

# A History of Immunosuppressive Drugs in the Treatment of Inflammatory Bowel Disease: Origins at The Mount Sinai Hospital

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## Abstract

Much of what we know about the role of immunopathologic mechanisms in causing Crohn's disease and ulcerative colitis originated from research at The Mount Sinai Hospital. The authors were privileged to have been able to share in this undertaking, along with many others, including Moschcowitz, Klemperer, Otani, Crohn, Ginzburg, Oppenheimer, Garlock, Lyons, Marshak, Janowitz, Aufses, Waye, Greenstein, Sachar, Meyers, Gelernt, Mayer, Lichtiger and Kornbluth.

In medical history, elucidation of disease processes is often serendipitous. Transplant surgery was successful because of the discovery by Hitchings and Elion of 6-mercaptopurine (6-MP) and azathioprine, which inhibited rejection. And the concept of immunosuppression slowly evolved into possible treatment of any disease thought to be caused by autoimmunity. This includes those diseases of the bowel seen so frequently at The Mount Sinai Hospital: ileitis, granulomatous colitis, ileocolitis, and ulcerative colitis.

This paper depicts the progressive role of immunosuppressive drugs, from corticosteroids to 6-mercaptopurine, cyclosporine and anti-tumor necrosis factor, in both the treatment and understanding of the pathogenesis of Crohn's disease and ulcerative colitis. Major contributions to these treatments have come from physicians and surgeons with roots at The Mount Sinai Hospital. **Key Words:** Immunosuppressive drugs, 6-MP, cyclosporine, anti-tumor necrosis factors, IBD.

WHEN WE ARRIVED AT MOUNT SINAI, several decades had already passed since the landmark publication on regional ileitis by Crohn, Ginzburg, and Oppenheimer (1). Management remained primarily in the hands of the surgeons. Drug therapy had been limited to a variety of sulfonamides, and gastroenterologists were slow to acknowledge that one (sulfasalazine) differed from all the others, and should be favored. Even so, sulfasalazine did not work as well in ileitis as it did in ulcerative colitis. The morbidity and surgical incidence for both diseases remained high and the mortality rate, particularly for children with ulcerative colitis, was unacceptable (2).

In 1949, the first edition of Dr. Crohn's book (83) included data on the course, complications, and treatment of ileitis. Corticosteroids, which became available soon thereafter, were not mentioned at all. Yet, never before had such dramatic improvements been seen as those that followed treatment with corticosteroids and corticotropin. The outcome was influenced so favorably that surgery could now be postponed and performed electively. The gastroenterologist inherited the primary responsibility for patient management and clinical observation (3).

In retrospect, this period was one of relative complacency, particularly with regard to the search for new drugs. The initial euphoria, although warranted by the success of the steroids in eliminating the inflammatory process, yielded to the sober realization that the effect was transient (4) and that the inflammation returned not only with discontinuation of the drug but even with dose reduction. Also, the inflammation responded less dramatically with subsequent courses of treatment; finally, corticosteroids were shown to be no more effective than placebos in

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maintaining remission (5). They also had the potential for major toxicity.

In the 1960s, the following factors rekindled an effort to provide new treatment for inflammatory bowel disease (IBD):

1. The causes remained unknown.
2. The concept of autoimmune diseases began to be appreciated (6, 7).
3. The question was frequently raised as to whether Crohn's disease and ulcerative colitis could be autoimmune diseases.
4. Studies demonstrating auto-antibodies in ulcerative colitis were being reported (8).
5. Azathioprine was shown to inhibit rejection of the donor's transplanted kidney (9).
6. Toxicity due to corticosteroids was reported (10).
7. Winkelman and Brown (11) reported a favorable experience with nitrogen mustard in the treatment of both ulcerative colitis and regional enteritis.
8. Bean had successfully treated an ulcerative colitis patient with 6-mercaptopurine (12), a metabolic product of azathioprine, and was pursuing this early success (13).
9. Brooke et al. (14, 15) reported previously unheard-of reversals of advanced Crohn's disease, including those with complex fistulas, when patients were treated with azathioprine after all surgical efforts had failed.

Although later epidemiologic data showed that the incidence of Crohn's disease was on the rise whereas the incidence of ulcerative colitis was stable, this was not yet apparent in the 1960s. One of us (BIK) had seen many ulcerative colitis patients with Banks and Zetzel at the Beth Israel Hospital in Boston (16). At Mount Sinai, he was disturbed by the large number of children with ulcerative colitis in whom corticosteroid therapy had failed, who were physically and emotionally traumatized by the toxicity of these drugs, and who required colectomy and ileostomy (with high mortality) (3, 17). In view of this experience, in January 1967 it was decided to add 6-mercaptopurine (6-MP) to the treatment of ulcerative colitis patients who had not responded favorably to cor-

ticosteroids and sulfasalazine treatment, and who did not have an absolute indication for surgical intervention (18).

