regular diet due to exacerbation of symptoms.

Numerous formulations are available for enteral delivery. Elemental formulations contain amino acids, glucose, essential fatty acids, vitamins, minerals and trace elements — all of which are absorbed in the first couple feet of small bowel. However, elemental formulations are hyperosmotic and are usually administered by tube due to their repulsive taste. Semi-elemental formulations contain peptides, oligosaccharides and medium chain triglycerides whereas polymeric formulation contain milk or non-milk based proteins, starch hydrolysates and frequently long-chain triglycerides. There is no compelling evidence that the type of enteral formulation greatly influences outcome although it would make sense to use a lactose-free product in patients with small bowel disease.

### *Antibiotics*

Considerable clinical and experimental evidence demonstrates an integral role of ubiquitous luminal bacteria in the pathogenesis of IBD and associated systemic complications. Controlled data are available only for metronidazole, which is effective (in doses of 10 mg/kg/day) as primary therapy for colonic or ileocolonic Crohn's disease (60, 61). Metronidazole (in doses of 20 mg/kg/day) has well-established efficacy in perianal disease associated with Crohn's disease (62, 63). Uncontrolled experience raises the possibility that ciprofloxicin may be useful in Crohn's ileitis (64).

***Nicotine***

As noted above, the risk of developing ulcerative colitis is higher among nonsmokers and former smokers than among smokers. The hypothesis was therefore tested that nicotine may be useful in the management of ulcerative colitis. In a randomized, placebo-controlled study transdermal nicotine modestly improved symptoms and histology in patients with active ulcerative colitis (65). More recently, the same group showed that transdermal nicotine was no better than placebo in maintaining remission of ulcerative colitis (66).

## Cancer Surveillance

Inflammatory bowel disease predisposes to the development of carcinoma. In ulcerative colitis, patients with extensive colitis (extending proximal to the splenic flexure) for more than 10 years are at greatest risk (67, 68). Estimates of the cancer risk in ulcerative colitis vary widely. Earlier reports based on retrospective review of patients seen at major referral centers clearly exaggerated the risk of malignancy. More recent population based studies indicate that the risk is considerably less (~0.5% per year after the first decade of colitis), but is still greatly increased relative to age- and sex-matched controls (Figure 17).

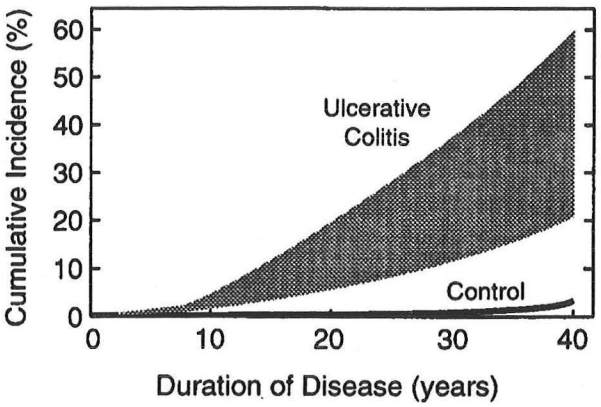



Figure 17. Cancer incidence in ulcerative colitis. Estimates of cancer risk vary widely but the lowest ranges are most accurate and indicate an annual concer risk of ~0.5% per year after the first decade of colitis (reference 5)

One option to minimize the risk that patients with ulcerative colitis will die from colorectal cancer is to perform prophylactic colectomy 10 years after the initial attack (when the increased risk begins). Ileoanal anastomosis allows the patient to avoid an ostomy bag or appliance and is currently the procedure most commonly chosen by ulcerative colitis patients, especially those under 50 years of age in whom the outcomes are better (69). This option reduces the risk of colon cancer to essentially zero. The ileal pouch-anal anastomosis, however, is a technically challenging, two-stage procedure with a technical failure rate of ~6% and chronic pouchitis in 5-10%. Patients average 6-7 bowel movements during the day and 1-2 at night (69).

Most patients, especially those who are relatively asymptomatic, prefer a less radical approach — that of colonoscopic surveillance — which has become the standard of care for reducing the risk of ulcerative colitis-associated colorectal cancer mortality. The rationale for colonoscopic surveillance is based on the finding that colon cancer in ulcerative colitis can be predicted by the finding of premalignant dysplastic changes at a distance from the cancer in up to 88% of patients (70). If cancer in ulcerative colitis evolves through a premalignant phase of dysplasia that can be detected on biopsy, colonoscopic surveillance should be able to identify those patients at particularly high risk of colorectal cancer. A secondary goal of surveillance, in the event that ulcerative colitis-associated colorectal cancer is not always preceded by obvious dysplasia, would be to diagnose cancer at an early, asymptomatic stage thereby reducing mortality.

