# PAPERS AND ORIGINALS

# Azathioprine in Ulcerative Colitis: An Interim Report on a Controlled Therapeutic Trial

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## Summary

**This interim report on a controlled therapeutic trial of azathioprine in ulcerative colitis deals with the first 40 patients to complete a one-year period of maintenance treatment with azathioprine or with dummy tablets. The patients all suffered from classical ulcerative colitis and were in an actual attack of the disease at the time of admission. The attack was treated with a standard corticosteroid regimen and the patients were assigned at random to maintenance treatment with real or dummy azathioprine tablets, using a stratified design. The treatment and control groups were closely similar at the beginning of the trial.**

**The effect of treatment has been assessed on the basis of the number of relapses of the disease occurring during the one-year trial period, supplemented by an assessment of the sigmoidoscopic picture and of the histological findings on serial rectal biopsy. In the patients receiving azathioprine the disease ran a more favourable course than in the control group. After the attack had been treated 11 of the 20 patients on azathioprine were symptom-free throughout the rest of the one-year trial period compared with only 5 out of 20 in the control group. The only three patients classed as failures were all in the control group. These differences just fail to reach conventional levels of statistical significance.**

**Azathioprine is not dramatically successful but may still be a useful addition to the medical treatment of ulcerative colitis, particularly if conventional medical treatment is ineffective and there are reasons for wishing to avoid radical surgery. In the dose used azathioprine was virtually free from undesirable side effects.**


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## Introduction

Since 1962 various reports have appeared suggesting that immunosuppressive drugs are beneficial in the treatment of ulcerative coltis. The drugs used have been chiefly antimetabolites, such as mercaptopurine and azathioprine, but there has been great variation in the dosage and in the length of treatment. Above all, the published reports have dealt with uncontrolled clinical trials; the variable course of ulcerative colitis makes it imperative that any new form of treatment be tested under the strict conditions of a controlled therapeutic trial.

In the present study we are testing the value of azathioprine as a maintenance treatment over the course of one year under the rigorous conditions of a "double-blind" controlled therapeutic trial. The present report deals with the results obtained in the first 40 patients admitted to the trial.

## Patients Studied

All the patients had classical ulcerative colitis. The diagnosis was made on the basis of a history of bloody diarrhoea, coupled with sigmoidoscopic evidence of diffuse inflammation, biopsy evidence of an inflammatory reaction compatible with ulcerative colitis, and changes on the barium enema of ulcerative colitis.

All patients were in a frank attack of the disease at the time they were admitted to the trial. Some were in their first attack of the disease, while others were suffering from a relapse of established disease. In every case it was explained to the patient that a new treatment was being tested and they were left free to volunteer to be included. The necessity for repeated attendances and serial sigmoidoscopic examinations with biopsy was included in the explanation. Married patients of fertile age were advised to avoid conception during the period of the trial.

## Experimental Design

A two by three stratified design was used. Patients were treated initially either as inpatients or as outpatients, depending on an overall clinical assessment of the severity of their attack. They were also subdivided according to the length of history into three categories: first attack, short history (less than five years),

and long history (more than five years). As a result of this double specification, patients fell into six cells:

| | Inpatients | Outpatients |
|---|---|---|
| First Attack | | |
| Short History | | |
| Long History | | |

Within each of these six cells patients were allotted at random to real or dummy azathioprine treatment, a system of restricted randomization being used so that each block of six patients contained three on azathioprine and three on dummy tablets. The trial treatment was prescribed as "azathioprine special," and the hospital pharmacists worked from a master sheet indicating whether a particular patient was to be given real or dummy azathioprine.

The attack which brought the patient into the trial was treated with a standard course of corticosteroids, together with other medical measures in the case of the inpatients. The regimens of cortico-steriod treatment were as follows:

*For outpatients.*—Oral prednisolone 5 mg four times a day and prednisolone disodium retention enemata nightly. If the therapeutic response was good this regimen was maintained for one month, and then tailed off over the next two weeks.

*For inpatients.*—As the attack was severe in every case treatment began with a five-day intensive course of intravenous therapy, as follows: nothing by mouth except water, intravenous control of water and electrolyte balance, prednisolone 21-phosphate 40 mg daily in the intravenous fluid, tetracycline 1 g daily in divided doses in the intravenous fluid, and rectal drip of hydrocortisone hemisuccinate sodium 100 mg twice daily. If the clinical response was good this was followed by resumption of feeding and oral prednisolone in a dose of 40 mg daily in divided doses. By the time of discharge the patients were on the outpatient regimen as detailed above and treatment was tailed off after one month from the start of treatment.