The co-worker in this study (18) was Nathaniel Wisch, a hematologist, who favored 6-MP over azathioprine (azathioprine is converted to 6-MP *in vivo*) only because he had had experience with its use in treating childhood leukemia. Furthermore, the Food and Drug Administration had approved 6-MP for use in the treatment of that disease. At the conclusion of this study, it was clear that 6-MP had no dramatic short-term influence on the course of the disease; moreover, transient nausea and vomiting occurred frequently. Apparently, 6-MP had no role in the treatment of fulminating ulcerative colitis or toxic megacolon. This finding confirmed those already demonstrated for azathioprine by Bowen et al. (19), who suggested that immunosuppressive drugs should not be used for the treatment of ulcerative colitis. Nonetheless, we had noted favorable results in a select group of patients, which led us to adopt new criteria for instituting 6-MP therapy. Our choice of candidates included those with chronic prolonged ulcerative colitis, those who had an incomplete response to steroids, those who had complications from the steroid treatment, those who had contraindications to the use of steroids, and those in whom sulfasalazine had failed.

Perhaps the most important observation we made was that the real value of 6-MP could only be determined after long-term observation. We found that 13 of 14 patients either went into remission or improved significantly; only one remained incapacitated. Based on this study, and our later experience when the series had been expanded to 25 patients (20), a long-term, double-blind, controlled study was planned.

Coincidentally, in the late 1960s the following events occurred:

1. One of us (DHP) completed his fellowship in gastroenterology at Mount Sinai. In addition to the teacher (BIK)-student (DHP) relationship, we became friends and found that we shared common interests in clinical investigation of IBD. We were both enthusiastic about conducting a double-blind trial of immunosuppressive therapy.
2. The Ileitis Foundation was launched by Irwin Rosenthal, William Modell, and our Chief of Gastroenterology at Mount Sinai, Henry D. Janowitz. The primary goal of the foundation was to encourage and support research in

IBD, and DHP became its first fellow and research grant recipient. The early participation of BIK was encouraged by the founders because of his accumulated experience with ulcerative colitis. Soon thereafter, the name of the organization was changed to the National Foundation for Ileitis and Colitis.

3. Dr. Janowitz suggested that the protocol place more emphasis on Crohn's disease than on ulcerative colitis. It was already known that ulcerative colitis is premalignant, and there was some concern that immunosuppressive drugs might provoke an earlier onset of neoplasia. It was not yet known that Crohn's colitis also predisposed to the development of colon cancer. Also, we knew that a colectomy "cured" ulcerative colitis, but Crohn's disease recurred in most patients after surgical resection.

### Crohn's Disease

In 1969, we launched a 2-year, placebo-controlled, double-blind, crossover study of 6-MP in the treatment of refractory Crohn's disease (21). Because there were no prior indices to measure the remission of Crohn's disease, we established our own for the controlled trial. These included "goals" of therapy for each case, as was done in the usual clinical management of Crohn's disease. We felt then, as we do now, that Crohn's disease has many diverse presentations and that this "goal index" was the most accurate way to interpret clinical responses in patients with chronic refractory disease. The most common goals were:

- elimination of corticosteroids
- closing of fistulas
- prevention of small bowel obstruction

Elimination of the primary bowel symptoms alone was not an objective, because steroid treatment temporarily accomplished this. Rather, symptoms had to be alleviated after stopping the steroids, which would indicate that 6-MP had been effective. It should be noted that although this study was initiated in 1969, it was until recently the only randomized controlled trial for treatment of fistulas in Crohn's disease, despite the fact that one-third of Crohn's disease patients have evidence of fistulization. Although initiated after our study was started, the National Cooperative Crohn's Disease Study (NCCDS)

was then being conducted at 14 other medical centers. In that study, the newly developed Crohn's Disease Activity Index (CDAI) was used as a measure of response to compare prednisone, sulfasalazine, azathioprine, and placebo (22, 23), and showed that azathioprine was ineffective (22). Based on the results of our own ongoing study, we and others submitted a critique of the NCCDS study, pointing out its shortcomings (24, 25). Although the results of the NCCDS study were presented at the plenary session of the annual meeting of the American Gastroenterological Association (AGA) in 1980, our own abstract was not scheduled for presentation at that time. Rather, it was scheduled for presentation one day later and at a smaller forum. At our presentation, we encouraged clinical researchers not to abandon the use of immunosuppressive drugs in this disease, and stated that physicians in private practice were capable of contributing significantly in the performance of randomized clinical trials. The basis of our concern regarding the outcome of the NCCDS study was the following:

1. The study terminated prematurely at 17 weeks, too soon for many patients to respond.
2. It eliminated azathioprine because it caused pancreatitis in a few instances. Consequently, there were insufficient entries assigned to azathioprine to reach statistical significance.
3. It withdrew steroids before starting the assigned drug or placebo, thereby enhancing the likelihood of exacerbating the underlying disease.
4. The dose of azathioprine used was relatively small.

