

# Controlled trial of sulphasalazine in the treatment of ulcerative colitis

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**EDITORIAL SYNOPSIS** This paper provides further evidence that sulphasalazine is an effective agent in the treatment of mild or moderate colitis. There was a high incidence of gastrointestinal side-effects and one patient developed haemolytic anaemia.

Sulphasalazine (salicylazosulphapyridine, Salazopyrin, Asulfidine) was first used by Svartz (1942) in the treatment of rheumatoid arthritis. Later, patients with arthritis associated with ulcerative colitis were treated with sulphasalazine with clinical improvement of both conditions (Svartz, 1948). The drug has since been used extensively in Scandinavia and in America in the treatment of ulcerative colitis, and many reports have indicated favourable results, some three-quarters of the patients showing improvement in most series (Bargen, 1949, 1956; Moertel and Bargen, 1959; Morrison, 1952; Svartz, 1954, 1960). However, at the time the present investigation was started in 1959 no controlled studies had been reported.

Lennard-Jones, Longmore, Newell, Wilson, and Avery Jones (1960) report the result of two consecutive trials. In the first prednisone was compared with an inert tablet and found to be effective in cases of left-sided colitis. Prednisone was then used as a standard with which to compare sulphasalazine and hydrocortisone hemisuccinate retention enemata. There was no doubt about the effectiveness of prednisone as compared with that of an inert tablet. The authors considered that sulphasalazine probably brought about remission almost as frequently as prednisone, although more slowly. Under the conditions of their trial, however, a statistically significant result for the effectiveness of sulphasalazine was not obtained. The dosage of sulphasalazine used was 4 g. daily and the patients were assessed at the end of a three-week period. Truelove, Watkinson, and Draper (1962) compared combined oral and topical corticosteroid therapy with sulphasalazine over a 14-day period using the sequential method of analysis. The combined

corticosteroid therapy, given as a dose of prednisone, 20 mg. a day, and hydrocortisone hemisuccinate 100 mg. by retention enema, was shown to be significantly more effective in the 14-day period of the trial than sulphasalazine. The latter was given in a dose of 8 g. a day for the first week and 4 g. a day for the second. At the end of the two-week period 78% of the patients on combined corticosteroids had shown sigmoidoscopic improvement as opposed to 43% on sulphasalazine. As emphasized by the authors, their trial shows only that combined corticosteroid treatment is better than sulphasalazine for rapidly checking an attack of the disease.

The only formal double-blind trial comparing sulphasalazine with a placebo, which has been reported, was carried out by Baron, Connell, Lennard-Jones, and Avery Jones (1962). They tested in addition a new drug, salicylazosulphadimidine, but this was abandoned after a short time as being obviously ineffective, and the trial continued only between sulphasalazine and an inert tablet. A statistically significant result was found in favour of sulphasalazine over a three-week period. The dosage used was 4 g. a day for the first week and 2 g. a day for the next two weeks. The patients all had mild active ulcerative colitis with little or no systemic upset and were fit to be treated as out-patients.

## PRESENT INVESTIGATION

The present investigation comprised a double-blind trial of sulphasalazine against an inert tablet in cases of ulcerative colitis or proctitis in which the disease was of mild or moderate activity at the time. The trial was carried out by considering pairs of patients, one of whom was treated with sulphasalazine and the other given a dummy control treatment, and noting which patient responded most favourably over a four-week period. The

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trial continued until a significant result was reached, sequential methods of analysis being used.

No patient with severe disease or with appreciable systemic upset was included, as clearly it would have been unjustifiable to withhold corticosteroid therapy from such cases. All the patients were fit enough to be treated as out-patients during the period of the trial, and, to avoid introducing additional factors, only out-patients were included. The patients were either in an initial attack, in relapse after a remission, or were chronic cases in an exacerbation. None had received sulphasalazine, corticosteroids, or adrenocorticotrophin during the preceding three months. In the great majority of cases the disease was limited to the left side or distal colon although a few had total colitis. A limiting factor in obtaining patients suitable for inclusion, many of whom were drawn from rural areas, was their difficulty in attending weekly or fortnightly during the trial period.

