OUT-PATIENT TREATMENT OF ULCERATIVE COLITIS

COMPARISON BETWEEN THREE DOSES OF ORAL PREDNISONE

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The efficacy of corticosteroids in the treatment of ulcerative colitis has been established (Truelove and Witts, 1955), but the optimum dose has been less thoroughly studied. In a comparative trial of different methods of treatment Truelove (1960) reported a remission rate of 35% in out-patients using prednisolone 20 mg. daily, and Watkinson (1961a, 1961b) observed remission in 12 out of 36 patients given the same dose of prednisone. However, using a larger dose of prednisone in two out-patient trials, a remission rate of 65% was obtained at this clinic (Lennard-Jones, Longmore, Newell, Wilson, and Avery Jones, 1960). The present study was therefore undertaken to compare the results of using 60, 40, and 20 mg. of prednisone daily as treatment for active ulcerative colitis.

Design of the Trial

The observations were made during 60 courses of treatment in 58 patients with active ulcerative colitis seen at a special out-patient clinic. Patients who entered the trial were allocated randomly to one of three treatment groups and received oral prednisone in a dose of 20, 40, or 60 mg. daily; both the patient and the doctor knew which treatment was given.

The activity of the colitis was judged by the patients' symptoms, especially bowel disturbance and rectal bleeding, and by the appearance of the colonic mucosa on sigmoidoscopy. Patients were accepted for the trial if they had already been treated for the present attack of colitis with drugs other than corticosteroids or with prednisone in a dose of less than 20 mg. daily and the treatment had proved ineffective. To be eligible for the trial a patient must have been judged suitable for treatment with any of the doses of prednisone used; those in whom corticosteroid treatment was contra-indicated were thus excluded. Patients were not included if the disease was confined to the rectum or if the colitis appeared to be improving spontaneously. Since all were treated as out-patients, the trial was necessarily limited to those whose colitis was of mild or moderate severity.

When a patient entered the trial the treatment was selected by drawing from a box a folded slip marked with the dose of prednisone to be used.

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The results were assessed at the end of one, two, three, and five weeks after starting treatment. At each visit to the clinic the patient might be seen by any one of us. The patient's statements about bowel habit, the presence or absence of bleeding or mucus in the stools, and his general sense of well-being since the last attendance at the clinic were assessed and recorded on a special form before sigmoidoscopy was performed. No inquiry about side-effects from treatment was made, and only those side-effects complained of spontaneously or noted objectively were recorded. The sigmoidoscopic appearances, assessed by the observer who had noted the symptoms and also independently by a second observer who had no knowledge of the symptoms, were graded as active, moderately active, inactive, or normal, as described by Lennard-Jones *et al.* (1960). If the two observers differed in their assessment the final grading was agreed by discussion.

The overall assessment at each visit was as follows: "remission" (no symptoms; inactive or normal mucosa); "improved," "no change," or "worse" (based on symptoms).

Prednisone was given as 5-mg. tablets to be taken in three or four equal doses spread through the day. The largest dose of prednisone, 60 mg. daily, was given for a maximum of three weeks; doses of 40 and 20 mg. daily were given for a maximum of five weeks. At each out-patient visit the blood-pressure was measured and the urine tested for sugar. Patients were withdrawn from the trial at any stage if the disease became worse or severe side-effects from treatment developed. If remission was noted at any visit the trial ended and the dose of prednisone was reduced.

Treatment Groups

Fifty-eight patients entered the trial and two of them entered the trial twice for different relapses of the disease. There were thus 60 entries to the trial, and these were divided equally between the three treatment groups, details of which are shown in Table I. It will be seen that there were more patients with a first attack of the disease, and more patients in whom previous treatment for the present relapse had failed, in the group treated with 20 mg. daily than in the other two groups, but the differences are not large. There were fewer patients with extensive involvement of the colon on *x*-ray examination in the group given 60 mg. than in the other groups.