In 1980, our own study was published and showed conclusively that 6-MP was effective in the treatment of Crohn's disease (21). The following is a list of the clearest results of the study:

1. The overall success rate was greater than 66%. Of the 39 patients who participated in each year of the 2-year crossover study in which either 6-MP or placebo was administered throughout one full year, the outcomes were significant ( $p < 0.0001$ ) (Table 1).
2. Thirty-three (33) patients completed only one year (refusing to cross over) and therefore received only one drug, either 6-MP or placebo; for the 19 receiving 6-MP, the rate of

**TABLE 1**  
*Results in 39 Crossover Patients*

Treatment	Number of patients	
	Improved*	Not improved
6-MP	26/39	13/39
Placebo	3/39	36/39

\*Whereas 67% of the patients improved with 6-MP, only 8% improved with placebo. The difference is 59% with 95% confidence limits of 32 to 86% ( $p < 0.0001$ ).

improvement was 79% as compared with 20% of the 14 patients treated with placebo ( $p < 0.05$ ) (Table 2).

- To determine whether the outcome of the first year of trial influenced the outcome of the second year, a separate analysis was performed for 36 patients. There was a highly significant difference for the patients receiving 6-MP, with improvement in 67% vs. 14% of patients treated with placebo ( $p < 0.0001$ ) (Table 3).
- In the study, steroids were completely eliminated in 55% of the patients, or the dose of steroids could be reduced by 20%.
- The healing of fistulas was accomplished. Closure of fistulas occurred in 24% compared with placebo closure of 6%.
- The study confirmed that the drug was slow acting (mean response time of 3.1 months) and in many instances, patients required con-

**TABLE 2**  
*Results in 33 Noncrossover Patients*

Treatment	Number of patients	
	Improved*	Not improved
6-MP	15/19	4/19
Placebo	4/14	10/14

\*Whereas 79% of the patients improved with 6-MP, only 29% improved with placebo. The difference is 50% with 95% confidence limits of 20 to 80% ( $p < 0.05$ ).

**TABLE 3**  
*Combined Results during First Year*

Treatment	Number of patients	
	Improved*	Not improved
6-MP	26/36	10/36
Placebo	5/36	31/36

\*Whereas 72% of patients improved with 6-MP, only 14% improved with placebo. The difference is 58% with 95% confidence limits of 40 to 77% ( $p < 0.001$ ).

tinuation of steroids. Almost 20% of patients who would ultimately respond had not done so at 17 weeks, the time at which the NCCDS already had been completed.

- Drug toxicity was modest and there was no early mortality.

Expanded data on fistulas of different sites followed (26). 6-MP seemed to close fistulas in one-third of the patients and it meaningfully reduced discharge from fistulas in another third, with a mean response time of 3.5 months. 6-MP (and azathioprine) proved to be the first drug to have this influence on fistulas in Crohn's disease, with the sole exception of metronidazole, which had a favorable effect only on perirectal fistulas. There has never been a controlled-trial confirmation of the efficacy of metronidazole on fistulas; in our clinical experience, many patients relapse after prolonged use of this antibiotic. Many also develop peripheral neuropathy. Abdominal wall fistulas improved or closed in 10 of 12 cases (83%), rectovaginal fistulas in 4 of 6 (67%), and enteroenteric fistulas in 5 of 7 (71%). Patients with perirectal abscesses and fistulas sometimes had diversionary operations, such as a colostomy or ileostomy. The results in many cases were disastrous, with recurrent Crohn's colitis in the stoma, diversion colitis in the rectum, and persistence of perirectal sepsis. A modified Parks' operation combined with 6-MP eradicated many perirectal abscesses and fistulas in those patients with recurrence after an incision and drainage procedure (27).

Our early observations noted that the use of immunosuppressive drugs was apparently more effective in the treatment of Crohn's disease when the colon (ileocolitis or colitis) and small bowels were both involved, rather than the small bowel alone. O'Donoghue et al. (28) had shown that the one-year remission, once established, was maintained by azathioprine in 95% of the patients compared with 59% on placebo. Early observations after completion of our own controlled trial showed maintenance of remission in 19 out of 20 patients (95%) after a mean of 37 months on 6-MP. After stopping 6-MP therapy, 81% of the 32 patients who had been studied relapsed after a mean interval of 6 months. When 6-MP was reintroduced in 16 of these patients after relapse, improvement was noted within a mean response time of 1.5 months, considerably more rapidly than had been the case for their first response (29).

Subsequently BIK and his colleagues at Lenox Hill reported a long-term experience with

6-MP in the treatment of Crohn's disease (30). Again, therapeutic goals were established for each of the 148 patients, and an index of Crohn's disease activity was calculated both before and after therapy. The goals, as defined previously, were achieved in 68% of cases. Major successes included elimination of steroids (66%;  $p < 0.001$ ) and healing of internal fistulas and abscesses, with elimination or reduction in drainage and tenderness (64%;  $p < 0.05$ ). Moreover, healing or marked improvement was noted in all cases of Crohn's disease involving the stomach and duodenum. Elective surgical resection was made much easier, if and when it had to be performed after 6-MP therapy, because the margins separating normal and diseased tissue were delineated much more clearly. However, prevention of recurrent small bowel obstruction and disappearance of abdominal masses were noted in only 43% and 55% of the cases, respectively.

