ADVANCES IN THERAPY OF INFLAMMATORY BOWEL DISEASE

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"Any student of ulcerative colitis must view with scepticism the use of a treatment based upon personal impressions, for the history of the disease includes a large variety of treatments which in their turn were introduced with enthusiasm on the strength of a few favourable responses and then slowly abandoned when they were found to be ineffective."

- S.C. Truelove, 1958.

INTRODUCTION

In 1875, Wilkes and Moxon first described the chronic, idiopathic inflammatory disease known as ulcerative colitis (1). A somewhat similar inflammatory disease was defined as regional enteritis in 1932 by Crohn, Ginzburg and Oppenheimer (2); this malady, now known to affect any part of the alimentary canal, is commonly referred to as Crohn's disease. The etiologies of these disorders, which may represent an entire group of diseases, is still unknown. Because the causes of ulcerative colitis and Crohn's disease are unclear, it is no surprise that there is currently no discussion of cures; fortunately, there are a growing number of drugs that can alleviate acute exacerbations or diminish the frequency of recurrent episodes (3).

The cornerstones of therapy for inflammatory bowel disease for a number of years have been sulfasalazine and corticosteroids. Both of these drugs represented major advances in treatment; however, many patients either cannot take these drugs due to intolerance or develop severe side effects from long term use that may become as great a problem as the disease itself. Some of the current advances in therapy are based on refinements of these drugs. Other major advances in therapy are the use of immunosuppressive agents, such as azathioprine, and the antibiotic, metronidazole. In addition, a large group of agents which have a variety of actions, from antituberculous drugs to sucralfate, show at least some suggestion of promise in preliminary trials. Over the next few years, the physician will have a growing and perhaps bewildering array of therapeutic choices to offer patients with inflammatory bowel disease. Safe and effective therapy will require a thorough understanding of the disease entities themselves, the individual patient, and the risks, advantages and limitations of the drugs available.

PROVEN AND POTENTIAL THERAPEUTIC AGENTS

Sulfasalazine and Related Drugs
Prednisone and Other Steroid Drugs
Immunosuppressive Agents
Metronidazole

Anti-Tuberculous Drugs
Chloroquine
Clonidine
Fish Oil
Immune Adjuvants
Methotrexate
Oxygen-Derived Free Radical Scavengers
Sodium Cromoglycate
Sucralfate

MAJOR FEATURES OF ULCERATIVE COLITIS AND CROHN'S DISEASE

Clinical features. The patient with ulcerative colitis most commonly presents with chronic, watery diarrhea, frequently containing blood, lower abdominal cramping pain,

and perhaps a low grade, intermittent fever. The diagnosis is frequently rapidly made by combining the clinical picture with sigmoidoscopy and biopsy, because 90 - 95% of patients will have an abnormal rectosigmoid mucosa (4). The mucosa becomes less translucent so blood vessels are not as well seen, and has a granular appearance. The mucosa is friable and in more severe cases, ulceration is present. Over time, pseudopolyps made of undermined mucosa and/or granulation tissue may appear. Extraintestinal manifestations of ulcerative colitis may include pyodermagangrenosum, erythema nodosum, arthritis, uveitis, sclerosing cholangitis and aphthous stomatitis. About 5% of patients will have a solitary episode of ulcerative colitis when followed for up to 15 years, about 5-15% will have unremitting disease, and the remaining majority will have intermittent symptoms.

The typical patient with Crohn's disease also presents with diarrhea and abdominal pain, and more than 50% of patients have fever (5-7). Many patients have a tender right lower quadrant mass, reflecting an inflamed ileum. Many patients will have atypical clinical pictures, depending on the severity and location of disease. At least half of patients with Crohn's disease will develop perianal or perirectal disease, and this may be the presenting problem. Extraintestinal manifestations include arthritis, iritis, episcleritis, erythema nodosum and pyoderma gangrenosum, aphthous ulcerations of the mucosa, sclerosing cholangitis and nephrolithiasis. About 20% of patients will have involvement of the colon only; this is the group of patients that may be difficult to distinguish from those with ulcerative colitis. Features of Crohn's disease in the colon that can differentiate it from ulcerative colitis include skip lesions, sparing of the rectosigmoid, stricture formation, and findings of granulomas on biopsy. After careful evaluation, about 10% of patients with inflammatory bowel disease still cannot be diagnosed definitively as having ulcerative colitis versus Crohn's disease. About 10-20% of patients with Crohn's disease will remain asymptomatic for up to 20 years after one or two attacks (6,8), but the majority of patients will have recurring disease.

Etiologic theories. Several theories have been postulated to explain the causes of ulcerative colitis and Crohn's disease. The obvious inflammatory features of the diseases have caused many investigators to pursue infectious agents, but this has been unsuccessful to date. There appear to be some genetic features to disease occurrence; both ulcerative colitis and Crohn's disease have a higher incidence in Jews than non-Jews, and the risk of disease increases if a family member has the disease. Although the role of psychological factors is important in patient management, current evidence does not support any causative role for stress or personality type. Currently, immunologic factors are receiving a lot of attention.

MEDICAL THERAPY

Management of patients with inflammatory bowel disease is highly variable. Clearly, the basic tendencies of ulcerative colitis and Crohn's disease to remit and recur makes it difficult to evaluate therapy unless trials are carried out for long periods of time, involve sufficient numbers of patients, and in most cases, include an appropriate control group. Nutritional therapy, surgical treatment and general supportive care all play major parts in the treatment of inflammatory bowel disease, and drug treatment is only one component of therapy. Consideration of drug treatment begins with one of the oldest drugs in the modern medical era.

Sulfasalazine. Sulfasalazine was developed in the 1930's by Dr. Nana Svartz, a rheumatologist, to treat rheumatoid arthritis. The benefit of aspirin in this condition was well known, and because a current theory held that rheumatoid arthritis was caused by a bacterium, the sulfonamide antibiotic sulfapyridine was combined with the aspirin analog 5-aminosalicylate (5-ASA) to form sulfasalazine. It was only a short step to treat patients with inflammatory bowel disease with sulfasalazine, since Crohn's disease was also an inflammatory disorder of possible bacterial etiology.

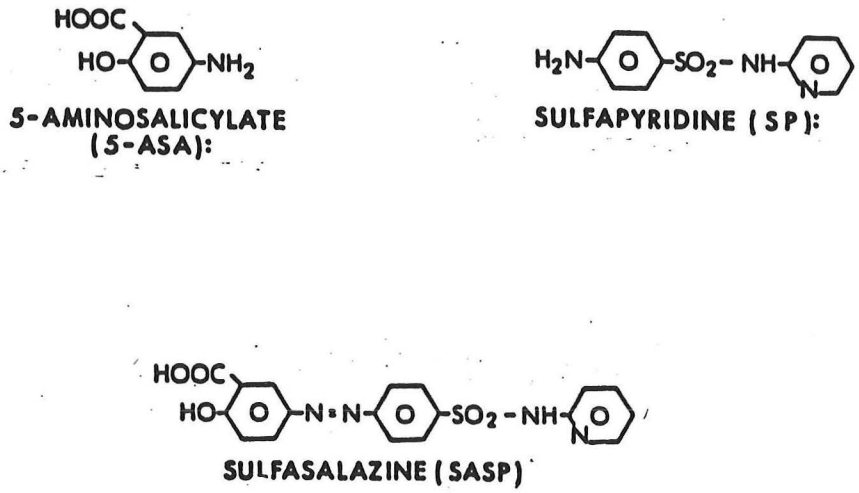

Fig. 1. The structure of sulfasalazine.

Patients responded very well to sulfasalazine which became standard therapy for treatment of Crohn's disease and ulcerative colitis based on a number of clinical trials (9-22). Data from one of these trials (20) are shown in Fig. 2.

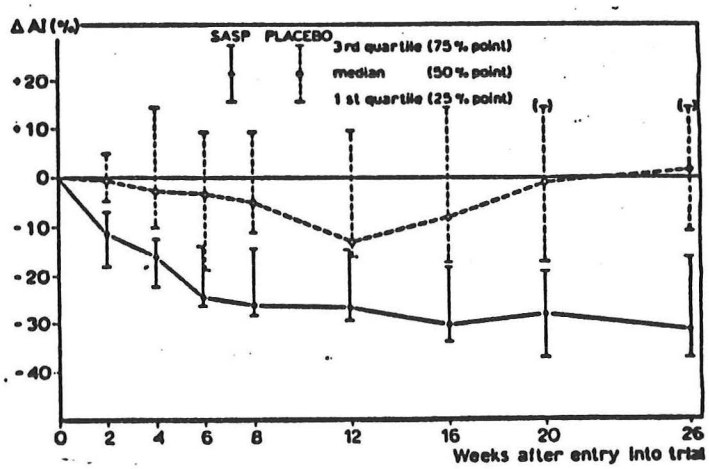

Fig. 2. Percent change in the activity index (AI) of patients treated with either sulfasalazine or placebo for 26 weeks (van Hees et al., Ref. 22).

In this Scandinavian study, patients with active Crohn's disease were randomized into two treatment groups with either 6 g/day of sulfasalazine in 4 doses or an equal number of placebo tablets. At the time intervals indicated in Fig. 2, the activity of disease was assessed. The activity index included variables which could be assessed objectively: serum albumin, sedimentation rate, body weight related to height, presence of an abdominal mass, sex, temperature, stool consistency, bowel resection and extraintestinal lesions related to Crohn's disease. Overall, although disease activity fluctuated during the trial, patients treated with placebo did not improve, while patients treated with sulfasalazine showed a steady decrease in disease activity. In this relatively small study, the location of Crohn's disease in the gastrointestinal tract did not influence the objective response to treatment.

In the larger and very well known National Cooperative Crohn's Disease Study (17), performed in the United States in the 1970's, assessment of disease activity included some subjective variables, such as abdominal pain and the patient's sense of well-being. As shown in Fig. 3, the group of patients treated with sulfasalazine for 17 weeks improved significantly compared to patients receiving placebo.

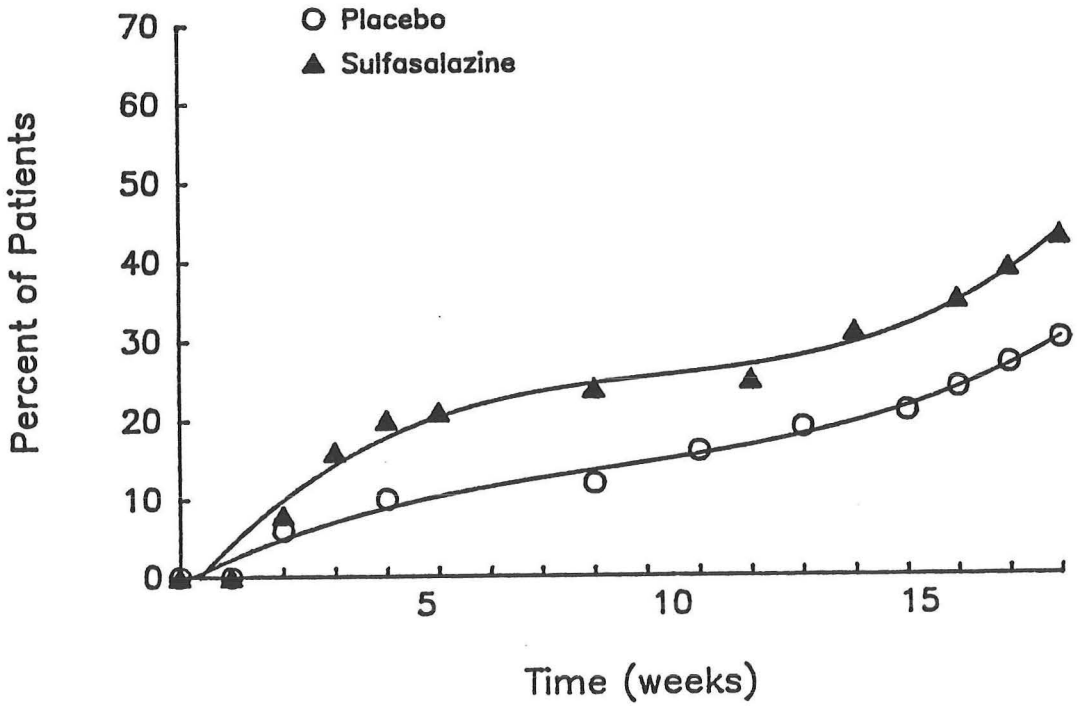

Fig. 3. The cumulative percent of patients with Crohn's disease in remission week-by-week during 17 weeks of therapy with either sulfasalazine or placebo (Redrawn from Summers et al., Ref. 17).