The dose of azathioprine was about 2·5 mg/kg body weight. After three months this was reduced to 1·5-2 mg/kg body weight. The dummy tablets were prescribed in an equivalent manner.

The patients were seen at a special clinic at least once a month. At each attendance the symptoms were recorded, a full blood examination was made, and sigmoidoscopy with biopsy was performed. In addition, liver function tests were performed on several occasions throughout the trial period.

The attack of ulcerative colitis which brought the patient into the trial was classified as mild, moderate, or severe by the criteria of Truelove and Witts (1955). The sigmoidoscopic appearances at each examination were graded from 0 to 3 according to the following standards: 0 = normal appearances, 1 = mild inflammation, 2 = moderate inflammation, and 3 = severe inflammation.

All the biopsy specimens were examined by one pathologist, Dr. R. Whitehead, who classified them according to the criteria of Truelove and Richards (1956) into the following categories: (1) no significant inflammation, (2) mild to moderate inflammation, and (3) severe inflammation.

During the one-year trial period some patients suffered from one or more relapses of the ulcerative colitis. A *relapse* was defined as the occurrence of diarrhoea with blood in the motions and with sigmoidoscopic evidence of inflammation. Each relapse was treated according to the regimens already outlined for the attack bringing the patients into the trial. If a patient suffered from *three* relapses during the trial period he was taken out of the trial and treated openly.

A few patients were defined as failures. These were patients who failed to go into clinical remission within six weeks of corticosteroid treatment either during the attack which brought them into the trial or in a subsequent relapse during the trial period.

## Results

### CLINICAL RESPONSE

Table I shows the overall clinical response of the treated and control groups. It will be seen that the patients on azathioprine ran a more favourable course than those on dummy tablets. Thus there were 11 of the azathioprine-treated patients who were symptom-free throughout the one-year period (after recovering from the attack which brought them into the trial) compared with only five of the patients on dummy treatment. At the other extreme, the only three failures occurred in patients on the dummy preparation.

As the number of patients is relatively small, the condensed versions of Table I are more appropriate for assessing the statistical significance of the differences between the treated and control groups. It will be seen that the differences are not significant at the conventional 0·05 level. However, the differences may represent a genuine superiority of azathioprine over dummy treatment; if so, the treatment of a larger number will show this. At present the clinical results with azathioprine can be judged to be encouraging but not definitely proved.

TABLE I—*Azathioprine in Ulcerative Colitis. Detailed clinical results*

| No. of Relapses during One-year Trial Period | Azathioprine Group | | | | | | | Dummy Treatment Group | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | First Attack | | Short History | | Long History | | Total | First Attack | | Short History | | Long History | | Total |
| | I.P. | O.P. | I.P. | O.P. | I.P. | O.P. | | I.P. | O.P. | I.P. | O.P. | I.P. | O.P. | |
| 0 | 2 | 4 | | 1 | | 4 | 11 | 1 | 3 | | | | 1 | 5 |
| 1 | | 1 | | 1 | | 1 | 3 | | 3 | | 2 | | 1 | 6 |
| 2 | | | | | | | 0 | | | | | | 1 | 1 |
| 3 | 2 | 1 | | 2 | | 1 | 6 | 1 | | | 2 | | 2 | 5 |
| Failure | | | | | | | 0 | 1 | | 1 | 1 | | | 3 |
| Total | 4 | 6 | 0 | 4 | 0 | 6 | 20 | 3 | 6 | 1 | 5 | 0 | 5 | 20 |

I.P. = Inpatient. O.P. = Outpatient.

| | Condensed Form I | | | | Condensed Form II | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Azathioprine | Dummy | Total | Statistical Significance of Differences | Relapses | Azathioprine | Dummy | Total | Statistical Significance of Differences |
| No relapse | 11 | 5 | 16 | $\chi^2$ test not appropriate | 0 | 11 | 5 | 16 | $\chi^2 = 4{\cdot}136$ n = 2 |
| One or more relapses | 9 | 12 | 21 | By Fisher's exact test | 1-2 | 3 | 7 | 10 | $0{\cdot}2 > P > 0{\cdot}1$ |
| Failed | 0 | 3 | 3 | P = 0·058 | 3 or failed | 6 | 8 | 14 | By Fisher's exact test P = 0·151 |
| Total | 20 | 20 | 40 | | Total | 20 | 20 | 40 | |