### Ulcerative Colitis

After the early success by Bean (12, 13) in the treatment of ulcerative colitis with 6-MP, uncontrolled trials of immunosuppressives in ulcerative colitis reported response rates of 70–80%. There was less enthusiasm for initiating controlled trials in ulcerative colitis than in Crohn's disease, due in part both to the risk of carcinoma of the colon and the knowledge that ulcerative colitis could be "cured" by colectomy. Furthermore, those who did undertake controlled trials of ulcerative colitis reported disappointing results, with one exception. In that study, it was noted that azathioprine permitted a significant reduction in steroid dosage (31).

Present et al. first reported, in an abstract in 1988 (*Gastroenterology* 1988; 94:A359), a good-to-excellent response to 6-MP in 25 patients (73%). The mean time to the response was 2.3 months. A subsequent report from Mount Sinai in 1996 (32) showed complete remission in 68 of 105 patients (65%) and partial remission in 25 (24%) with 12 (11%) failures. Although 6-MP was maintained, subsequent relapse was seen in 35% of the patients. In this group, steroids were required in 12% to restore remission. Fifteen (15) patients stopped 6-MP electively and 13 relapsed after a median interval of 14 months. Thus, it was recognized that maintenance 6-MP was important after patients had responded favorably.

Adler and Korelitz (33) reported the results of 87 patients refractory to steroids who had been treated with 6-MP. In 42 patients (48%), steroids could be eliminated, with good control of symp-

toms after a mean treatment period of 2.5 months. The mean steroid-free period while on 6-MP was 10.9 months. Eleven cases (13%) demonstrated an intermediate but significant reduction in steroid usage.

Hawthorne et al. (34) reported the results of a randomized, 1-year, controlled-withdrawal study of azathioprine vs. placebo involving 67 patients with ulcerative colitis who had been taking azathioprine for 6 months or longer. In the 2-year interval, 59% of those switched to placebo relapsed, in contrast to 36% of those maintained on azathioprine ( $p = 0.04$ ).

Despite the lack of controlled trials, it has been our experience that 6-MP has proven to be both safe and effective in treating severe chronic ulcerative colitis. We have been able to avoid urgent surgery in more than 75% of cases. In many cases, surgery had been recommended without making the patient aware of the efficacy of 6-MP. Perhaps to some physicians and surgeons, this is justified by the advent of the ileal pouch-anal anastomosis. This position, however, has been compromised by the lack of universal and consistent success with this procedure (mean technical failure rate of 6%) and the inability to predict which patients will do well and which patients will exchange one affliction for another (chronic pouchitis in 6–8%) (35–37).

### Toxicity of Immunosuppressive Agents

#### Historical Aspects

Experience with 6-MP and azathioprine has shown that bone marrow suppression can occur and is dose related. Both leukopenia and thrombocytopenia have been reported. Hepatotoxicity is seen less frequently.

6-MP and azathioprine can cause chromosomal aberrations in animals and humans, but these are reversible in humans. The drugs are carcinogenic in animals at the dosages used and therefore may theoretically increase the risk of neoplasia in humans. Again, the risk has been greater in transplant cases than in autoimmune disorders such as rheumatoid arthritis, perhaps because of the higher doses used.

Allopurinol, used to lower blood uric acid, may retard the catabolism of 6-MP and accentuate its toxicity. When the two drugs are used concurrently, the initial dose of 6-MP should be reduced by at least one third.

Toxicity to 6-MP in IBD has been compiled for 396 patients seen by the authors in their pri-

vate practices (38). Four types of toxicity directly attributable to 6-MP have been identified. These are pancreatitis, bone marrow depression, idiosyncratic and/or hypersensitivity reactions, and drug-induced hepatitis.

Data on all toxicity to 6-MP has been updated since the earlier report, providing a larger number of IBD patients followed for longer periods of time with similar outcomes (39).

**Pancreatitis.** Pancreatitis after 6-MP was observed in 12 of 396 (3%) patients with Crohn's disease and one with ulcerative colitis (40). The peak incidence was 21 days after starting the drug, and all but one case occurred within 32 days. Clinically, each case was mild, with symptoms of abdominal pain, nausea, vomiting, and elevation of serum amylase, all resolving quickly upon discontinuation of the drug. No hemorrhagic pancreatitis, hypocalcemia, pancreatic abscess, or pseudocyst formation was observed. Seven patients were later rechallenged with 6-MP or azathioprine, and in each, the symptoms recurred rapidly. Clinically, the pancreatitis behaved like a sensitivity reaction, but attempts at desensitization were unsuccessful. Therefore, a single bout of 6-MP pancreatitis is considered a contraindication for future use, but a trial using small doses of azathioprine may be clinically warranted.

**Bone Marrow Depression.** In 2% of patients, bone marrow suppression sufficient to necessitate hospitalization occurred during the early years, before experience was gained in blood count monitoring and individual dosage adjustment (38). In these 8 patients, the lowest white blood count ranged from 300–2500/mm<sup>3</sup>. Fever was present in 7, and blood cultures were positive in 3. Major septic complications were seen in one patient, but there were no deaths. Characteristically, the bone marrow depression was usually followed by prolonged remission of Crohn's disease or ulcerative colitis. This observation has also been noted by others in relation to ulcerative colitis (41). Leukopenia was noted in most patients at some time. White blood counts above 3500/mm<sup>3</sup> were rarely associated with clinical problems and were managed by temporarily stopping the 6-MP and then resuming it at a lower dosage.