In contrast to the Scandinavian study discussed earlier, patients with disease limited to the small bowel did not show any significant improvement during treatment with sulfasalazine.

Sulfasalazine has also been used extensively in ulcerative colitis. The first controlled clinical trials establishing the usefulness of sulfasalazine in mild to moderate ulcerative colitis were performed in the early 1960's by Baron et al. and Dick et al. (9,11). In the study by Baron et al. (11), outpatients with active but mild ulcerative colitis were randomized to treatment with oral sulfasalazine 1 g QID for one week followed by 0.5 g QID for three weeks, an identical regimen of a drug called salicylazosulphadimidine, which proven to be without any efficacy and was dropped, or placebo. The patients' response was assessed using both symptoms and the sigmoidoscopic appearance of the rectum. As shown in Tables I and II, sulfasalazine produced a significant improvement in symptoms, with 35% of the 20 patients reporting a complete remission, compared to only 1 patient with a complete remission in the control group. Similarly, sigmoidoscopic appearance significantly improved in patients receiving sulfasalazine. Patients treated with sulfasalazine were more likely to experience side effects.

Table 1.

EFFECT OF SULFASALAZINE VERSUS PLACEBO ON ULCERATIVE COLITIS SYMPTOMS

	Complete Remission	Improvement	No Change
Sulfasalazine	35%	45%	20%
Placebo	5%	5%	65%

- Baron, 1962

Table 2.

EFFECT OF SULFASALAZINE VERSUS PLACEBO ON ULCERATIVE COLITIS SIGMOIDOSCOPIC APPEARANCE

	Complete Remission	Improvement	No Change
Sulfasalazine	45%	35%	20%
Placebo	5%	35%	60%

- Baron, 1962

For some patients with distal ulcerative colitis or ulcerative proctitis, sulfasalazine could be given as a suppository or enema with good therapeutic effect and minimal

side effects (23-26), even in some patients who were unable to tolerate oral sulfasalazine. The metabolism of sulfasalazine is as follows:

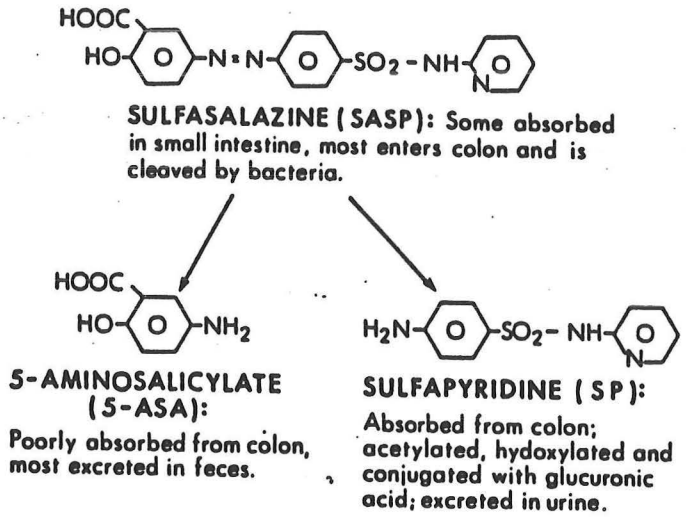

Fig. 4. The metabolism of sulfasalazine. (From Stenson, Ref. 27).

Twenty to thirty percent of orally administered sulfasalazine is absorbed in the small intestine, taken up into the liver and then excreted essentially unchanged into the bile, where it rejoins the 70 - 80% of unabsorbed sulfasalazine. In the colon, the azo bond joining sulfapyridine and 5-aminosalicylate (5-ASA) is cleaved by bacterial flora. 5-ASA is poorly absorbed and remains in the lumen and is eventually excreted in the stool. Sulfapyridine is efficiently absorbed and then acetylated, hydroxylated and conjugated with glucuronic acid in the liver. Acetylation varies greatly from one individual to another, and the degree of acetylation determines the serum levels of sulfapyridine. Toxicity but not hypersensitivity reactions correlate with the serum levels of sulfapyridine. Rectal administration of sulfasalazine results in similar metabolism; decreased toxicity results from decreased time for absorption of the cleaved sulfapyridine. Most patients with Crohn's disease and many patients with ulcerative colitis have proximal disease and cannot use rectal preparations of sulfasalazine. About a third of patients with inflammatory bowel disease cannot tolerate oral sulfasalazine (28-30).

In a classic study, Azad Khan et al. (31) demonstrated that the therapeutic effects of sulfasalazine were due to the aspirin moiety rather than the antibiotic moiety. In a double-blinded clinical trial, patients with proctoscopic evidence of distal ulcerative colitis were randomized to treatment with enemas containing either sulfasalazine, 5-ASA, or sulfapyridine. Patients receiving either sulfasalazine or 5-ASA improved significantly compared to those receiving sulfapyridine (Table 3), based on symptoms and sigmoidoscopic and histologic appearance on biopsy.

Table 3.

IMPROVEMENT AFTER TWO WEEKS OF THERAPY
(Percent of Patients)

Drug	Symptoms	Sigmoidoscopic Appearance	Histologic Appearance
Sulfasalazine	75	64	30
5-ASA	73	71	29
Sulfapyridine	38	37	5

-Azad Khan, 1977

When sulfapyridine or 5-ASA are given orally as individual agents, they are absorbed in the proximal small intestine and are present in subtherapeutic concentrations in the distal small intestine and colon (32). Thus sulfasalazine, the parent compound, probably serves simply to transport the active 5-ASA to the areas where it has its therapeutic effect. Much effort has been expended, with considerable success, to develop enemas and oral agents which exploit the therapeutic advantages of 5-ASA while avoiding the toxicity and hypersensitivity reactions to sulfapyridine. This class of drugs, one of which has been released in the United States, are reviewed next.

Topical 5-ASA and 4-ASA. 5-ASA is known in the United States as mesalamine and in Europe as mesalazine. The mechanism of action of 5-ASA probably involves inhibition of leukotriene concentrations in the bowel (33) rather than inhibition of prostaglandins (34). A number of investigators have reproduced the positive results of Azad Khan et al. for 5-ASA enemas (35-39); one such study is shown in Table 4.

Table 4.

5-ASA VERSUS HYDROCORTISONE ENEMAS:
IMPROVEMENT AFTER FIFTEEN DAYS OF THERAPY
(Percent of Patients)

Drug	Symptoms	Sigmoidoscopic Appearance	Histologic Appearance
5-ASA	93	93	77
Hydrocortisone	57	54	33

- Campieri, 1981

In this double-blind, controlled trial (40) in 86 patients with mild to moderate distal ulcerative colitis treated with 4 g 5-ASA enemas vs 100 mg hydrocortisone enemas, more than 90% of patients treated with 5-ASA had a clinical remission, significantly more than the 57% who improved on hydrocortisone.

The more stable 5-ASA isomer, 4-ASA, is just as effective for distal ulcerative colitis as 5-ASA, and is superior to placebo (40-43). Similarly, suppository forms of 5-ASA are effective for patients with ulcerative proctitis (44-46). The suppository form is generally given several times a day in doses ranging from 200 mg to 1 g. Not surprisingly, 5-ASA shares sulfasalazine's ability to maintain remission in patients with ulcerative colitis (47), and like sulfasalazine, withdrawal of 5-ASA therapy is likely to result in a recurrence of symptoms after a period of time (48). Fig. 5 demonstrates the increased duration of remission in patients treated with 5-ASA compared to placebo.

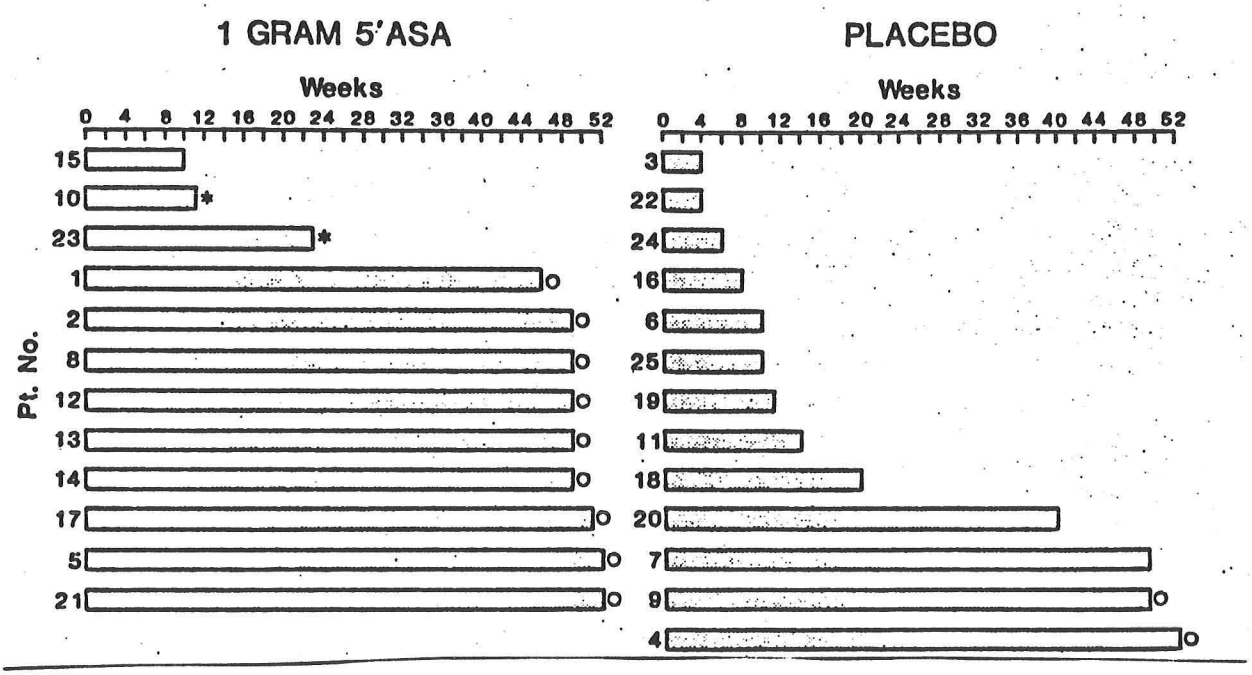

Fig. 5. Duration of remission in patients with distal ulcerative colitis randomized to 5-ASA versus placebo. Asterisks indicate patients who withdrew from the trial for non-drug related reasons while still in remission. Circles indicate patients who were still in remission at the end of the trial (From Biddle et al., Ref. 47).

Oral 5-ASA and its congeners. There are three main forms of 5-ASA currently being investigated for oral use. These are summarized in Table 5 (taken from Peppercorn, Ref. 3).

Table 5.

5-ASA Preparations

Generic Name	Proprietary Name	Form of Drug
Mesalamine	Asacol, Claversal, ROWASA	5-ASA with an enteric coating
Mesalamine	Pentasa	5-ASA in slow-release micro-spheres
Olsalazine	Dipentum	5-ASA linked to itself by an azo bond (requires bond bacterial cleavage)
Balsalazide	Colazide	5-ASA linked to an inert vehicle by an azo bond (requires bacterial cleavage).

Oral forms of 5-ASA potentially offer advantages to two groups of patients; 1. those with ulcerative colitis involving the proximal as well as distal large bowel, and the many patients with Crohn's disease who have small bowel or distal colonic involvement, and 2. those requiring a more convenient long term prophylactic therapy than the use of enemas. It appears that 80 - 90% of patients intolerant of sulfasalazine can take 5-ASA preparations orally (49), the remaining 10 - 20% have reactions similar to those they originally experienced with sulfasalazine, suggesting that 5-ASA itself may be responsible for at least some of the allergic reactions and intolerance previously blamed on sulfapyridine. It should be noted that 5-ASA has been reported to be associated with pancreatitis and perimyocarditis (50-52). Obviously, like any new agent, the safety of 5-ASA and congeners needs to assessed in a large number of patients over time.