TABLE I.—*Comparison Between Treatment Groups*

Dose of Prednisone (mg./Day)	No. of Patients	Males	Age (Mean and S.D.)	1st Attack	Relapse	Previous Failed Treatment	Involvement of Colon at Last Barium Enema*				
							Transverse Colon Downwards	Descending and Pelvic Colon	Pelvic Colon	Normal *X*-ray	No *X*-ray
60	20	9	40±14	3	17	3	1	9	8	2	—
40	20	9	43±13	1	19	5	4	4	7	3	1
20	20	12	41±14	4	16	7	4	5	10	1	—

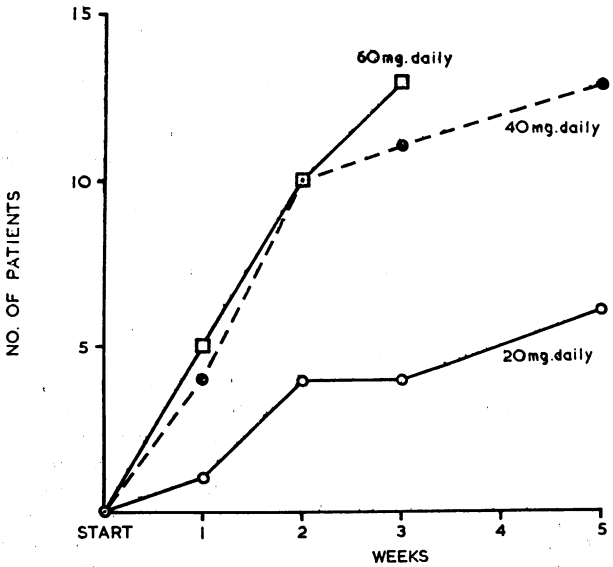
* *X*-ray examination was not ordered for the purpose of the trial.

Results

The number of patients whose disease was in remission one, two, three, and five weeks after starting treatment is shown in the Chart. By the end of treatment, at three and five weeks, remission had occurred in about two-thirds of the patients given 60 and 40 mg. of

prednisone daily but in only one-third of those given 20 mg. daily.

The results after treatment for two weeks are shown in more detail in Table II. With doses of 60 and 40 mg. daily the findings were similar: 18 out of 20 patients were improved, compared with 9 out of 20 in the group given 20 mg. daily. Conversely, two patients in each of the groups given the larger doses, but 11 of those



Number of patients whose disease was in remission at different times after starting treatment with prednisone 60, 40, and 20 mg. daily.

TABLE II.—*Results of Treatment for Two Weeks with Different Doses of Prednisone*

	Daily Dose of Prednisone		
	60 mg.	40 mg.	20 mg.
Remission	10	10	4
Improved ..	8†	8	5†
No change	2†	1	5†
Worse ..	0	1	6*
Total ..	20	20	20

* Two of these patients were withdrawn after treatment for one week because their symptoms were worse.
† One patient from each of these groups stopped treatment because of side-effects.

The results using 60 and 40 mg. daily are similar. If the results using either of these two doses are compared with the results using 20 mg. daily (combining the categories "no change" and "worse" as the numbers are small), the difference is such as might have occurred by chance less than once in 50 times. ($X^2_c=9{\cdot}48$; n=2; $0{\cdot}02>P>0{\cdot}01$.)

given 20 mg. daily, were unchanged or worse. This difference in result between each of the groups given the larger doses and the group given 20 mg. daily is unlikely to have occurred by chance ($\chi^2_c=9.48$; n=2; $0.02>P>0.01$). The disease was in remission in 10 out of 20 patients treated with the larger doses, compared with 4 out of 20 given the smallest dose.