Subsequently, Connell et al. (42) reported the experience from St. Mark's Hospital, London in 739 patients with IBD treated with azathioprine. Only 9 (1.2%) developed severe leukopenia (white blood cell count < 2000/mm<sup>3</sup>); 5 of the 9 patients had complications which resulted in 2 deaths. Neither of the deaths was pre-

dictable, based on monitoring of the white blood cell count. Our own experience suggests that current methods of monitoring are adequate and that this severe complication is rare and may be modified by the availability of the colony-stimulating factor.

#### **Idiosyncratic/Hypersensitivity Reactions.**

In addition to pancreatitis, other allergic type reactions occurred within the first 3 weeks of treatment with 6-MP in 2% of patients: drug fever was seen in 8, skin rash in 2, arthralgia in one, and abdominal pain with normal serum amylase in one. We have also seen severe muscle pain soon after initiating treatment with 6-MP. Rechallenging with 6-MP or azathioprine produced similar reactions. Nevertheless, desensitization with gradually increasing doses has often allowed reinstatement of a drug without recurring adverse reaction (43). Whether these reactions are idiosyncratic or represent an allergic phenomenon is unknown, because no definitive immunologic hypersensitivity mechanism has been defined.

Recent data confirm the proportion, nature and outcome of allergic reactions to 6-MP, including the usual failure of desensitization to tiny doses, but occasional success with crossover to AZA (44).

**Drug-Induced Hepatitis.** Eleven patients in this study developed a type of hepatitis (38), but in only one patient could it clearly be attributed to 6-MP. For this patient, who had severe ulcerative colitis that had remitted, results of liver function tests returned to normal after the drug was discontinued. These same tests became abnormal again after rechallenge. This is the only allergic-type form of toxicity that seems to occur late in the course in most cases. Hepatitis is also unique in that rechallenge is often tolerated. The only instance of immediate toxicity occurred at a later date in a patient whose 6-MP was initiated at 3 mg/kg of body weight. Recent studies have shown that abnormal liver function tests are often associated with high levels of 6-MP, which return to normal when doses are lowered.

#### **Infections**

Almost every type of infection reported in patients with IBD treated with 6-MP has also been reported in patients not treated with immunosuppressive drugs. This is especially true of patients with Crohn's disease, in which infectious complications are frequent.

All our patients receiving 6-MP who developed fever were instructed to discontinue the drug

regardless of whether we thought the fever was related to the underlying bowel disease, the drug, or an incidental illness such as an upper respiratory tract infection or a viral infection. Two patients developed liver abscesses that required drainage.

Five patients developed pneumonia; all responded to antibiotics and cessation of 6-MP therapy. Some patients with pneumonia responded equally well to antibiotics while continuing 6-MP. Some patients reported frequent colds and upper respiratory tract infections, and elected to discontinue 6-MP. It is difficult, however, to document any increased incidence of respiratory infection.

Herpes zoster occurred in 8 patients while they were taking 6-MP. In all cases, the "shingles" took its usual course. Many years later, one patient had a recurrence of herpes zoster on his trunk when he was again taking 6-MP, and also suffered a 3-day syndrome consistent with encephalitis. There has been no residual defect during a 9-year follow-up, and the patient's ulcerative colitis has remained in remission. Subsequent experience suggests there is no advantage to stopping the 6-MP during the course of herpes zoster if it is mild. When shingles is severe, the 6-MP should be stopped and then reintroduced after a benign course is confirmed (45).

### Neoplasms

The situation in regard to neoplasms is similar to that with infections. Neoplasms occur more frequently in patients with IBD whether they have received immunosuppressive medication or not. In Crohn's disease particularly, an increased risk of extraintestinal neoplasms has been recognized (46). An appraisal of neoplastic risk was made for our patients during or after 6-MP therapy (38), and in one instance, the neoplasm was considered to be probably related to the 6-MP. This tumor was a diffuse cerebral histiocytic lymphoma in a man with Crohn's disease, who had taken 6-MP for approximately 9 months. The drug had been discontinued 11 months before the onset of headaches and the discovery of the tumor. The tumor did not respond to therapy. Two more cases of cerebral lymphoma in patients with Crohn's disease treated with azathioprine have subsequently been reported (47).

Other neoplasms occurring in patients who had earlier received 6-MP included an islet cell carcinoma of the pancreas, carcinoma of the lung in a heavy cigarette smoker, one carcinoma of the breast, and a basal cell carcinoma. One patient with

ulcerative colitis developed malignant melanoma; an excision with an axillary node dissection was curative. We have subsequently seen three patients who developed carcinoma of the breast 5, 25, and 27 years after first receiving 6-MP.

Two simultaneous carcinomas of the colon occurred in one patient with long-standing ulcerative colitis who had refused the recommendation of colectomy. In these cases, the carcinomas clearly anteceded the initiation of 6-MP. Subsequently, one additional patient with long-standing left-sided ulcerative colitis, who had received 6-MP for one year, developed a carcinoma of the rectum. Benign adenomatous polyps have been encountered on sigmoidoscopy or colonoscopy in patients receiving 6-MP; the polyps have been removed endoscopically and no recurrence has been encountered despite continuation of 6-MP.