Efficacy of these agents appears very promising. Coated 5-ASA (Asacol) has been shown to be effective therapy for mild to moderately active ulcerative colitis in a double-blind trial involving 88 patients (Table 6) (53).

Table 6.

CLINICAL RESPONSES TO ORAL 5-ASA THERAPY FOR ULCERATIVE COLITIS (Percent of Patients)

Clinical Response	Oral 5-ASA (g/day)		Placebo
	4.8	1.6	
Complete	24	9	5
Partial	50	18	13
None	26	73	82

- Schroeder, 1987

When two doses of oral 5-ASA were compared to placebo, the higher dose of 5-ASA (4.8 g/d) significantly improved complete and partial clinical response compared to the low dose of 5-ASA or placebo.

When coated 5-ASA (Mesasal) was compared to sulfasalazine in 220 patients (54), both drugs were equally efficacious but fewer adverse side effects in those treated with 5-ASA. At least two studies show that various forms of oral 5-ASA are equivalent to oral sulfasalazine in preventing recurrences of ulcerative colitis (55,56).

Table 7.

ORAL 5-ASA VERSUS SULFASALAZINE FOR 8 WEEKS FOR TREATMENT OF ACTIVE ULCERATIVE COLITIS (Percent of Patients)

	Clinical Remission	Adverse Events
5-ASA	74	14
Sulfasalazine	81	24

- Rachmilewitz, 1989

There are currently two published trials of oral 5-ASA in treatment of Crohn's disease (57,58). In an open trial (57), 18 patients who had failed other medical therapies were treated with of slow-release 5-ASA (Pentasa), 500 mg TID. All 18 patients had small bowel involvement and 10 had colonic involvement as well. The clinical course was improved in 72%, unchanged in 11% and worsened in 17%. The change in the Crohn's disease activity index over the course of the study is shown in Fig. 6.

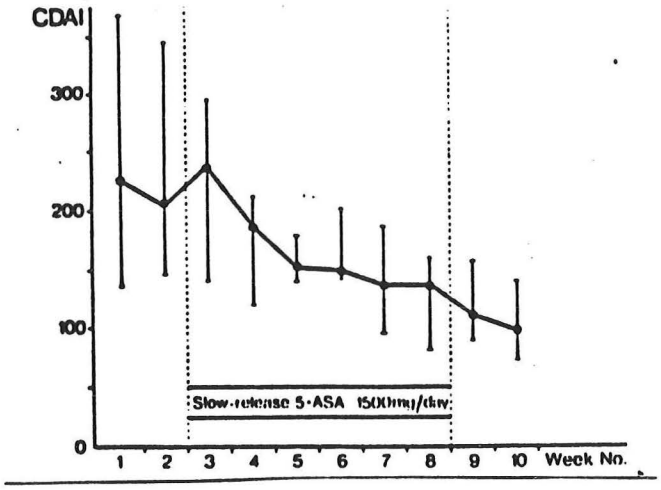

Fig. 6. Weekly Crohn's disease activity index scores (median and 25-75 percentiles) in 16 patients completing the study (from Rasmussen, Ref 57).

These encouraging findings were not confirmed in a larger, double-blind placebo-controlled trial by the same group expanded to other centers (58). This trial was restricted to patients with only small bowel involvement. There was a trend toward improvement in the patients treated with 5-ASA (40% improvement vs. 30% on placebo). Four patients on 5-ASA left the trial due to clinical deterioration while 10 of the placebo treated patients had to leave the trial. These results make it unclear at this point whether response might be better in only some subsets of patients with Crohn's disease, and also emphasizes the importance of a proper control group.

Corticosteroids. Recognizing the inflammatory natures of Crohn's disease and ulcerative colitis, corticosteroids were tried in these conditions soon after this family of drugs became available. Intravenous steroids are clearly life-saving in severe cases of both ulcerative colitis and Crohn's disease. In fact, after initial dramatic reports of the efficacy of parenteral steroids in severe cases (59), it became unethical to have controlled trials with placebo groups in these critically ill patients. Parenteral steroids, along with improvement in general intensive care and an appropriate surgical approach to selected cases, have decreased the mortality of the severe, acute forms of the diseases. Steroids, generally prednisone in current medical practice, are also extremely useful agents for outpatient treatment of acute flares of inflammatory bowel disease.

Kirsner and Palmer (60,61) in the United States and Truelove and Witts (62) in the United Kingdom first showed beneficial effects of oral ACTH and cortisone in ulcerative colitis. Shortly thereafter steroids given as enemas or suppositories became widely used for ulcerative proctitis and more distal ulcerative colitis based on a controlled trial by Truelove (63). Although the rectal administration of steroids decreased absorption and systemic side effects considerably, some significant absorption can still occur. Lee et al. (64) showed that rectal prednisolone, 0.36 ng/l, caused a significant increase in plasma concentrations of prednisolone (Fig. 7). Rectal administration resulted in 44% absorption when compared to an oral dose of 20 mg, (using areas under the curve).

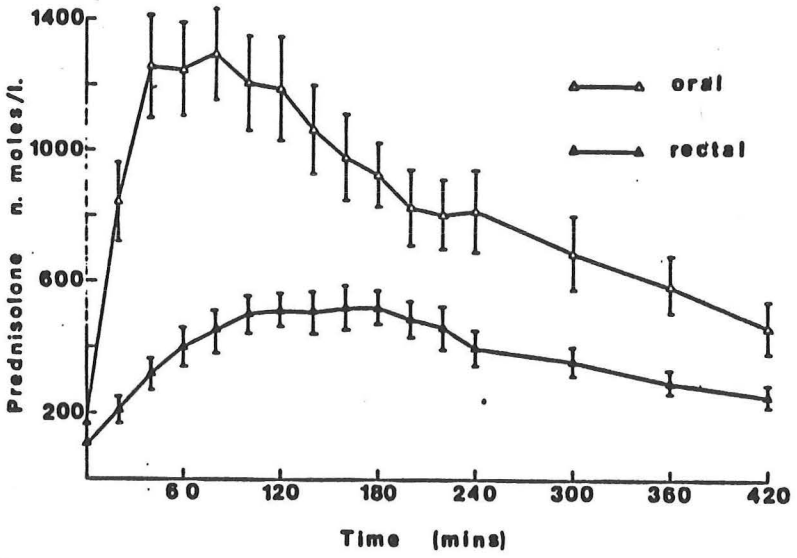

Fig. 7. Mean plasma concentration of prednisolone after enema and oral administration of drug (from Lee, et al., Ref. 64).

Patients with active Crohn's disease clearly respond to oral steroids as demonstrated in the National Cooperative Crohn's Disease Study. This was the first prospective, controlled trial of steroids for Crohn's disease. Results of 17 weeks therapy with prednisone are shown compared to the results with placebo and sulfasalazine shown earlier (Fig. 8). Prednisone appeared superior to sulfasalazine in inducing remission; in addition, it was found that prednisone was more effective in patients who had not been previously taking any medication for their Crohn's disease. When patients were treated with prednisone, sulfasalazine or placebo after remission or surgical extirpation of active Crohn's disease, neither prednisone nor sulfasalazine appeared to have any ability to prevent recurrence.

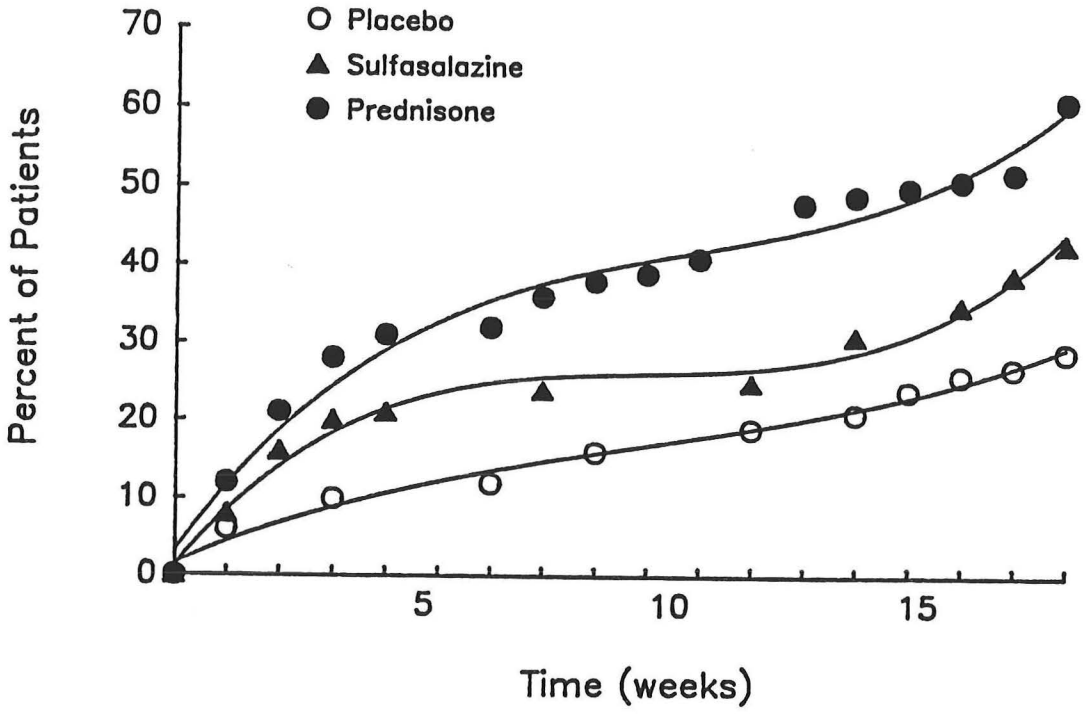

Fig. 8. The cumulative percent of patients with Crohn's disease in remission week-by-week during 17 weeks of therapy with prednisone, sulfasalazine or placebo (Summers et al., Ref. 17).

Unfortunately, prednisone caused evident side effects in more than 50% of patients treated with high doses for acute episodes and about one third of those taking smaller prophylactic doses. The most common side effects in patients treated with high dose prednisone compared to placebo are shown in Fig. 9 (p 15).

Since long-term corticosteroid therapy of both ulcerative colitis and Crohn's disease does not prevent recurrence and is associated with serious side effects, current interest in corticosteroid therapy is focused on the development of agents given rectally that cause little or no absorption and systemic side effects but that work well in the intestine. Most of these agents will be best for distal disease, so their uses in cases of small bowel Crohn's disease and Crohn's disease or ulcerative colitis involving the cecum will be more limited. Presently none of these agents have been released for general clinical use.

Tixocortol pivolate is a C-21 thioester derivative of cortisol with neither glucocorticoid or mineralocorticoid properties (66). Tixocortol is very rapidly transformed by red cells and the liver and has no systemic effects. When Levinson (67) compared tixocortol (250 mg/100 ml) to hydrocortisone (100 mg/100 ml) in patients with distal ulcerative colitis, both agents produced comparable improvement in rectal pain, diarrhea, and appetite (Table 8, p 15).