SIGMOIDOSCOPIC RESPONSE

The sigmoidoscopic findings are in the same direction as the clinical responses. The mean sigmoidoscopic scores registered by the patients on azathioprine and dummy treatment respectively are shown in Fig. 1, using the quantitative assessment described above. Each patient was sigmoidoscoped regularly throughout the trial and each dot represents 10 times the mean value for a given patient. The sigmoidoscopic advantage enjoyed by the azathioprine group is evident.

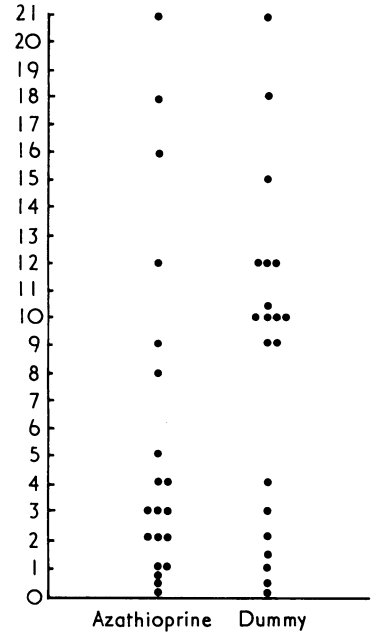


FIG. 1—Comparison of the sigmoidoscopic scores in the treatment and control groups.

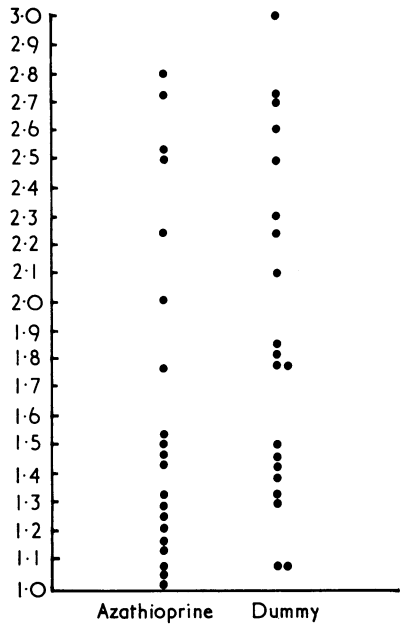


FIG. 2—Comparison of the histological scores in the treatment and control groups.

Another way of comparing the sigmoidoscopic responses in the two treatment groups is to take the proportion of sigmoidoscopic examinations which showed normal appearances. With this criterion the patients on azathioprine were normal sigmoidoscopically at 50% of their examinations whereas the patients on dummy treatment were normal at only 30% of their examinations.

HISTOLOGICAL RESPONSE

The mean histological scores for the two groups, calculated in a similar manner to the sigmoidoscopic scores, are shown in Fig. 2. The differences between the two groups are small but there were more patients who had low scores in the azathioprine group than in the control group. In addition, the rectal biopsy specimens of the azathioprine-treated group showed no significant inflammation on 52% of occasions compared with only 39% for the control group.

TABLE II—*Clinical Grading at the Beginning of Treatment*

| | Azathioprine | Dummy | Total |
|---|---|---|---|
| Mild .. .. .. | 8 | 10 | 18 |
| Moderate .. .. | 11 | 8 | 19 |
| Severe .. .. .. | 1 | 2 | 3 |
| Total .. .. .. | 20 | 20 | 40 |

COMPARABILITY OF TREATED AND CONTROL GROUPS

The most important single factor determining the outcome in ulcerative colitis is the clinical severity of the attack when the patient begins treatment. The treated and control groups were closely similar in terms of clinical grading (Table II). Likewise, the two treatment groups were closely similar in respect of the sigmoidoscopic and histological appearances on entry into the trial (details not shown).

The age composition was similar for the two groups, the mean ages being 43·6 years for the azathioprine group and 43·7 years for the control group. The azathioprine group contained a relative excess of men when compared with the control group, but as studies of prognosis have shown no major difference between the two sexes this seems to be of no consequence.