Cancer of the colon could be a complication of particular concern, because both ulcerative colitis and Crohn's colitis are diseases prone to the development of cancer even without immunosuppressive drugs. We reviewed our own experience and counted 34 patients with cancer of the colon following ulcerative colitis, during a 20-year period; two patients had taken 6-MP and 32 had not. As for cancer of the intestinal tract complicating Crohn's disease, we identified 17 patients in whom carcinoma of the ileum or colon developed; only two had been treated with 6-MP. Although these figures are not controlled and do not include a denominator, carcinoma seems to be far more common in Crohn's disease and ulcerative colitis independent of immunosuppressive therapy than associated with it. Subsequently, Connell et al. (48), reporting their data from St. Mark's, also concluded that the incidence of colorectal cancer and death from cancer in patients with IBD who had been treated with azathioprine is not greater than in those patients who had not been so treated.

Recent data from the IBD Center at Lenox Hill Hospital confirm the earlier observations of no increase in neoplasms in patients with IBD who have been treated with 6-MP or AZA (49). Nevertheless, concern persists as to whether the onset of a neoplasm is accelerated, but there are no controlled data to answer this question. Currently one of us (BIK) is investigating the possible role of sustained leukopenia as a contributing factor.

### Nausea

Nausea is seen as a fairly common side effect during the first month of therapy. Occasionally

the dose of 6-MP has to be temporarily reduced. Rarely does the drug need to be eliminated on this basis.

### Mortality

With the single exception of the patient with cerebral lymphoma, no deaths were attributable to 6-MP. Lymphomas of the brain (50) and other lymphomas (51) also have been reported in transplant patients on immunosuppressive therapy. Although it is most likely that these tumors were caused by 6-MP, two reports (52, 53) suggest an increased incidence of lymphomas in patients with Crohn's disease who were not taking immunosuppressives.

### Considerations in Pregnancy

6-MP and azathioprine cause reversible chromosome damage in humans, but the true teratogenic effect of these drugs has not been studied in a systematic or controlled manner. On theoretical grounds, most obstetricians have advised that conception is contraindicated for both women and men receiving 6-MP. We advise chronically ill female patients with persistent bowel activity not to become pregnant. Therefore, before initiating 6-MP therapy, a female patient should have her serum tested for human chorionic gonadotropin level to eliminate the possibility of early pregnancy. All couples are instructed to practice a reliable method of birth control. The authors (BIK and DHP), however, differ with respect to the continued use of maintenance 6-MP therapy after suitable remission in patients who want to become pregnant.

When pregnancy becomes a priority, BIK recommends stopping 6-MP before discontinuing contraception. In a toxicity study (38), the authors found that 16 pregnancies had occurred. In 10 patients, 6-MP had been terminated before contraception. In the remaining 6 patients, 6-MP had been continued for 3–4 weeks before the pregnancy was recognized. In 3 of the 6 patients, as well as the 10 who stopped 6-MP earlier, the pregnancies were continued. All 13 patients delivered full term. No abnormalities have been found in any of the 13 children. Additional data reported from St. Marks support the conclusion that there is little danger to the mother or the fetus by taking azathioprine throughout pregnancy (54).

A recent extensive study of DHP's patients compared the outcomes of 240 live births from 155 patients with IBD who had either stopped 6-MP before conception, or had conceived while

taking 6-MP, and then either stopped or continued the drug throughout the pregnancy, to matched controls. There were no significant differences between the groups. It was concluded that 6-MP therapy either before conception or after conception and during pregnancy was not associated with prematurity, spontaneous abortion, congenital abnormalities, neonatal and childhood infections or neoplasia. These more recent data support the conclusion that 6-MP is safe when used during pregnancy (55).

Nevertheless, a study at Lenox Hill Hospital found that pregnant patients treated in their first trimester with 6-MP had an increased risk of spontaneous abortions, and (in 2 cases) chromosomal abnormalities (mosaicism and trisomy 22) found at amniocentesis, leading to therapeutic abortion (56). Furthermore a study of men with IBD treated with 6-MP, whose wives became pregnant, showed a significant increase in congenital anomalies in the offspring when the father was taking 6-MP during the 3 months before impregnation (57).

### Cyclosporine

The marked difference between cyclosporine and 6-MP or azathioprine in the treatment of inflammatory bowel disease is that a favorable response, when seen, is more apt to be seen earlier after administration of the former drug, usually within 1–2 weeks rather than the 3–4 months for the latter drugs. Cyclosporine acts on T rather than B lymphocytes and inhibits their proliferation. The rapid onset of action is due to inhibiting the production of interleukin-2 and the consequent release of multiple cytokines.