Dysplasia is arbitrarily divided into low-grade and high-grade. When high-grade dysplasia is found on colonoscopic surveillance biopsies, as many as 30%-50% will be found to have clinically unsuspected carcinoma in the resected specimen, depending on the period of time since the preceding colonoscopy (67). Definite high-grade dysplasia is universally accepted as an indication for immediate colectomy. The finding of low-grade dysplasia is more problematic. Low-grade dysplasia can be difficult to differentiate from the reactive changes associated with chronic

inflammation. Nevertheless, when low-grade dysplasia is found on colonoscopic biopsies, roughly 10% of those undergoing colectomy will be found to have clinically unsuspected cancer in the specimen. The natural history of low-grade dysplasia is uncertain (67, 70) although some reports suggest that low-grade dysplasia will progress to high-grade dysplasia or cancer within 3-5 years in the majority of cases (71) . These data suggest that definite low-grade dysplasia should be an indication for colectomy in most patients with ulcerative colitis.

Although colonoscopic surveillance beginning 8-10 years after the onset of extensive ulcerative colitis makes a great deal of sense and is the standard of care in most countries, its efficacy in reducing ulcerative colitis-associated colorectal cancer has never been examined in a controlled trial. The cost-effectiveness and true benefit to patients therefore remain unknown and sources of debate (68, 72-74). Clearly, patients have developed latestage colorectal cancer while enrolled in surveillance programs. In many cases, these patients presented with symptomatic cancer after being lost to follow-up for a period of time or after not undergoing colectomy despite the finding of definite dysplasia. In addition, dysplasia develops as a patchy process, and a key technical point — frequently not appreciated early on — is that approximately 30 biopsies must be taken throughout the colon to achieve a 90% confidence of detecting dysplasia (75). Finally, colorectal cancer will simply not be preceded by dysplasia in ~10-25% of patients with ulcerative colitis (70, 76).

Thus, in contrast to prophylactic colectomy, colonoscopic surveillance does not totally eliminate the risk of colorectal cancer in ulcerative colitis. Nevertheless, it is extremely uncommon for a patient to progress to a late-stage incurable colorectal cancer while participating in a surveillance regimen as currently recommended. Current recommendations for surveillance in patients with extensive ulcerative colitis include colonoscopy (with ~30 biopsies) every 1-2 years starting between 8-10 years after disease onset (70, 77, 78). Such a regimen is costly, labor intensive and inconvenient for the patient. It would appear that somewhere between 200-300 colonoscopies are performed for every patient who presumably benefits (undergoes colectomy for severe dysplasia or early-stage cancer).

Patients with left-sided ulcerative colitis appear to have an intermediate risk of colorectal cancer (less than with extensive disease but more than in the normal population) that begins to rise after ~20 years of disease (rather than after 10 years as in the extensive colitis group). Since the cancer risk is less and tends to develop later in the course of the disease, surveillance is generally initiated after ~15-20 years of disease.

Patients with long-standing extensive Crohn's colitis have an increased risk for developing colorectal carcinoma although the magnitude of this risk is difficult to ascertain. Colonoscopic surveillance in patients with Crohn's colitis is technically difficult and cancers that develop in the setting of Crohn's colitis are much less likely to be preceded by dysplasia at a distance. For these reasons, colonoscopic surveillance is generally not recommended for Crohn's colitis.

As in sporadic colon cancer arising from adenomatous polyps, a number of genetic abnormalities have been described in ulcerative colitis-associated colon cancer (Figure 18). During the progression from normal epithelium through low-grade and high-grade dysplasia to cancer

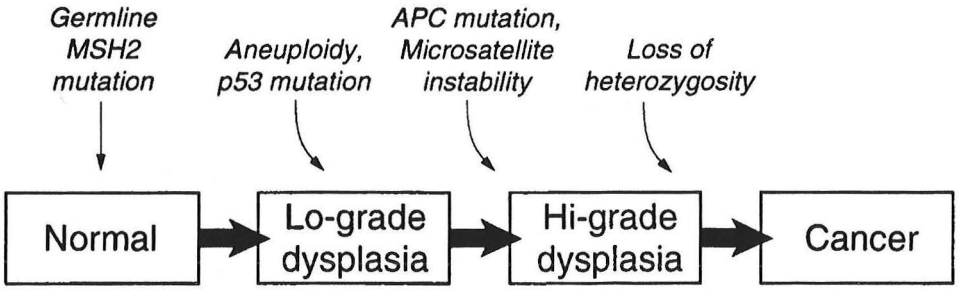



Figure 18. Model of development of neoplasia in chronic ulcerative colitis (references 70, 71)

there is continued accrual of genetic alterations including mutations of the *p53*, K-*ras* and APC genes as well as microsatellite instability and loss of heterozygosity at many loci (79). In some studies, DNA aneuploidy and *p53* mutations seemed to be early genetic events (80). In another study, ulcerative colitis patients with a germline polymorphism/mutation in the DNA mismatch repair gene *MSH2* appeared to be three times more likely to develop colorectal neoplasia than those who did not carry it (81). Although the clinical significance of the molecular genetic information is not yet evident, these abnormalities may eventually be useful as more accurate indicators of the propensity to develop malignancy.

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