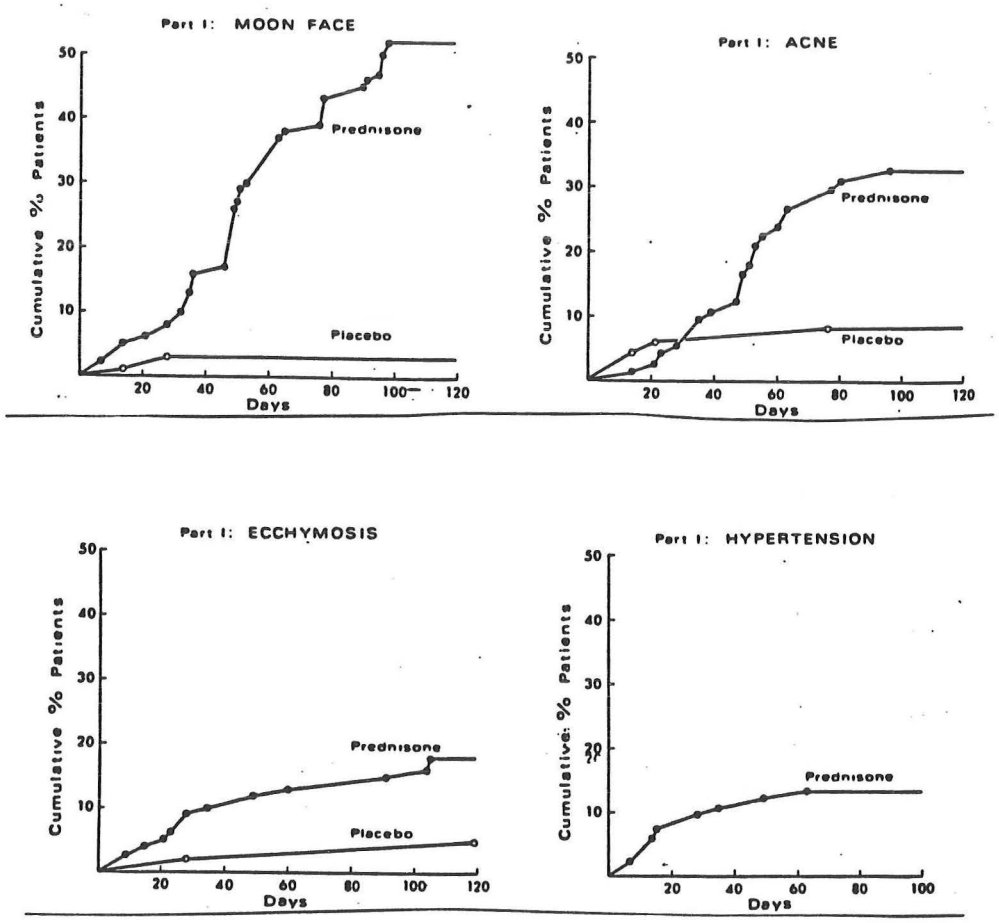

Fig. 9. Cumulative incidence of side effects in patients treated with high dose prednisone versus placebo (Taken from Singleton, Ref. 65).

Table 8.

COMPARISON OF TIXOCORTOL PIVOLATE AND HYDROCORTISONE ENEMAS FOR ULCERATIVE COLITIS

	Percent of Patients Improved
Tixocortol	50
Hydrocortisone	40

- Levinson, 1986

After 3 weeks of therapy, 50% of patients treated with tixocortol had improved compared to 40% of patients treated with hydrocortisone. No steroid-related side effects were noted with tixocortol (i.e. nausea, fluid retention). There are preliminary reports of similar results in another controlled trial (68) and an open trial of patients with refractory distal ulcerative colitis (69).

Beclomethasone dipropionate has also been shown to improve distal ulcerative colitis (70). Kumana et al. compared betamethasone and beclomethasone enemas in a small number of patients with acute exacerbations of ulcerative colitis; patients served as their own controls because they were treated with each of the drugs during two separate exacerbations. Betamethasone and beclomethasone produced similar clinical improvement, but when adrenocortical function was evaluated with an injection of synthetic corticotropin, only beclomethasone did not affect plasma cortisol response (Fig. 10).

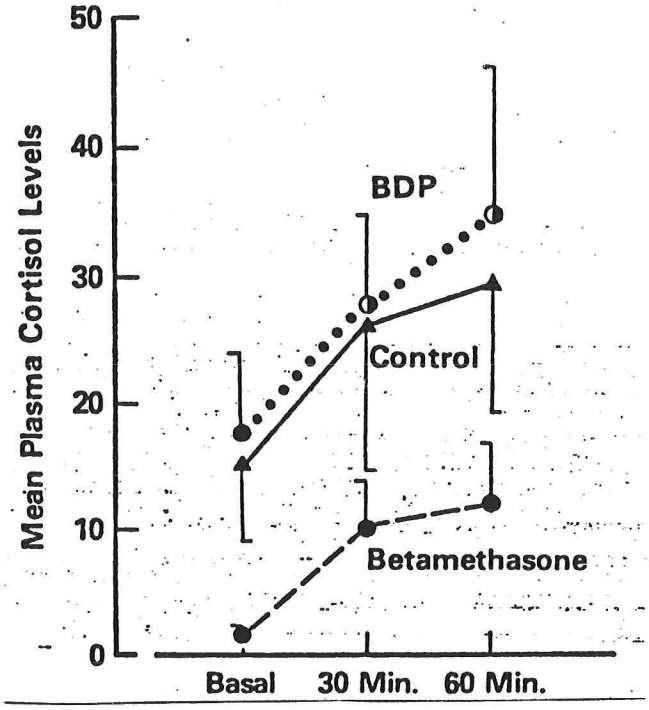

Fig. 10. Results of stimulation with 0.25 mg synthetic corticotropin on mean plasma cortisol concentrations. Control studies were performed prior to entry into the trial. Studies with beclomethasone (BDP) and betamethasone were performed after two weeks of therapy (Kumana, Ref. 70)

Budesonide, like beclomethasone, is a potent but rapidly metabolized corticosteroid with correspondingly low systemic effects. In a multicenter, double-blind randomized trial (71) of 64 patients with distal ulcerative colitis treated for four weeks with enemas of budesonide (2 mg/100 ml) versus prednisolone disodium phosphate (31.25 mg/100 ml), budesonide was superior to prednisolone in subjective symptoms as well as scores of sigmoidoscopic and histologic appearance (Fig. 11).

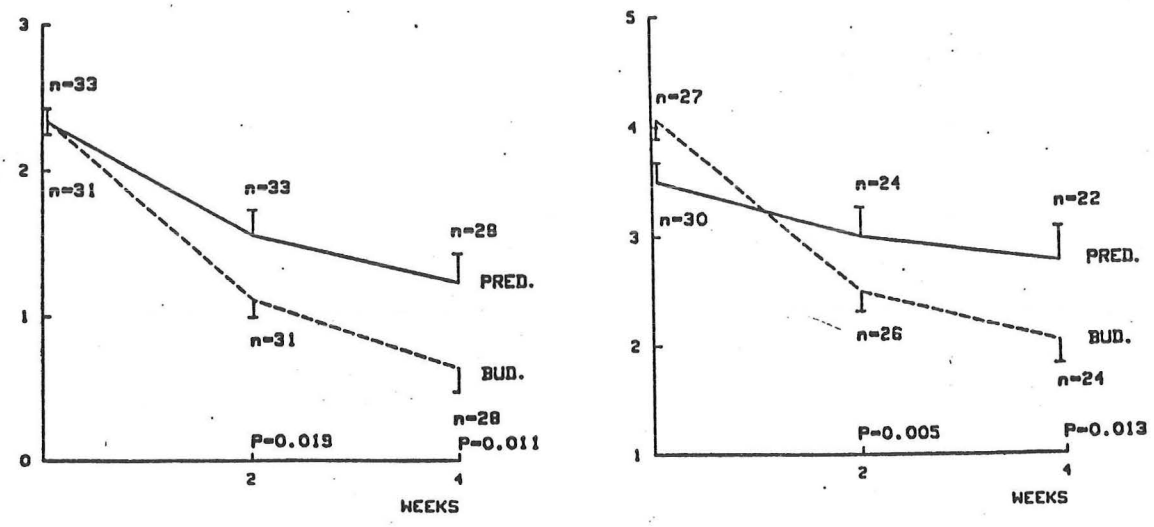

Fig. 11. Comparison of budesonide versus prednisolone enemas for four weeks for treatment of distal ulcerative colitis. Left panel shows change in rankings of sigmoidoscopic appearance and right panel shows change in rankings of histologic appearance (From Danielsson, Ref 71).

In addition, budesonide did not produce the decrease in endogenous concentrations of plasma cortisol seen after treatment with prednisolone (Table 9).

Table 9.

MEAN MORNING PLASMA CORTISOL CONCENTRATIONS (nmol/L) BEFORE AND DURING TREATMENT WITH BUDESONIDE OR PREDNISOLONE ENEMAS

	Before Treatment	At 2 Weeks	At 4 Weeks
Prednisolone	366	163	239
Budesonide	402	360	413
Significance	p=0.5	p=0.00008	p=0.00008

- Danielsson, 1987

Immunosuppressive Agents. Immunosuppressive agents have been in use for inflammatory bowel disease for some time. These agents have great theoretical appeal because host immunologic response is probably an important factor in the pathogenesis

of inflammatory bowel disease. The agents used for the longest period of time are azathioprine, and its metabolite, 6-mercaptopurine (6-MP). After a period of popularity in the late 1960's, azathioprine and 6-MP fell into some disfavor when placebo-controlled trials appeared to show little important benefit in patients with either Crohn's disease (72-75) or ulcerative colitis (76,77). In the National Cooperative Crohn's Disease Study (17), azathioprine was clearly not as effective as prednisone at inducing a remission (Fig 12), and in fact was not significantly better than placebo ($p = 0.17$). In fact, azathioprine was worse than placebo at preventing recurrence once remission had been achieved.

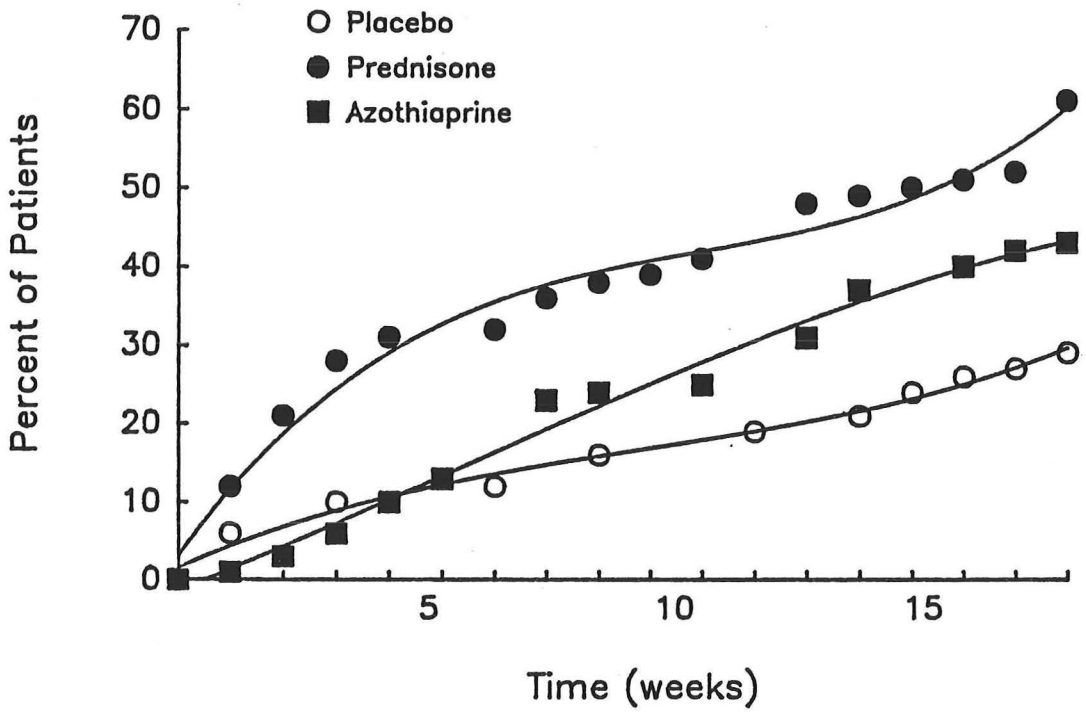

Fig. 12. The cumulative percent of patients with Crohn's disease in remission week-by-week during 17 weeks of therapy with either azathioprine, prednisone or placebo (Redrawn from Summers et al., Ref. 17).

However, in a study by Present et al.(78), when patients were carefully selected and treatment goals clearly defined for each patient, long-term use of 6-MP was clearly shown to be effective compared to placebo. The study was designed so than patients were randomly assigned to either 6-MP or placebo and then crossed over after a year of treatment. Almost half the patients did not cross over after a year, the majority of these because they were doing well on the first agent. Results were analyzed for both cross over and non-cross over groups and then the combined groups were analyzed (Table 10). One important observation made was that it took a fairly long time for many patients to show improvement; more than two months of treatment in 44% and more than four months of treatment in 19%. Another important observation was that 6-MP was significantly better than placebo in closing fistulas (31% vs. 6%, respectively).