The first controlled trial of oral cyclosporine (using 5–7 mg/kg/day) in patients chronically ill with Crohn's disease, performed by Brynskov et al. (58), showed a statistically significant response rate of 59%, but coincidentally, a 31% response for placebo. A subsequent controlled trial failed to confirm this response in chronically active patients, although lower doses were used (59). Another controlled trial showed no difference in relapse rate with cyclosporine as compared to placebo, using low doses of cyclosporine (less than 5 mg/kg/day) (60). A new 12-month study (61) has been reported by European investigators using 5 mg/kg/day, and no major difference has been found when comparing cyclosporine plus low-dose steroids versus low-dose steroids alone.

At Mount Sinai, Present and Lichtiger used intravenous cyclosporine to treat Crohn's disease

(62). At an intravenous dose of 4 mg/kg/day for 14 days, which was then followed by oral doses of 6–8 mg/kg/day, a favorable response rate was noted in 88% of the patients. Closure of Crohn's disease fistulas occurred in 44% of these patients and improvement was noted in another 44%. Two-thirds maintained improvement in the chronic phase, and steroids could be discontinued in 75%. Hanauer and Smith (63) showed a similar response rate using this technique. Thus, oral cyclosporine seems to be less effective than intravenous cyclosporine, which may be due to malabsorption of the drug and/or the need for higher doses in inflammatory bowel disease patients with IBD.

The most promising data on cyclosporine comes from another study by Present and Lichtiger (64), who treated patients with ulcerative colitis via the intravenous route at 4 mg/kg/day for 14 days after a 7 to 10-day trial of parenteral steroids had been unsuccessful. A mean response time of 6.4 days was observed, and colectomy was avoided in 75%. A subsequent controlled trial has confirmed the efficacy of intravenous cyclosporine under these circumstances (65). Further observation has shown that oral cyclosporine has been successful for 6 months in 69% (66). This major long-term difference between the response in Crohn's disease and in ulcerative colitis might be attributed to the malabsorption so prevalent in the former and not in the latter. Also, the oral doses used in the Crohn's disease trial are far below the comparable IV dose. It is of interest that more than one-third of the patients entered into the controlled trial were referred by the surgical colleagues of Drs. Present, Gelernt and Bauer. The collegial relationship between our surgeons and gastroenterologists has encouraged many IBD advances at Mount Sinai.

Toxicity is of great concern when using cyclosporine, particularly intravenously. The foremost concern is nephrotoxicity. Fortunately, this toxicity can be minimized by carefully monitoring the blood urea nitrogen (BUN) and creatinine, keeping the cyclosporine blood level in a therapeutic range, and avoiding nonsteroidal anti-inflammatory agents and other drugs which may enhance the levels of cyclosporine and its toxicity. The risk of lymphoma and carcinoma is of concern, but in view of the doses and duration used for the treatment of IBD, cyclosporine has not been contraindicated. Other complications, such as tremors, hirsutism, gingival hyperplasia, paresthesia, headaches, and hypertension, although common, are almost always transient.

Intravenous administration of cyclosporine in the management and treatment of very sick patients with ulcerative colitis, in whom treatment with intravenous steroids has failed, is justified. The major risk in using intravenous cyclosporine when intravenous steroids have failed is waiting too long. Although the waiting period probably should be no longer than 7–12 days, some patients are already too ill to wait even that long for any hoped-for response to cyclosporine. Patients who are that ill are vulnerable to pneumonia, sepsis, and death, when they might have been saved by a timely colectomy. On the other hand, the risk of pneumocystis has been markedly reduced in some patients by the concurrent use of Bactrim (sulfamethoxazole-trimethoprim). In addition, should there be time for a trial of intravenous cyclosporine, its success will allow for introduction of the slow-acting immunosuppressive drugs 6-MP and AZA, which may then maintain remission for many years thereafter. This decision, of course, has to be based on a finely attuned clinical evaluation of the individual patient.

Although patients who respond to intravenous cyclosporine have continued with oral cyclosporine as well, the results on maintaining remission have been disappointing, presumably due to poor absorption, even with the advent of a newer preparation (Neoral) which has been shown to be better absorbed than the original drug (67). Consideration of the use of cyclosporine has been discussed by us elsewhere (67–69).

### **Anti-Tumor Necrosis Factor (anti-TNF) Alpha (Infliximab, Remicade)**

In a short-term, multicenter study (including Mount Sinai), using a chimeric monoclonal antibody to tumor necrosis factor, 65% of patients with Crohn's disease improved vs. 17% on placebo, including 33% of the patients on anti-TNF in clinical remission after a single 2-hour infusion, with a better response after a lower dose of 5 mg/kg than after 10 mg/kg and 20 mg/kg (70).

Subsequently, Present et al. (71) used 3 infusions of anti-TNF to treat Crohn's disease fistulas, and demonstrated at least 50% healing in 62% of patients but in only 26% of patients on placebo ( $p = 0.002$ ). Most recently, the results of a third multicenter study by Rutgeerts et al. (including DHP) (72) best documented the rates of relapse following the 3 infusions and recommended that the infusion be repeated every 8 weeks to maintain the remission. The reported toxicity so far

has not been greater than that seen with 6-MP and AZA, but the development of anti-chimeric antibodies and hypersensitivity reactions after later infusions have been reported. No data is thus far available regarding the long-term potential for neoplasm.