Each case was assessed on clinical and sigmoidoscopic criteria. The clinical state, number and consistency of the stools, the presence of blood, pus, or mucus, and the result of a full blood count and sedimentation rate were noted on a form. The findings on sigmoidoscopy were then recorded, the appearance being classified into five grades, as follows:—

O = normal mucosa

I = faintly granular, pink mucosa without visible vessels, of quiescent colitis

II = granular, reddened, oedematous and somewhat friable mucosa

III = very reddened oedematous and very friable mucosa, usually with actual ulceration, pus and blood often being present

IV = flaming red mucosa of a fulminating case

#### ALLOCATION OF TREATMENTS

Allocation of active and dummy tablets was done by the hospital pharmacist without the knowledge of the doctor in charge of the case. Treatments were allocated strictly at random using random sampling numbers, and, for the purpose of assessing the trial, treated and control patients were subsequently paired at random with the restriction that colitis cases were paired with colitis cases and proctitis with proctitis.

#### DOSAGE

The optimal dosage of sulphasalazine is uncertain, but dosages varying from 4 to 12 g. daily have been suggested. In this trial an arbitrary daily dosage depending on body weight was given. Patients up to 9 stone received eight half-gram tablets per day in divided doses, patients weighing from 9 to 10 stone received nine tablets, 10 to 11 stone, 10 tablets, 11 to 12 stone, 11 tablets, and patients over 12 stone received 12 tablets per day in divided doses. The daily dosage thus varied from 4 to 6 g. of sulphasalazine.

The dummy tablets were specially prepared by the manufacturer to have a similar appearance to the active tablet and were in all respects identical except that they did not have the same bitter taste.

#### PROCEDURE

After the initial assessment the patients usually attended weekly, sometimes every second week, when data regarding the clinical symptoms and stools were recorded and a repeat blood count and sedimentation rate were evaluated. A blood film was also examined for Heinz bodies in view of the report of Spriggs, Smith, Griffith, and Truelove (1958) of Heinz body anaemia occurring during sulphasalazine therapy. A four-week trial period was decided on, as previous experience had suggested that response to sulphasalazine was often slow.

At the end of four weeks, each patient was assessed clinically, sigmoidoscopy was carried out, and an overall assessment made. The clinical state, sigmoidoscopic appearance, and overall state were in each case assessed as being worse, unchanged, improved, or much improved since the start of the trial. In the case of clinical state, 'improved' or 'much improved' was based on improvement in the patient's feeling of well-being, decrease in the frequency of the stools and a return towards normal of their consistency, and decrease or disappearance in the amount of pus, mucus, and blood in the stools. Whether the patient was classified as 'unchanged', 'improved', or 'much improved' must clearly be to some extent a subjective judgment on the part of the patient and on the part of the observer, the only factual data being the alteration in the stools. The sigmoidoscopic appearances at the end of the month were assessed as 'worse', 'unchanged', 'improved', if they were one grade better, or 'much improved' if they were two grades better, which in some instances was equivalent to a return to normal. The placing of cases in a sigmoidoscopic grade is clearly to an appreciable extent a subjective process and open to observer error (Baron, Connell, and Lennard-Jones, 1964), but normally two observers were present at each examination and formed independent opinions of the grade before disclosing their view to the other.

After the response had been assessed, the nature of the tablets with which the patient had been treated was then ascertained from the pharmacy. Patients on active treatment who had responded continued to receive sulphasalazine in gradually reducing doses. Any patients in the control group, *i.e.*, taking inert tablets, who were still having symptoms were then changed over to active tablets for a month, the same data being recorded. These patients were assessed again at the end of this further four-week period. This month on active treatment, following a month on dummy tablets, is not included in the trial and the results are noted separately.

#### STATISTICAL METHOD

The chance that the patient of a pair receiving the active treatment shows more overall improvement than the patient receiving the dummy treatment can be denoted by  $\theta$ . It was anticipated that about one third of the patients receiving the placebo would show some improvement after four weeks, and it was felt that sulphasalazine would be of little clinical interest unless at least 60% of the patients showed some improvement after four weeks. Accordingly, a paired sequential trial was planned along

the lines described by Armitage (1960) to test the null hypothesis that  $\theta = 0.5$ , *i.e.*, that sulphasalazine has no effect, against the alternative hypothesis that  $\theta = 0.75$ , which corresponds to 60% of patients responding to sulphasalazine and one third of the patients responding to control.