Table 10.

PERCENT OF PATIENTS IMPROVED ON 6-MP VERSUS PLACEBO THERAPY

	6-MP	Placebo
Crossover Patients	67	8
Non-Crossover Patients	79	29
All Patients	71	13

- Present, 1980

The need for a long treatment period was also noted in 1985, in an open trial of azathioprine and 6-MP in 42 patients with severe Crohn's disease with colonic involvement (79). Significant improvement was seen (Fig. 13) but frequently required some months.

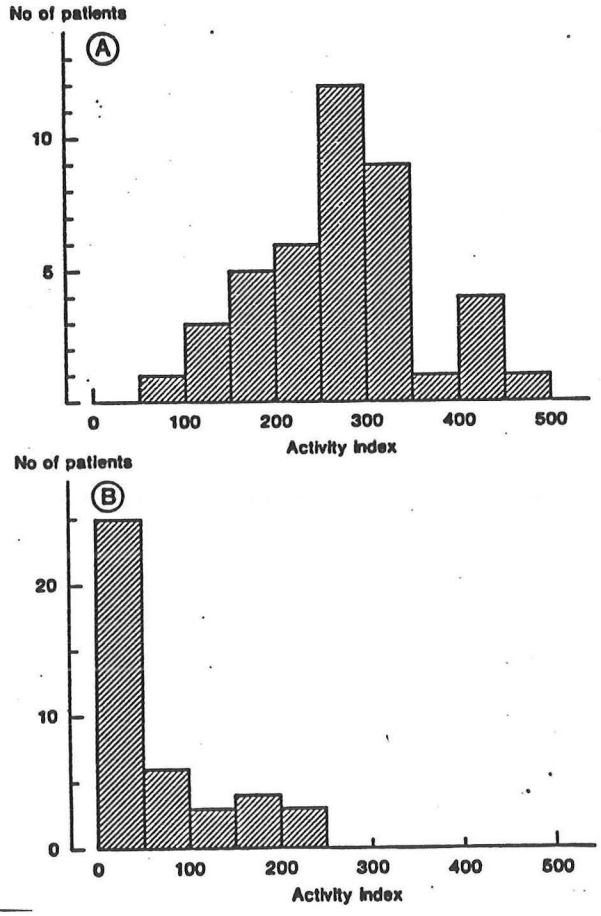

Fig. 13. Crohn's disease activity index in (A) patients at entry and (B) at follow-up study (Nyman, Ref 79).

The length of treatment in this study varied considerably, from 1 - 165 months, with a median treatment time of 34 months. This study, in contrast to the National Crohn's Disease Cooperative Trial, also emphasized that azathioprine and 6-MP helped prevent remission, as also reported by O'Donoghue et al. (80).

The toxicity of immunosuppressive agents may not be as great as originally feared. In the study discussed earlier (80), about 10% (7/68) of patients treated with 6-MP had significant adverse reactions, all of which were reversible on stopping the drug (bone marrow depression - 2, fever - 2, severe nausea - 1, pancreatitis - 1, and bilateral osteomyelitis of the hips - 1. When Present et al. reviewed toxicity in 396 patients with either Crohn's disease or ulcerative colitis for a mean period of 5 years (81), toxicity was relatively low, as summarized in the following table (Table 11).

Table 11.

COMPLICATIONS IN 396 PATIENTS WITH INFLAMMATORY BOWEL DISEASE TAKING 6-MP

Complication	Number (percent)
Infection	29 (7.3)
Pancreatitis	13 (3.3)
Bone Marrow Depression	8 (2.0)
Allergic Reactions	8 (2.0)
Drug Hepatitis	1 (0.3)

- Present, 1989

Cyclosporine is another immunosuppressive agent which has received some attention for the treatment of Crohn's disease. Several letters and abstracts reported that uncontrolled trials of cyclosporine suggested that the drug could be beneficial in both Crohn's disease and ulcerative colitis (81-85). To date there is a single published placebo-controlled, double-blind, randomized trial of cyclosporine therapy in active chronic Crohn's disease (86). The 71 patients entered into this trial were either resistant to or intolerant of corticosteroids. Patients were treated for three months; after this time, 59% of the patients treated with cyclosporine had improved compared to 32% of the placebo-treated patients ($p = 0.032$). This is demonstrated in Fig. 14.

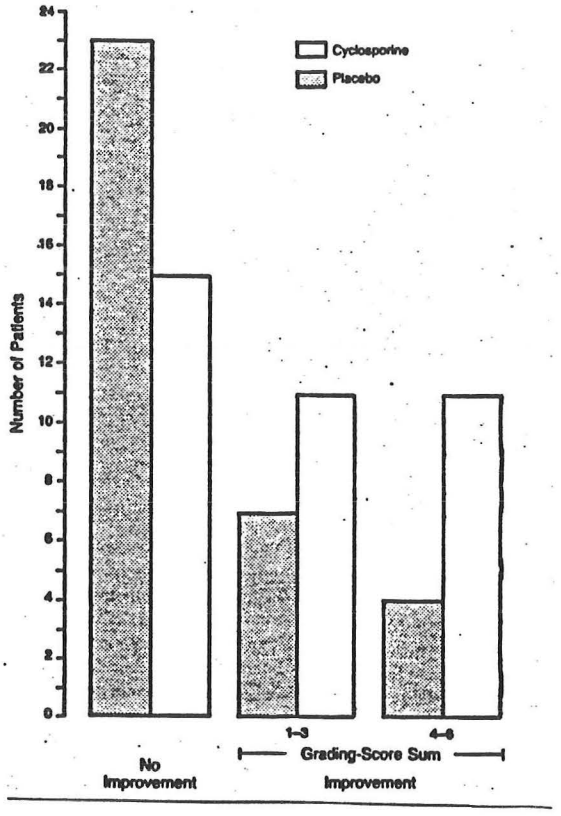

Fig. 14. Outcome of three months of treatment with cyclosporine or placebo in 71 patients with active chronic Crohn's disease. Greater degrees of improvement are indicated by higher grading-score sums (Brynskov, Ref 86).

Further work is needed, but it appears so far that cyclosporine produces about the same response rate as azathioprine and 6-MP, but seems to have a more rapid effect. In this trial, 86% of patients who would eventually improve had shown improvement after the first two weeks of therapy. One of the unresolved problems with cyclosporine is that pharmacokinetics vary considerably in individual patients; Brynskov et al. found that 26% of patients had some cyclosporine malabsorption. Thus at least some treatment failures may represent failures of drug absorption rather than drug action.

Metronidazole is an antibiotic which has become important in the treatment of Crohn's disease in the last few years. Metronidazole appears to be useful for treatment of Crohn's colitis rather than enteritis and the fistulas associated with Crohn's disease. Metronidazole does not appear to have any efficacy in ulcerative colitis (87,88). Metronidazole was compared to sulfasalazine for treatment of active Crohn's disease in a multicenter trial in Scandinavia (89); the study employed two treatment periods of four months in a cross-over design. Clinical evidence of improvement was documented using the Crohn's disease activity index while laboratory evidence of improvement was measured using plasma orosomucoid concentrations, which are a measure of mucosal inflammation. During the first treatment period, both metronidazole and sulfasalazine decreased the disease activity index equally but metronidazole caused a significantly greater decrease in orosomucoid concentrations. Of the 78 patients entered into the first treatment period, 22 dropped out for a variety of reasons. The mean Crohn's disease activity index and mean plasma orosomucoid concentrations for the 56 patients who

completed the first phase are shown in Fig. 15.

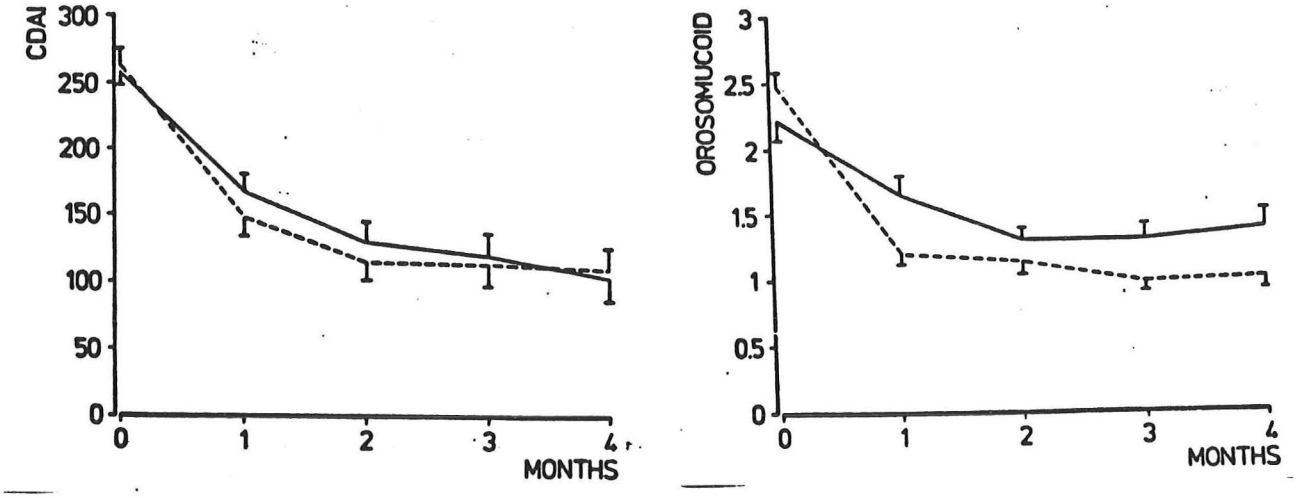

Fig. 15. Left Panel: Mean Crohn's disease activity index in patients treated with metronidazole (dashed line) versus sulfasalazine (solid line). Panel B. Mean plasma orosomucoid concentration (g/l) in patients treated with metronidazole (dashed line) versus sulfasalazine (solid line). (Ursing et al., Ref.89).

Patients who were classified as responders in the first phase of the trial did not change for either better or worse when medications were reversed in the second part of the trial. In the patients who were nonresponders in the first phase of the trial, those who switched from sulfasalazine to metronidazole improved significantly but not those who switched from metronidazole to sulfasalazine. Thus it appears in this trial that metronidazole is at least as effective as sulfasalazine if not better for treatment of active Crohn's disease, and that patients who do not respond to sulfasalazine may respond to later treatment with metronidazole.

Perhaps one of the more promising uses for metronidazole in Crohn's disease is in treatment of fistulas; uncontrolled trials show encouraging results (90,91). In one study (Table 12), complete healing occurred in 10 of 18 patients and partial healing occurred in 5 others.

Table 12.

EFFECT OF METRONIDAZOLE ON HEALING OF PERINEAL FISTULAS OF CROHN'S DISEASE

Healed	10/18
Improved	5/18
No change	3/18

- Bernstein, 1980

Maintenance of metronidazole therapy appears to be necessary to prevent relapse; this raises serious concerns about the complications of metronidazole treatment that may occur, particularly peripheral neuropathy (92) and mutagenesis/carcinogenesis (93,94).

POTENTIAL NEW DRUGS FOR INFLAMMATORY BOWEL DISEASE.

Due to the sizeable group of patients with inflammatory disease who either do not respond to therapy or cannot tolerate current medications, we are still in search of safe and effective agents. The agents discussed below are all in very early stages of testing; data from studies appears primarily in abstract form. It is fair to say that probably only a very few will stand the test of controlled trial and widespread clinical use; however, at the present time we cannot predict which agents these will be.

Antituberculous drugs. One of the theories about the etiology of Crohn's disease hypothesizes that at least some portion of patients with Crohn's disease have an infection with an atypical mycobacterium. There are currently three studies underway using various antituberculous antibiotics (95,96,97). Parker et al. have some promising preliminary results (96); as shown in Table 13, of 17 patients with active Crohn's disease treated with rifampicin, isoniazid, ethambutol and pyrazinamide, 12 showed a significant improvement in the Crohn's disease activity index, and 10 of these were able to discontinue steroid therapy. Side effects were common, particularly a flu-like illness which occurred in 7 of 17 patients, 4 with arthralgias, and 2 with abnormalities of liver enzymes.