### The Present and the Future

Of all the immunosuppressive drugs now available, 6-MP and azathioprine have had the most enduring role and continue to show the most promise for the future. Despite the disadvantage of its slower onset, 6-MP has been consistently effective in two-thirds of patients with otherwise refractory Crohn's disease and those with ulcerative colitis. Azathioprine has also been effective for the same groups of patients. Because 6-MP is a metabolic byproduct of azathioprine, presumably weight-for-weight, the favorable effect of azathioprine is not as great as that of 6-MP. Nevertheless, this has never been submitted to any controlled trial. What is more important is the answer to the question as to why favorable results of treatment are consistently about two-thirds in patients with IBD. Why is it not 100%? What accounts for the other one-third? Perhaps the answer in Crohn's disease lies with the underlying pathology, particularly of the small bowel, in which repeated attacks of inflammation result in fibrosis which to date has been irreversible. After all, success with 6-MP in preventing small bowel obstruction has been consistently less than for other indications, such as elimination of steroids and closure of fistulas. A role for 6-MP in prevention of recurrence after bowel resection for Crohn's disease has now been confirmed (73), and it is now our practice to start 6-MP in the perioperative period.

Perhaps the answer lies in the role of inducing leukopenia with 6-MP or azathioprine. In retrospect, those patients who did develop leukopenia had greater success than those who did not (74). Furthermore, the successes came earlier and lasted longer, and those who did develop leukopenia had no clinical bone marrow depression. This can be attributed in part to what we have learned about careful monitoring. Our approach is to perform complete blood counts weekly for the first 3–4 weeks, and then if the white blood count does not fall and clinically there is no indication for increasing the dose of 6-MP, the time between blood counts can be extended. If, however, at any time, the symptoms recur and the white blood count permits, the dose of 6-MP should be raised. At this point, monitoring should be done weekly

for 3 weeks. Another time for particularly careful monitoring is when steroids have been reduced or are about to be eliminated. Because the steroids had served to raise the white blood count, this stimulus may be lost and the patient may be vulnerable. In all cases, the patient must call after the blood count to receive new directions as to dose and when the next count should be done. Platelets also should be counted, because thrombocytopenia is sometimes seen during 6-MP therapy.

Another question is why leukopenia develops so easily in one patient but not in another. Although some patients tolerate as much as 200 mg a day without apparent effect on the white blood count, others tolerate only tiny doses such as 12.5 mg per week, or even less. This has been attributed to the absence or low levels of the enzyme thiopurine methyltransferase, which results in loss of catalytic activity. While the resulting leukopenia may lead to a rapid clinical response of IBD, the risks of bone marrow depression and allergic complications are proportionately increased (75, 76). This has led to the measurement of 6-thioguanine metabolites in an attempt to predetermine both the efficacy of the drug and its potential toxicity (77).

When leukopenia is first recognized in these patients, they have almost improved more than those without leukopenia, but when the dose has to be reduced further and further, the value of leukopenia is replaced by loss of overall drug efficacy.

The role of anti-TNF is being clarified very rapidly. Whether repeated infusions will maintain remissions of Crohn's disease on their own, supplement the maintenance role of 6-MP or AZA (or vice versa), or serve to effect earlier remissions then better maintained by 6-MP/AZA, is yet to be determined. Furthermore it must be clarified whether the temporary remission for sick hospitalized patients with Crohn's disease is better accomplished by intravenous steroids or Remicade, since the success rate for IV steroids is 88% within 10 days (78). Data comparing long-term steroid and Remicade toxicity might play a major role in deciding which drug should be used to initiate remission.

### Other Immunosuppressive Drugs for IBD

Methotrexate has been effective for Crohn's disease, just as it has been for rheumatoid arthritis, but the toxicity profile has been greater than that of 6-MP/AZA and the maintenance less enduring. It has been reserved for patients who fail or are intolerant to 6-MP/AZA (79). Recent

studies have shown that the combination of Remicade and methotrexate is very effective in rheumatoid arthritis patients. Future studies in Crohn's disease are required to see whether Remicade plus 6-MP or azathioprine is more effective than Remicade plus methotrexate.

The role of tacrolimus (FK506) has not yet been adequately tested (80). A controlled trial is currently underway using the newly formed Crohn's and Colitis Foundation of America Clinical Alliance. Other immunosuppressive drugs, including IL-10, IL-11, mycophenolate mofetil, and ICAM-1 (an anti-sense oligonucleotide) are being tried. Thalidomide has reappeared and has proved to have anti-TNF activity; since this drug can be given orally, it has already shown promise for treating Crohn's disease (81, 82).

### Conclusion

Physicians at Mount Sinai and those who have trained there have played a major role in describing the clinical spectrum of inflammatory bowel disease. The opportunity to see and treat many of these patients has provided the experience to evaluate the many therapeutic innovations including the current use of immunosuppressive drugs. This evaluation is not yet completed, nor do we anticipate that treatments will be perfected until a better understanding of the pathogenesis of the disease has been achieved. The continuing clinical experiences at Mount Sinai and other institutions and the collaborative efforts of clinical and research scientists should help to attain the goal either of limiting the pain and suffering imposed by this disease or of eradicating it.

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