In effect, the two treatment groups were closely similar and any difference in the clinical course can be regarded as attributable to the effects of therapy and not to any bias due to lack of similarity between the groups.

SIDE EFFECTS

The serial haematological observations yielded no examples of frank marrow depression. Two patients developed rather low white blood counts of 3,300 and 3,700/mm$^3$ respectively and the azathioprine special was temporarily prescribed in a reduced dose. In the event, when the code was broken one of these was on real azathioprine and the other on dummy tablets.

One patient developed nausea, abdominal discomfort, and diarrhoea after having been in the trial for four weeks, though the ulcerative colitis was in remission. The azathioprine special was stopped and there was rapid relief from the symptoms. Resumption of the azathioprine special was followed by a recurrence of the same symptoms, once again with relief when the azathioprine special tablets were stopped. When the code was broken he proved to have been on real azathioprine. The blood count remained normal throughout these episodes and the tests of liver function were also normal.

Two patients complained of excessive loss of head hair during the trial period, but in the event both had been treated with dummy tablets.

TABLE III—*Reported Experience of Antimetabolites in Treatment of Ulcerative Colitis*

| | No. of Patients | Drug | Length of Treatment | Marrow Depression | Results |
|---|---|---|---|---|---|
| Winkleman and Brown (1965) | 14 | Nitrogen mustard | Weeks | Common | Satisfactory in 11 |
| Bean (1966) | 7 | Busulphan. Mercaptopurine. 6-Thioguanine | Months | Common | Remission in 7 |
| Caprilli *et al.* (1966) | 7 | Azathioprine | Months | Negligible | Remission in 4. Improvement in 2 |
| Bowen *et al.* (1966) | 10 | Azathioprine | Months | Common | Improvement in 8 |
| Mackay *et al.* (1966) | 7 | Mercaptopurine. Azathioprine | Months | Negligible | Improvement in 6 |
| Lal *et al.* (1967) | 16 | Mercaptopurine | Weeks-months | Negligible | Remission in 14 |
| Theodor *et al.* (1968) | 7 | Azathioprine | Weeks-months | Negligible | Remission in 4 |
| Arden Jones (1969) | 10 | Azathioprine | Weeks-months | Common | Remission in 9 |

In effect, during the part of the trial now being reported there was only one patient out of 20 on real azathioprine who suffered from an undesirable side effect of therapy—namely, gastrointestinal disturbance.

## Discussion

Although we have planned to include 80 patients in this controlled therapeutic trial, it seemed worth while to break the code for the first 40 patients who had completed their one-year course of treatment. It will be another two years before the trial is finally completed, and in the meantime it is helpful to have some notion of the efficacy, if any, of azathioprine therapy. This is particularly so because no other controlled therapeutic trial has been published and azathioprine is being used more frequently in ulcerative colitis without any firm evidence to justify its use. The main reports which have been published are summarized in Table III; it will be seen that marrow depression has been a common feature in some centres, but in general this seems to be related to the use of high doses of the immunosuppressive drug.

The present interim results suggest that azathioprine is of some benefit in ulcerative colitis although the effect is far from being dramatic. If the present results are maintained with bigger numbers, the benefits of azathioprine will be established. In the meantime, it seems to be worth considering the use of azathioprine when conventional medical treatment is not proving successful and when there are reasons for being reluctant to resort to radical surgery.

If azathioprine is used in such circumstances the dangers of this form of treatment must be kept in mind. The chief short-term danger is of marrow depression with associated risk of overwhelming infection; however, in the dosage which we have used, this risk seems to be small. Nevertheless, strict clinical supervision with repeated haematological examination is an essential prerequisite for embarking on this form of therapy.

In addition to these short-term risks animal experiments suggest that there may be a long-term risk of neoplasia associated with immunosuppressive therapy (Doell *et al.*, 1967; Casey, 1968a, 1968b). In man some examples of neoplasia have occurred after renal transplantation, in which immunosuppressive therapy is an integral part of the procedure (Karnofsky, 1967; Schneck and Penn, 1971). At present it is totally unknown whether such a risk applies to other patients treated with immunosuppressive drugs, but even the possibility of it implies that azathioprine and other immunosuppressive drugs should not be used in a light-hearted way.

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