This formulation presupposes only two classes of results, 'responded' and 'did not respond', but when assessing the overall response three grades were used; the classification 'worse' was never used. It may, however be shown that for the type of results we were interested in detecting, the formulation of the trial is unaltered by assessing response as no change, improved, or much improved.

As the overall assessments of response fell into one of three categories, it was not surprising that in several cases both patients of a pair were assessed the same and so contributed nothing to the analysis. Suitable patients were scarce and progress was slow. We therefore attempted to make better use of the data collected. For this reason, from records of hospital in-patients suffering from colitis, a scoring system, based on the change in sigmoidoscopy gradings and changes in the number of stools per day, was developed to measure improvement. The chance of two patients having the same score on this system is extremely small. Details of how this response score was constructed may be found elsewhere (Carpenter, Petrie, and Dalton, 1964).

The above hypothesis, formulated in terms of  $\theta$ , can be reformulated in terms of the difference,  $d$ , between the response scores of the two patients of a pair, and tested by means of a sequential *t* test (Davies, 1956).

## RESULTS

**CLINICAL OBSERVATIONS** As early results were not expected, the trial was left to proceed for some time before the results were examined. At this stage, the results merely indicated that the trial should continue. The trial then proceeded for another six months when it was decided to call a temporary halt and develop the scoring system. By this time 44 patients had entered the trial, 30 suffering from colitis and 14 from proctitis. Three of the colitis patients who had been treated with sulphasalazine had to be excluded from the analysis as the tablets were discontinued after a short time. Two stopped taking the tablets after a few days because of vomiting while the third discontinued treatment after a fortnight saying she was cured. Of the remaining 41 patients, 18 (10 with colitis and eight with proctitis) were treated with sulphasalazine, and 23 (17 with colitis and six with proctitis) were treated with the dummy control tablets.

Table I shows how the severity of disease differed between the treated and control groups and gives the mean duration of disease for these groups. In neither case is the difference statistically significant, and so it appears that the random allocation of

TABLE I  
SEVERITY OF DISEASE AND MEAN DURATION OF DISEASE IN TREATED AND CONTROL GROUPS

Patients	Severity			Mean Duration of Disease (mth.)
	Mild	Moderate	Total	
Treated	4	14	18	49.4
Control	10	13	23	60.1
Total	14	27	41	55.4

$\chi^2$  (with 1 degree of freedom) = 2.03  
not significant ( $P > 0.1$ )

$t_{99} = 0.58$  not significant ( $P > 0.25$ )

active and inert treatment satisfactorily balanced the two groups with respect to these factors.

All the 23 patients who were started on dummy tablets completed the first period of a month. Of these, 19 were subsequently started on sulphasalazine, four being excluded for diverse reasons. One had recovered on dummy tablets. In one, further treatment was discontinued because Crohn's disease of the rectum was incorrectly suspected. A third was started on prednisone largely because of a rheumatoid-like arthritis thought not to be associated with the colitis, while the fourth patient felt he was sufficiently recovered not to wish to continue attending from a long distance at intervals for supervision. Nineteen cases thus started treatment. In two it had to be discontinued after seven and 14 days respectively because of nausea and vomiting, while in a third patient the drug was stopped after three weeks because of the development of a haemolytic anaemia. In a further three patients detail was not complete, mainly owing to difficulties in attendance, but two of these patients appeared to have improved on sulphasalazine, one considerably.

Thirteen patients were thus left who completed the four-week period on sulphasalazine after a previous four-week period on dummy tablets.

Table II shows the various combinations of changes in overall state, clinical state, and sigmoidoscopic appearance, both for the 18 treated and 23 control patients and also for the 13 patients who were subsequently given a month's treatment with sulphasalazine after a month's treatment with the dummy tablets. From Table II it may be seen that nine (39%) of 23 patients receiving dummy tablets were assessed as improved or much improved compared with 14 (78%) of 18 patients on sulphasalazine in the trial. Among the controls subsequently treated with sulphasalazine 10 (77%) of 13 were improved or much improved. The trial was, however, planned and conducted sequentially and hence the statistical significance of the difference between the treatments may only be judged by a sequential test.