Table 13.

RESULT OF QUADRUPLE ANTIMYCOBACTERIAL THERAPY FOR 6 MONTHS IN PATIENTS WITH CROHN'S DISEASE

Improvement	10/17
Side Effects	13/17

- Parker, 1988

Chloroquine has also been proposed for treatment of inflammatory bowel disease based on its ability to slow antigen processing, a possible mechanism of pathophysiology in inflammatory bowel disease. An open trial of chloroquine (98) in 10 patients with ulcerative colitis and 4 patients with Crohn's disease was undertaken; results are shown in Table 14. Eight of 10 patients with ulcerative colitis improved after three to eight weeks of therapy and one of four patients with Crohn's disease showed improvement.

Table 14.

EFFICACY OF CHLOROQUINE IN THE TREATMENT OF INFLAMMATORY BOWEL DISEASE

	Ulcerative Colitis	Crohn's Disease
Improvement	8/10	1/4

- Mayer, 1988

Based on these results, the authors are currently in the midst of a controlled trial.

Clonidine, a centrally acting alpha-2 agonist used for hypertension, has been used in a controlled trial for ulcerative colitis (99) at a dose of 0.3 mg TID versus both prednisone (20 mg TID) or sulfasalazine (1.5 g TID). Interestingly enough, not only symptoms but sigmoidoscopic and histological findings improved in patients treated with clonidine (Table 15).

Table 15.

COMPARISON OF CLONIDINE, PREDNISONE AND SULFASALAZINE IN THE TREATMENT OF ULCERATIVE COLITIS

	Rating Scale Initial/Final		
Drug	Clinical	Sigmoidoscopic	Histologic
Clonidine	3.5/0.3	3.7/0.5	3.8/1.4
Prednisone	3.5/0.5	3.4/0.6	3.6/1.8
Sulfasalazine	3.4/1.5	3.5/1.5	3.5/2.6

- Lechin, 1985

Clonidine in this trial was as effective as prednisone and more effective than sulfasalazine. Although this study is tantalizing, the lack of understanding of the potential mechanism in ulcerative colitis and the hypotensive side effects of clonidine make it prudent to await confirmation of this initial report.

Fish oil (eicosapentanoic acid). Since 5-ASA and sulfasalazine may work by decreasing leukotriene production, EPA, which inhibits the formation of leukotriene B_4, has been tried in a small number of patients with ulcerative colitis (100). Patients and normal volunteers were treated for 8 weeks with 2 - 4 g/day of EPA (Table 16).

Table 16.

CHEMILUMINESCENCE OF NEUTROPHILS IN PATIENTS WITH ULCERATIVE COLITIS AND IN NORMAL CONTROLS

	Chemiluminescence (mV)	
Subjects	Pretreatment	Posttreatment
Ulcerative colitis	220 ± 20	160 ± 10
Normals	100 ± 20	Unchanged

- McColl, 1988

Patients were said to improve clinically and histologically. Leukotriene B_4 production from neutrophils form patients and controls decreased. Neutrophil chemiluminescence was significantly elevated in patients with ulcerative colitis compared to normal subjects prior to treatment; chemiluminescence decreased in patients with ulcerative colitis after 8 weeks of treatment but was unaltered in the control subjects. Perhaps other specific inhibitors of arachidonic acid metabolism will become useful treatments in the future.

Immune adjuvants have been tried in Crohn's disease based on the possibility that Crohn's disease may be caused by a viral agent. Neither transfer factor nor BCG has been of any value. Vantrappen (101) treated a small number of patients with interferon for 6 weeks with a favorable response in several. However, although nearly a decade has passed since this study, no further information has been forthcoming. T-lymphocyte apheresis has been successfully used to treat patients with Crohn's disease in an open trial (102). Patients were steroid dependent, had at least one complication of steroid treatment, and had a recurrence of disease within 6 months after radical surgery. Treatment initially consisted of plasmapheresis (7 patients), and then was changed to removal of 40 billion T-lymphocytes, which generally took 8 treatments of 3 hours each (24 patients). Eventually, treatment was expanded to removal of 80 billion T-lymphocytes. Because patients were generally malnourished, they were additionally placed on total parenteral nutrition. Clinical remission was defined as the discontinuation of all steroids and the ability to return to work or school. Of the total of 54 patients treated, 51 patients achieved a remission lasting at least a year. Of the 23 patients treated by removing 80 billion T-lymphocytes, all 23 achieved a remission lasting at least two years. A remarkable feature of this treatment was that 5 patients, as they became clinically well, developed a psychotic depression. The technical difficulties, cost and apparent great stress of this treatment probably preclude its use in any widespread fashion; however, the high rate of prolonged remission suggests that T-cell lymphopheresis may be treating Crohn's disease relatively close to its roots.

Methotrexate, an antiinflammatory drug, has been used in an uncontrolled trial of patients with refractory ulcerative colitis or refractory Crohn's disease (103). The drug was given intramuscularly (25 mg) at weekly intervals for 12 weeks. The patients other medications were continued, except prednisone doses were decreased if possible. Results are summarized in the following table (Table 17).

While the majority of patients with either Crohn's disease or ulcerative colitis improved clinically, colonoscopic changes clearly lagged behind in patients with ulcerative colitis. The reason for this is not clear; however, there seems to be a general trend for immunosuppressive therapy to be of more benefit in Crohn's disease than ulcerative colitis when studies with azathioprine and 6-MP are reviewed.

Table 17. **EFFECT OF METHOTREXATE FOR 12 WEEKS IN PATIENTS WITH REFRACTORY INFLAMMATORY BOWEL DISEASE**

	Improvement		
	Clinical	Colonscopic	Histologic
Crohn's Disease	11/14	5/5	4/5
Ulcerative Colitis	5/7	0/7	5/7

- Kozarck, 1989

Oxygen-derived free radical scavengers may protect cells by reacting with free radicals released by inflammatory cells. Superoxide dismutase has been used in small trials in patients with Crohn's disease or ulcerative colitis. Three cases of pyoderma gangrenosum and vulvar ulcerations in patients with Crohn's disease responded to treatment with superoxide dismutase (104). Patients with active Crohn's disease and ulcerative colitis are said to have improved during treatment with superoxide dismutase, but limited data is available (105,106).

Sodium cromoglycate, used to treat IgE-mediated hypersensitivity reactions such as asthma, was ineffective orally in treating patients with active ulcerative colitis (107), or in maintaining remission in patients with inactive ulcerative colitis (108). However, more recently, sodium cromoglycate has been used in enema formulation in patients with distal ulcerative colitis or proctitis, with patients receiving prednisolone enemas for comparison (109). Both groups did equally well, as shown in Table 18.

Table 18. **COMPARISON OF SODIUM CROMOGLYATE AND PREDNISOLONE ENEMAS FOR TREATMENT OF ULCERATIVE COLITIS**

		Percent of Patients Treated	
Variable	Period	Cromoglyate	Prednisolone
Stool frequency/ 24 h	Baseline	16	31
	8 weeks	64	84
Normal Sigmoidoscopic Appearance	Baseline	0	0
	8 weeks	44	52
Normal or mildly Abnormal Histology	Baseline	41	56
	8 weeks	70	75

- Grace, 1987

Patients were treated with either sodium cromoglycate (600 mg/100 ml) enemas or with prednisolone (20 mg/100 ml) enemas over a nine week period. Symptoms, sigmoidoscopic appearance and histology all improved in both groups to the same extent.

Sucralfate, a mucopolysaccharide which heals peptic ulcers by an unknown mechanism, has been used in two controlled trials in enema form to treat ulcerative colitis which have been reported in preliminary form. The first study (110) compared sucralfate enemas to prednisolone enemas. Prednisolone produced a remission in 71% of patients while sucralfate-treated patients achieved remission in only 28% of cases (Table 19).

Table 19.

COMPARISON OF SUCRALFATE AND PREDNISOLONE ENEMAS FOR TREATMENT OF ULCERATIVE COLITIS

	Percent Patients Achieving Remission
Sucralfate	28
Prednisolone	71

- Riley, 1988

In the second study, patients were randomized to treatment with either placebo, sucralfate or 5-ASA enemas (111). As expected, patients receiving 5-ASA enemas did well, but patients treated with sucralfate did not fare any better than placebo-treated patients (Table 20).

Table 20.

COMPARISON OF SUCRALFATE, 5-ASA AND PLACEBO ENEMAS FOR TREATMENT OF ULCERATIVE COLITIS

		Improvement		
	Patients	Clinical	Sigmoidoscopic	Histologic
Sucralfate	18	4	4	3
5-ASA	18	17	16	15
Placebo	14	2	2	1

- Campieri, 1988

RECOMMENDATIONS FOR THERAPY

Current recommendation for therapy are somewhat limited by the drugs currently available, however, one may expect several useful agents to be released shortly.

ULCERATIVE COLITIS.

Mild to moderate distal ulcerative colitis and proctitis are probably best treated initially with either sulfasalazine or steroid enemas. These treatments are usually effective and have been used with relative safety for years. For patients who develop systemic side effects, the rapidly metabolized steroid enemas such as beclomethasone, budesonide or tixocortol may be useful, or one of the forms of 5-ASA. These newer agents are expected to be considerably more expensive. For long-term prophylaxis, the newer enemas or 5-ASA suppositories may offer fewer side effects, although some of these patients will not require continuous therapy.

Patients with mild to moderate ulcerative colitis involving the whole colon, or patients with left-sided disease who do not respond to enemas are frequently adequately treated with oral sulfasalazine. Oral forms of 5-ASA may be useful (when available) for patients intolerant of sulfasalazine. Patients who do not respond to sulfasalazine or 5-ASA should be tried on a course of rapidly tapering steroids. Prednisone, 40-60 mg/day, is the choice of most clinicians. Sulfasalazine clearly reduces recurrences and can be used long-term in many patients, usually at a somewhat reduced dose such as 2 g/day.

Severe ulcerative colitis, regardless of anatomic extent, should be treated with steroids, frequently intravenously in the hospital, with surgical consultation in case the patient does not respond. After the crisis is over, the patient can usually be given oral steroids and gradually tapered off while sulfasalazine is started.

Refractory ulcerative colitis, like severe ulcerative colitis, is a relative indication for surgery. Although every reasonable effort should be made to obtain a clinical response (hospitalization, intravenous feeding, prolonged medical therapy), it should be remembered that ulcerative colitis, unlike Crohn's disease, can be cured by colectomy and truly refractory cases need not drag on for years. Fortunately, this represents a fairly small percentage of total patients.

CROHN'S DISEASE.

New onset or intermittently active Crohn's disease is probably best treated with sulfasalazine or short courses of steroids on a tapering schedule. Although sulfasalazine is not as effective in ileal Crohn's disease, it may be useful as acute therapy in some patients. The greater the colonic involvement, the more likely it is that the patient will respond to sulfasalazine or 5-ASA. Metronidazole is worthy of a trial in patients who cannot take or are resistent to sulfasalazine and steroids, but should probably be tapered after four or five months. Perhaps one of the new oral forms of 5-ASA will fulfill its early promise in treatment of Crohn's disease involving the ileum. Neither prednisone or sulfasalazine are generally useful for prophylaxis of ileal Crohn's disease, and many patients will not require therapy between flares.

Crohn's disease with fistulas is probably best treated with metronidazole. If the patient has a good response, long-term therapy, despite some theoretical/actual risks, may be warranted, since fistulas recur in a very high proportion of patients in whom metronidazole is discontinued.

Refractory Crohn's disease refers to cases that have failed therapy with sulfasalazine, steroids and metronidazole. These patients should be considered for immunosuppressive therapy with azathioprine or 6-MP. Cyclosporine may eventually be added to this group of drugs. In light of the morbidity of refractory Crohn's disease, the risks of immunosuppressive agents seem warranted. Probably the best drugs for prophylaxis of Crohn's disease are the immunosuppressive drugs, but these are best reserved for patients with multiple severe exacerbations.