**RESULTS OF SEQUENTIAL ANALYSIS** Because of the restrictions regarding the formation of pairs it was

TABLE II  
COMBINATIONS OF CHANGES IN OVERALL STATE, CLINICAL STATE, AND SIGMOIDOSCOPIC APPEARANCE FOR TREATED AND CONTROL PATIENTS AND FOR 13 CONTROL PATIENTS SUBSEQUENTLY TREATED WITH SULPHASALAZINE

Combination of Response			Number of Patients on		
Change in Overall State	Change in Clinical State	Change in Sigmoidoscopic Appearance	Sulphasalazine	Dummy	Sulphasalazine after Dummy
0	0	-1	—	1	—
0	0	0	3	11	3
0	0	1	1	—	—
0	+1	0	—	2	—
+1	0	+1	1	—	—
+1	0	+2	1	—	—
+1	+1	0	—	3	—
+1	+1	+1	5	4	7
+1	+1	+2	1	—	—
+2	0	+2	—	1	—
+2	+1	+2	—	—	2
+2	+2	+1	2	—	—
+2	+2	+2	4	1	1
Total			18	23	13
Mean change in overall assessment			1.11	0.48	1.00
Mean change in clinical state			1.00	0.48	0.85
Mean change in sigmoidoscopic appearance			1.17	0.30	1.00
1 = worse    0 = unchanged    +1 = improved    +2 = much improved					

possible to form only 16 pairs from the 41 patients. Figure 1 shows the progress of the trial, as assessed by the response score when it was developed, and shows that a decision was reached in favour of sulphasalazine after 11 pairs of patients had entered the trial. Further details are given elsewhere (Carpenter *et al.*, 1964). It should, however, be noted that had the plot of the response scores shown in Fig. 1 failed to cross either of the boundaries, the trial would have continued until a decision one way or the other had been reached.

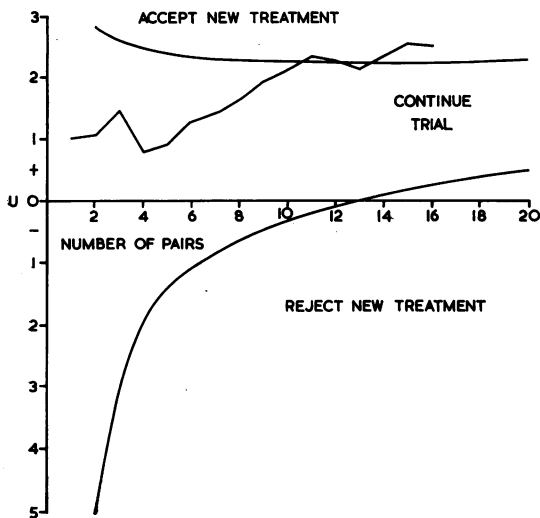


FIG. 1. The sequential progress of the trial as judged by the scores measuring response to treatment.

By making use of the response score which was developed to assess the trial, it was also possible to investigate the effect of age, sex, and type of disease on the response treatment. The patients in the trial were divided into 12 groups by classifying them according to one of three age groups, sex, and whether they had proctitis or colitis, and an analysis of variance performed on the response scores of the treated and control patients in these 12 groups. The age groups chosen for this classification were less than 30, 30 to 49, and 50+. The analysis, which is given in detail in the companion paper (Carpenter *et al.*, 1964), showed that patients both with proctitis and colitis responded similarly to both treatments, and that the response was unaffected by either the age or sex of the patients.

COMPLICATIONS The incidence of gastrointestinal symptoms was high. Nausea, vomiting, anorexia, indigestion, heartburn, or abdominal discomfort were the usual complaints. Sometimes they began immediately on taking the drug, but usually after a few days or occasionally not until a fortnight had passed. The symptoms often became less severe in a few days but in some patients persisted. Of the 21 patients who were started on sulphasalazine in the trial, eight had gastrointestinal symptoms and in two the drug had to be discontinued because of these. Of the 23 patients who were on dummy tablets initially, abdominal discomfort occurred in two while taking these tablets. One of these patients felt sick for the first fortnight on dummy tablets but took active tablets without symptoms. The other patient had epigastric discomfort for a few days on

dummy tablets and had similar symptoms when started on the active preparation. Nineteen of these 23 patients, who had taken dummy tablets for a month, were given sulphasalazine subsequently. Of these, 10 had nausea, vomiting, or heartburn, starting from one to 10 days after beginning the active preparation, and in two treatment had to be discontinued.