Although many drugs are currently being discussed for treatment of inflammatory bowel disease, it seems apparent that for many patients we do not have truly satisfactory treatment. The comments of Robert Summers about the institution of the National Cooperative Crohn's Disease Study in 1971 seem ironic (Summers);

> "Stimulated by an apparent increase in the frequency of Crohn's disease, enthusiastic reports of the efficacy of azathioprine, and a concern that patterns of drug usage might soon become so fixed as to preclude a randomized, controlled double-blind trial of treatment, a group of investigators in 1971 decided to initiate a multicenter drug study."

Eventually clinical research and our patients will be the beneficiaries of current active laboratory investigation into the etiologies and pathogenesis of inflammatory bowel disease.

REFERENCES

1. Wilks S and W Moxon. Lectures on Pathological Anatomy. 2nd edition. London. J and A Churchill, 1875.

2. Crohn BB, L Ginzberg and GD Oppenheimer. Regional ileitis. A pathologic and clinical entity. JAMA 99:1323, 1932.

3. Peppercorn, MA. Advances in drug therapy for inflammatory bowel disease. Ann Int Med. 112:50, 1990.

4. Matts SF. The value of rectal biopsy in the diagnosis of ulcerative colitis. Q J Med. 30:393, 1961.

5. Mekhjian HS, DM Switz, CS Melnyk, GB Rankin and RK Brooks. Clinical features and natural history of Crohn's Disease. Gastroenterology 77:898, 1979.

6. Farmer RG, G Whelan and VW Fazio. Long-term follow-up of patients with Crohn's disease. Relationship between the clinical pattern and prognosis. Gastroenterology 88:1818-1825, 1985.

7. Greenstein AJ, HD Janowitz and DB Sachar. The extraintestinal complications of Crohn's disease and ulcerative colitis: a study of 700 patients. Medicine 55:401, 1976.

8. Bergman L and U Krause. Crohn's disease: A long-term study of the clinical course of 186 patients. Scand J Gastroenterol 12:937, 1977.

9. Baron JH, PM Connell, JE Lennard-Jones, F Avery Jones. Sulphahasalazine and salicylazosulphadimidine in ulcerative colitis. Lancet. 1:1094, 1962.

10. Truelove SC, G Watkinson, G Draper. Comparison of corticosteroid and sulphasalazine therapy in ulcerative colitis. Br Med J. 2:1708, 1962.

11. Dick AP, MJ Grayson, RG Carpenter and A Petrie. Controlled trial of sulphasalazine in the treatment of ulcerative colitis. Gut. 5:437, 1964.

12. Misiewicz JJ, JE Lennard-Jones and AM Connell. Controlled trial of sulphasalazine in maintenance therapy for ulcerative colitis. Lancet. 1:185, 1965.

13. Riis P, P Anthonisen, H Wulff, O Folkenborg, O Bonnevie and V Binder. The prophylactic effect of salazosulphapyridine in ulcerative colitis during long-term treatment. A double-blind trial on patients asymptomatic for one year. Scan J Gastroenterol. 8:71, 1973.

14. Dissanayake AS and SC Truelove. A controlled therapeutic trial of long-term maintenance treatment of ulcerative colitis with sulphasalazine (Salazopyrin). Gut. 14:923, 1973.

15. Anthonisen P, F. Barany, O Folkenborg, A Holtz, S Jarnum, M Kristensen, P Riis, A Walan and H Worning. The clinical effect of salazosulphapyridine (Salazopyrin) in

Crohn's disease. Scand J Gastroent 9:549, 1974.

16. Davies PS and J Rhodes. Maintenance of remission in ulcerative colitis with sulphasalazine or a high-fibre diet: A clinical trial. Br Med J. 1:1524, 1978.

17. Summers RW, DM Switz, JT Sessions, JM Becktel, WR Best, F Kern and JW Singleton. National Cooperative Crohn's disease study: Results of drug treatment. Gastroenterology. 77:847, 1979.

18. Azad Khan AK, DT Howes, J Piris and SC Truelove. Optimum dose of sulphasalazine for maintenance treatment in ulcerative colitis. Gut. 21:232, 1980.

19. Goldstein F and MG Murdock. Clinical and radiologic improvement of regional enteritis and enterocolitis after treatment with salicylazosulfapyridine. Am J Dig Dis. 16:421, 1981.

20. van Hees, PAM, HJJ van Lier, PH van Elteren, WMM Driessin, RA van Hogezand, GPM ten Velde, JH Bakker, JHM van Tongeren. Effect of sulphasalazine in patients with active Crohn's disease: a controlled double-blind study. Gut. 22:404, 1981.

21. Malchow H, K Ewe, JW Brandes, H Goebell, H Ehms, H Sommer and H Jesdinsky. European cooperative Crohn's disease study (ECCDS): Results of drug treatment. Gastroenterology. 77:847,1979.

22. Goldstein F, S Farquhar, JJ Thornton and DJ Abramson. Favorable effects of sulfasalazine on small bowel Crohn's disease: a long-term study. Am J Gastroenterol. 82:848, 1987.

23. Moller, C, O Kiviluoto, S Santavirta et al. Local treatment of ulcerative proctitis with salicylazosulphapyridine (salazopyrine) enema. Clin Trials J. 15:199, 1978.

24. Fruhmorgen, P and L Demling. On the efficacy of ready-made-up commercially available salicylazosulphapyridine enemas in the treatment of proctitis, proctosigmoiditis and ulcerative colitis involving the rectum, sigmoid and descending colon. Hepatogastroenterology. 27:473,1980.

25. Palmer, KR, JR Goepal and CD Holdsworth. Sulphasalazine retention enemas in ulcerative colitis: Double-blind trial. Br Med J. 282:1571, 1981.

26. Kruis, W, V Bull, J Eisenburg et al. Retrograde colonic spread of sulphasalazine enemas. Scand J Gastroenterol. 17:933, 1982.

27. Stenson, WF. Pharmacology of sulfasalazine. Viewpoints of Digestive Diseases. 16:13, 1984.

28. Collins, JR. Adverse reactions to salicylazosulfapyridine (azulfidine) in the treatment of ulcerative colitis. Southern Med J. 61:354, 1968.

29. Das, KM, MA Eastwood, JPA McManus, W Sircus. Adverse reactions during salicylazosulfapyridine therapy and the relation with drug metabolism and acetylator

phenotype. N Engl J Med. 289:491, 1973.

30. Taffet, SL and KM Das. Desensitization of patients with inflammatory bowel disease to sulfasalazine. Am J Med 62:520, 1982.

31. Azad Khan, AK, J Piris and SC Truelove. An experiment to determine the active therapeutic moiety of sulphasalazine. Lancet. 2:892, 1977.

32. Peppercorn, MA and P Goldman. Distribution studies of salicylazosulfapyridine and its metabolites. Gastroenterology. 64:240, 1973.

33. Nielsen, OH, K Bukhave, J Elmgreen and I Ahnfelt-Ronne. Inhibition of 5-lipoxygenase pathway of arachadonic acid metabolism in human neutrophils by sulfasalazine and 5-aminosalicylic acid. Dig Dis Sci. 6:577, 1987.

34. Kaufman HJ and HL Taubin. Nonsteroidal anti-inflammatory drugs activate quiescent inflammatory bowel disease. Ann Intern Med. 107:513, 1987.

35. Campieri, M, GA Lanfranchi, G Bazzocchi, C Brignola, F Sarti, G Franzin, A Battocchia, G Labo and PR DalMonte. Treatment of ulcerative colitis with high-dose 5-aminosalicylic acid enemas. Lancet. 2:270, 1981.

36. Campieri, M, G Lanfranchi, S Boschi, C Brignola, G Bazzocchi, P Gionchetti, MR Minguzzi, A Beluzzi and G Labo. Topical administration of 5-aminosalicylic acid enemas in patients with ulcerative colitis. Studies on rectal absorption and excretion. Gut. 26:400, 1985.

37. Willoughby, CP, M Campieri, G Lanfranchi, SC Truelove and DP Jewell. 5-Aminosalicylic acid (Pentasa) in enema form for the treatment of active ulcerative colitis. Ital J Gastroenterology. 18:15, 1986.

38. Sutherland, LR, F Martin, S Greer, M Robinson, N Greenberger F Saibil, T Martin, J Sparr, E Prokipchuk and L Borgen. 5-Aminosalicylic acid enemas in the treatment of distal ulcerative colitis, proctosigmoiditis and proctitis. Gastroenterology. 92:1894, 1987.

39. Danish 5-ASA Group. Topical 5-aminosalicylic acid versus prednisolone in ulcerative proctosigmoiditis. A randomized, double-blind multicenter trial. Dig Dis Sci. 32:598, 1987.

40. Campieri, M, GA Lanfranchi, F Bertoni, C Brignola, G Bazzocchi, MR Minguzzi and G Labo. A double-blind clinical trial to compare the effects of 4-aminosalicylic acid to 5-aminosalicylic acid in topical treatment of ulcerative colitis. Digestion. 29:204, 1984.

41. Selby, WS, MK Bennet, and DP Jewell. Topical treatment of distal ulcerative colitis with 4-aminosalicylic acid enemas. Digestion. 29:231, 1984.

42. Ginsberg, AL, LS Beck, TM McIntosh,and LE Nochomovitz. Treatment of left-sided ulcerative colitis with 4-aminosalicylic acid enemas. A double-blind, placebo-controlled trial. Ann Intern Med. 108:195, 1988.

43. Gandolfo, J, M Farthing, G Powers, K Eagen, M Goldberg, P Berman and M Kaplan. 4-Aminosalicylic acid retention enemas in treatment of distal colitis. Dig Dis Sci. 32:700, 1987.

44. van Hees, PA, JH Bakker and JH van Tongeren. Effect of sulphapyridine, 5-aminosalicylic acid and placebo in patients with idiopathic proctitis: a study to determine the active therapeutic moiety of sulphasalazine. Gut. 21:632, 1980.

45. Williams, CN, G Haber and JA Aquino. Double-blind, placebo-controlled evaluation of 5-ASA suppositories in active distal proctitis and measurement of extent of spread using 99mTc-labelled 5-ASA suppositories. Dig Dis Sci. 32:71S, 1987.

46. Borgen, LA, SB Hanauer, L Good, CN Williams and G Haber. Mesalamine suppository efficacy in ulcerative proctitis: a multicenter placebo-controlled trial [Abstract]. Gastroenterology. 90:1364, 1986.

47. Biddle, WL, NJ Greenberger, JT Swan, MS MCPhee, and PB Miner. 5-Aminosalicylic acid enemas:effective agent in maintaining remission in left-sided ulcerative colitis. Gastroenterology. 94:1075, 1988.

48. Hanauer, SB and PA Schultz. Relapse rates after successful treatment of refractory colitis with 5-ASA enemas [Abstract]. Gastroenterology. 92:1424, 1987.

49. Rao, SS, PA Cann and CD Holdsworth. Clinical experience of the tolerance of mesalazine and olsalazine in patients intolerant of sulphasalazine. Scand J Gastroenterology. 22:332, 1987.

50. Agnholt, J, HT Sorensen, SN Rasmussen, CO Gotzsche, and P Halkier. Cardiac hypersensitivity to 5-aminosalicylic acid [Letter]. Lancet. 1:1135, 1989.

51. Poldermans, D and M van Blankenstein. Pancreatitis induced by disodium azodisalicylate. Am J Gastroenterology. 83:578, 1988.

52. Sachedina, B, F Saibil, LB Cohen and J Whittey. Acute pancreatitis due to 5-aminosalicylate. Ann Intern Med. 110:490, 1989.

53. Schroeder, KW, WJ Tremaine and DM Ilstrup. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. N Engl J Med. 317:1625, 1987.

54. Rachmilewitz, D. Coated mesalazine (5-aminosalicylic acid) versus sulphasalazine in the treatment of active ulcerative colitis: a randomised trial. Brit Med J. 289:82, 1989.

55. Mulder, CJJ, GNY Tytgat, IT Weterman, W Dekker, P Blok, M Schrijver and HVD Heide. Double-blind comparison of slow-release 5-aminosalicylate and sulfasalazine in remission maintenance in ulcerative colitis. Gastroenterology. 95:1449, 1988.

56. Riley SA, B Many, MJ Goodman, ME Herd, S Dutt and LA Turnberg. Comparison of delayed-release 5-aminosalicylic acid (Mesalazine) and sulfasalazine as maintenance treatment for patients with ulcerative colitis. Gastroenterology. 94:1383, l988.

57. Rasmussen, SN, V Binder, K Maier, S Bondesen, C Fischer, U Klotz, SH Hansen and EF Hvidberg. Treatment of Crohn's disease with peroral 5-aminosalicylic acid Gastroenterology 85:1350, 1983.

58. Rasmussen, SN, K Lauritsen, U Tage-Jensen, OH Nielsen, P Bytzer, O Jacobsen, K Ladefoged, M Vilien, V Binder, J Rask-Madsen, S Bondesen, SH Hansen and EF Hvidberg. 5-Aminosalicylic acid in the treatment of Crohn's disease. Scand J Gastroenterol 22:877, 1987.

59. Truelove, SC and DP Jewell. Intensive intravenous regimen for severe attacks of ulcerative colitis. Lancet 1:1067, 1974.

60. Kirsner, JB and WL Palmer. Effect of corticotropin (ACTH) in chronic ulcerative colitis: observations in forty cases. JAMA. 147:541, 1951.

61. Kirsner, JB and WL Palmer. Ulcerative colitis: therapeutic effects of corticotropin (ACTH) and cortisone in 120 patients. Ann Int Med. 41:232, 1954.

62. Truelove, SC and CJ Witts. Cortisone in ulcerative colitis. Brit Med J. 2:4947, 1955.

63. Truelove, SC. Treatment of ulcerative colitis with local hydrocortisone hemisuccinate sodium. Brit Med J. 2:1072, 1958.

64. Lee, DAH, GM Taylor, VT James and G Walker. Plasma prednisolone levels and adrenocortical responsiveness after administration of prednisolone-21-phosphate as a retention enema. Gut. 20:349, 1979.

65. Singleton, JW, DH Law, ML Kelley, HS Mekhjian and RL Sturdevant. National cooperative Crohn's disease study: adverse reactions to study drugs. Gastroenterology. 77:870, 1979.

66. Larochelle, P, P Du Souich, J Lelorier and R Goyer. Tixocortol pivalate, a corticosteroid with no systemic glucocorticoid effect after oral, intrarectal and intranasal application. Clin Pharmacol Ther. 33:343,1983.

67. Levinson, RA. Comparative safety and efficacy of tixocortol pivalate enema vs. hydrocortisone enema in the treatment of left-sided ulcerative colitis. In Recent Developments in the Therapy of Inflammatory Bowel Disease. Proceedings of a symposium. Baltimore, Meyerhoff Center for Digestive Disease, at Johns Hopkins, p 26, 1986.

68. Hanauer, SB, JB Kirsner and WE Barrett. The treatment of left-sided ulcerative colitis with tixocortol pivalate (TP) [Abstract]. Gastroenterology. 90:1449, 1986.

69. Freidman G. Treatment of refractory proctosigmoiditis and left-sided colitis with a rectally instilled nonglucocorticoid, nonmineralocorticoid steroid [Abstract]. Gastroenterology. 88:1388, 1985.

70. Kumana, CR, T Seaton, M Meghji, M Castelli, R Benson and T Sivakumaran.

Beclomethasone dipropionate enemas for treating inflammatory bowel disease without producing Cushing's syndrome or hypothalamic pituitary adrenal suppression. Lancet. 1:579, 1982.

71. Danielsson, A, G Hellers, E Lyrenas, R Lofberg, A Nilsson, O Olsson, S-A Olsson, T Persson, L Salde, J Naesdal, M Stenstam and R Willen. A controlled randomized trial of budesonide versus prednisolone retention enemas in active distal ulcerative colitis. Scand J Gastroenterol. 22:987, 1987.

72. Willoughby, JM, J Beckett, PJ Kumar, and AM Dawson. Controlled trial of azathioprine in Crohn's disease. Lancet. 2:944, 1971.

73. Rhodes, J, D Bainton, P Beck and H Campbell. Controlled trial of azathioprine in Crohn's disease. Lancet. 2:1273, 1971.

74. Klein, M, HJ Binder, M Mitchell, R Aaronson and H Spiro. Treatment of Crohn's disease with azathioprine: a controlled evaluation. Gastroenterology. 66:916, 1974.

75. Rosenberg, JL, B Levin, AJ Wall and JB Kirsner. A controlled trial of azathioprine in Crohn's disease. Am J Dig Dis. 20:721, 1975.

76. Kirk, AP and JE Lennard-Jones. Controlled trial of azathioprine in ulcerative colitis. Br Med J. 284:1291, 1962.

77. Rosenberg, JL, AJ Wall, B Levin, HJ Binder and JB Kirsner. A controlled trial of azathioprine in the management of ulcerative colitis.

78. Present, DH, BI Korelitz, N Wisch, JL Glass, DB Sachar and BS Pasternack. Treatment of Crohn's disease with 6-mercaptopurine. N Engl J Med. 302,981, 1980.

79. Nyman, M., I Hansson and S Eriksson. Long-term immunosuppressive treatment in Crohn's disease. Scand J Gastroenterol 20:1197, 1985.

80. O'Donoghue, DP, AM Dawson, J Powell-Tuck, RL Bown and JE Lennard-Jones. Double-blind withdrawal trial of azathioprine as maintenance treatment for Crohn's disease. Lancet. 2:955, 1978.

81. Present, DH, SJ Meltzer, MP Krumholz, A Wolke and BI Korelitz. 6-Mercaptopurine in the management of inflammatory bowel disease:short- and long-term toxicity. Ann Int Med. 111:641, 1989.

82. Peltekian, K, C Williams, A MacDonald, P Roy and E Czolpinska. Open study of cyclosporin A (CyA) in Crohn's disease (CD) [Abstract]. Gastroenterology. 92:A1571, 1987.

83. Allison, MC and RE Pounder. Cyclosporin for Crohn's disease [Letter]. Lancet. 1:902, 1984.

84. Bianchi, PA, M Modelli, F Quarto diPalo and T Ranzi. Cyclosporine for Crohn's

disease [Letter]. Lancet. 2:1242, 1984.

85. Lichtiger, S and DH Present. Cyclosporine A in the treatment of severe, refractory ulcerative colitis [Abstract]. Gastroenterology 96:A301, 1989.

86. Brynskov,J, L Freund, SN Rasmussen, K Lauritsen, O Schaffalitzky de Muckadell, N Williams, AS MacDonald, R Tanton, F Molina, MC Campanini, P Bianchi, T Ranzi, F Quarto de Palo, A Malchow-Moller, OO Thomsen, U Tage-Jensen, V Binder and P Riis. A placebo-controlled, double-blind, randomized trial of cyclosporine therapy in active chronic Crohn's disease. N Engl J Med. 321:845, 1989.

87. Davies, PS, J Rhodes, RV Heatley and E Owen. Metronidazole in the treatment of chronic proctitis: a controlled study. Gut. 18:680, 1977.

88. Chapman, RW, WS Selby, and DP Jewell. Controlled trial of intravenous metronidazole as an adjunct to corticosteroids in severe ulcerative colitis. Gut. 27:1210, 1986.

89. Ursing, B, T Alm, F Barany, I Bergelin, K Ganrot-Norlin, J Hoevels, B Huitfeldt, G Jarnerot, U Krause, A Krook, B Lindstrom, O Nordle and A Rosen. A comparative study of metronidazole and sulfasalazine for active Crohn's disease: the cooperative Crohn's disease study in Sweden. Gastroenterology. 83:550, 1982.

90. Bernstein, LH, MS Frank, LF Brandt and SJ Boley. healing of perineal Crohn's disease with metronidazole. Gastroenterology, 798:357, 1980.

91. Brandt, LJ, LH Bernstein, SJ Boley and MS Frank. Metronidazole therapy for perineal Crohn's disease: a follow-up study. Gastroenterology. 83:383, 1982.

92. Duffy, LF, F Daum, SE Fisher, J Selman, SM Vishnubhakat, HW Aiges, JF Markowitz and M Silverberg. Peripheral neuropathy in Crohn's disease patients treated with metronidazole. Gastroenterology 88:681, 1985.

93. Roe, FJC. Toxicologic evaluation of metronidazole with particular reference to carcinogenic, mutagenic and teratogenic potential. Surgery 93:158, 1983.

94. Krause, JR, HQ Ayuyang, LD Ellis. Occurrence of 3 cases of carcinoma in individuals with Crohn's disease treated with metronidazole. Am J Gastroenterol. 80:978, 1985.

95. Thayer, WR, JA Coutu, RJ Chiodine, HJ Van Kriuningen, and RS Merkal. Use of rifabutin and streptomycin in the therapy of Crohn's disease [Abstract]. Gastroenterology. 94:A458, 1988.

96. Parker, MC, SH Savegmutter, JJ McFadden and H Herman Taylor. Results of quadruple antimycobacterial chemotherapy in 17 Crohn's disease patients completing six months treatment [Abstract]. Gastroenterology. 94:A1770, 1988.

97. Rutgeerts, P, G Vantrappen, J Van Isreldy and K Gebres. Rifabutin therapy in patients with recurrent Crohn's disease after ileocolonic resection [Abstract]. Gastroenterology. 94:A391, 1988.

98. Mayer L and DB Sachar. Efficacy of chloroquine in the treatment of inflammatory bowel disease [Abstract]. Gastroenterology. 94:A293, 1988.

99. Lechin F, B van der Dijs, CL Insausti, F Gomez, S Villa, AE Lechin, L Arocha and O Oramas. Treatment of ulcerative colitis with clonidine. J Clin Pharmacol. 25:219, 1985.

100. McColl, T, J O'Leary, J Bloomfield and CA O'Morain. Eicosapentaenoic acid [Abstract]. Gastroenterology. 94:A294, 1988.

101. Vantrappen, G, G Coremans and A Billiau. Treatment of Crohn's disease with interferon. A preliminary clinical trial. Acta Clin Belg. 35:238, 1980.

102. Bicks RO, KD Groshart. The current status of T-lymphocyte apheresis (TLA) of Crohn's disease. J Clin Gastroenterol 11:136, 1989.

103. Kozarek RA, DJ Patterson, MD Gelfand, VA Botoman, TJ Ball and KR Wilske. Methotrexate induces clinical and histologic remission in patients with refractory inflammatory bowel disease. Ann Intern Med. 110:353, 1989.

104. Emerit, J, J Loeper and G Chomette. Superoxide dismutase in the treatment of post-radiotherapeutic necrosis and of Crohn's disease. Bull Eur Physiopathol Respir. 17(Suppl):287, 1981.

105. Szegli, G, A Herold, E Negut et al. Clinical efficacy of a new antiinflammatory drug with free radicals scavenging properties. Superoxide dismutase and catalase of human origin. Arch Roum Pathol Exp Microbiol. 45:75, 1986.

106. Petkau, A. Scientific basis for the clinical use of superoxide dismutase. Cancer Treatment Reviews. 13:17, 1986.

107. Buckell, NA, SR Gould, DW Day, JE Lennard-Jones and AM Edwards. Controlled trial of disodium cromoglycate in chronic persistent ulcerative colitis. Gut. 19:1140, 1978.

108. Dronfield, MW and MJ Langman. Comparative trial of sulphasalazine and oral sodium cromoglycate in the maintenance of remission in ulcerative colitis. Gut. 19:1136, 1978.

109. Grace, RH, AE Gent and MD Hellier. Comparative trial of sodium cromoglycate enemas with prednisolone enemas in the treatment of ulcerative colitis. Gut. 28:88, 1987.

110. Riley, SA, J Gupta and V Mani. A comparison of sucralfate and prednisolone enemas in the treatment of active distal ulcerative colitis [Abstract]. Gastroenterology. 94:A377, 1988.

111. Campieri, M, P Gionchetti, A Belluzzi, C Brignola, GM Tabanelli, M Migaldi, M Miglioli and L Barbara. 5-Aminosalicylic acid, sucralphate and placebo enemas in the treatment of distal ulcerative colitis (UC) [Abstract]. Gastroenterology. 94:A58, 1988.