The only other complication seen was in a woman aged 52, who developed a haemolytic anaemia while taking the drug. After four weeks on dummy tablets without change in her active proctosigmoiditis, her haemoglobin was 11.2 g. per 100 ml. She was started on sulphasalazine, 4 g. daily, and after one week her haemoglobin had fallen to 10.5 g.%. After two weeks it was 10.1 g.% and after three weeks 9 g.%, at which time she was noticed to be slightly jaundiced but without bile in the urine. Her reticulocytes were 9% at this stage. The drug was stopped. Three days later the jaundice had cleared, her haemoglobin was 10 g.% and reticulocytes 7.1%. After a further three days her haemoglobin had risen to 10.3 g.%, and her reticulocytes were 3.9%. Thereafter, her haemoglobin gradually returned to its usual level of 11 g.%. Her colitis remained unchanged during this period.

#### DISCUSSION

This trial has shown that sulphasalazine, in a dosage of between 4 and 6 g. daily, is more effective than dummy tablets in producing improvement in cases of mild or moderate active colitis and proctitis. It confirms the findings of Baron *et al.* (1962) and the clinical impression of many previous authors. About three-quarters of the patients appeared to derive benefit from the drug, both in the formal trial and again in those cases which were treated with sulphasalazine after an initial period on dummy tablets.

Against this benefit must be set the high incidence of gastrointestinal side-effects, 18 out of 40 patients (45%) on sulphasalazine experiencing them. Of these, four had to stop the drug. Only two out of 23 patients had similar symptoms on the inert preparation. The authors have no experience of the recently introduced enteric-coated tablets of sulphasalazine. In a further patient, treatment had to be stopped because of the development of a haemolytic anaemia. This incidence of side-effects in our patients was similar to that in previous series. Baron *et al.* (1962) noted that, although 16 out of 20 of their patients had benefited from the drug, eight had side-effects, consisting of nausea and vomiting, dizziness, or epigastric discomfort, while one patient had a generalized rash. Lennard-Jones *et al.* (1960)

reported 12 out of 20 patients with unpleasant symptoms while on the drug, and a high incidence is also noted by Truelove *et al.* (1962). Nausea, anorexia, vomiting, and indigestion are much the most commonly reported symptoms, but dizziness, rashes, and diarrhoea are occasionally noted. Svartz (1954) states that in 5% of her patients treatment had to be discontinued owing to side-effects, usually drug fever and rash. Five out of her 366 cases developed leucopenia. Morrison (1952) noted that 21% of his patients were intolerant of the drug, developing headache, nausea, dermatitis, or a secondary anaemia.

Haematological complications are the only serious ones. Spriggs *et al.* (1958) report three cases of toxic haemolytic anaemia associated with the presence of Heinz bodies due to sulphasalazine. Withdrawal of the sulphasalazine was followed by an immediate fall in the Heinz body count and cessation of the haemolytic anaemia, and they conclude that the anaemia was due to sulphasalazine intoxication. They recommend that the blood of all patients on sulphasalazine should be examined for Heinz bodies. One case in our series developed a haemolytic anaemia while on sulphasalazine which ceased as soon as the drug was stopped. No Heinz bodies were seen in this case, and although looked for routinely were not in fact seen in any patient in this series.

Thirkettle, Gough, and Read (1963) reported two patients with agranulocytosis associated with sulphasalazine therapy, both of whom died of septicaemia. They quote four previously reported cases from the literature, one of which died. They note that a preceding rash may occur and is an indication that the treatment should be stopped. In these six cases therapy had continued for variable periods of two and a half to three months, with a dosage of 3 or 4 g. daily, before symptoms associated with the agranulocytosis appeared. Leucopenia is mentioned as a complication by other writers, but agranulocytosis must be rare in view of the scarcity of the reported cases, considering how extensively the drug has been used.

The place of sulphasalazine in the treatment of ulcerative colitis and proctitis is more debatable. The rapid response produced in a high proportion of cases by steroids indicates their use in severe and moderately severe cases of colitis, save in exceptional circumstances. Mild and distal cases frequently respond to general and dietetic therapy and the use of local steroids. Sulphasalazine may be regarded as having a place in cases which do not respond in this way but are not severe enough to warrant systemic steroid therapy or in which steroids are contra-indicated. The value of sulphasalazine in combination

with systemic or local corticosteroid therapy has not been determined. The frequency of disagreeable side-effects and also the small risk of serious blood disorders limit the value of the drug.

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