The number of patients in remission increased between two weeks and the end of treatment (Table III). There was an increase of three in the groups given 60 and 40 mg. and of two in the group given 20 mg. The total number who had improved, however, altered little between two weeks and the end of the trial: in the group receiving 60 mg. daily there were 19 in place of 18, in the group receiving 40 mg. there were 14 in place of 18 (a decrease because of worsening symptoms in four patients), and in the group receiving 20 mg. there were nine as before. Thus of those who improved within two weeks some improved further and the disease

TABLE III.—*Results at End of Treatment. Prednisone 60 mg. Daily Was Given for a Maximum of Three Weeks, 40 and 20 mg. Daily for a Maximum of Five Weeks*

	Daily Dose of Prednisone		
	60 mg.	40 mg.	20 mg.
Remission	13	13	6
Improved ..	6†	1	3†
No change	1†	3	5†
Worse ..	0	3*	6*
Total ..	20	20	20

* Withdrawn at three weeks or earlier because their symptoms were worse.
† One patient from each of these groups stopped treatment because of side-effects.

passed into remission as treatment was continued, but the condition of some patients deteriorated despite continued treatment. Only one of the eight patients who were unchanged at two weeks benefited from continued treatment with the same dose of prednisone.

During the course of the trial nine patients were withdrawn because their symptoms became worse. The subsequent course of these patients is shown in Table IV. The dose of prednisone was increased in four of the six patients initially given 20 mg. daily, and in each case the increased dose was apparently beneficial. No improvement occurred in two of the three patients initially given 40 mg. daily when the dose was increased to 60 mg.

TABLE IV.—*Subsequent Course of Patients Withdrawn from Trial Because of Worsening Symptoms*

Case No.	Sex and Age	Trial Dose	Time Withdrawn	Subsequent Treatment	Outcome
1	M 46	20 mg.	1 week	Prednisone, 60 mg.	Remission, 2 weeks
2	F 33	,,	1 ,,	,, 60 ,,	,, 3 ,,
3	M 56	,,	2 weeks	,, 60 ,,	,, 3 ,,
4	F 19	,,	3 ,,	,, 40 ,,	Symptom-free but mucosa unchanged, 2 weeks
5*	M 54	,,	2 ,,	(1) Hydrocortisone enemas (2) Prednisone 60 mg.	No improvement Improved, 1 week
6	F 53	,,	2 ,,	Prednisone 20 mg. + Prednisolone enemas	No change, 2 weeks
7*	M 33	40 ,,	2 ,,	Prednisone, 60 mg.	No improvement, severe dyspepsia, 1 week
8	M 23	,,	3 ,,	,, 60 ,,	Deterioration over 3 weeks
9*	M 55	,,	3 ,,	(1) Hydrocortisone enemas (2) A.C.T.H.	No response, 10 days Symptom-free, 4 weeks

* Admitted to hospital after failure of treatment.

Side-effects.—The side-effects of treatment are shown in Table V. They occurred in six patients given prednisone 60 mg. daily, and in four in each of the groups given 40 and 20 mg. daily. Facial mooning occurred in three patients after two to three weeks'

TABLE V.—*Side-effects of Treatment*

Sex and Age of Patient	Dose of Prednisone	Side-effects	Weeks after Starting Treatment
F 24	60 mg.	Mooning. Acne. Weight gain	3
F 62	60 ,,	,, Oedema	2
F 37	60 ,,	,,	2
M 21	60 ,,	Acne	3
F 56	60 ,,	Hypertension*	1
F 35	60 ,,	Dyspepsia*	1
F 62	40 ,,	Mooning	5
M 37	40 ,,	Acne	2
M 50	40 ,,	Dyspepsia	2
F 63	40 ,,	,,	1
F 23	20 ,,	Mooning	5
M 54	20 ,,	Glycosuria	2
F 48	20 ,,	Dyspepsia*	1
M 45	20 ,,	,, *	1

* Stopped treatment because of side-effects.

treatment with 60 mg. daily, but occurred once only in each of the other groups and then after five weeks' treatment. The mooning was severe in only one patient and rapidly regressed when the dose of prednisone was reduced. Dyspepsia was an early side-effect and occurred in all the treatment groups: three patients stopped taking the tablets on this account.

Discussion

Our results suggest that in these mild cases of colitis treated as out-patients definite advantage is to be gained by using 60 or 40 mg. of prednisone daily rather than 20 mg. daily. There is some disadvantage in using 60 mg. daily in that side-effects may be more frequent than with the lower doses. The incidence of side-effects with 40 mg. daily was not greater than with 20 mg. daily, and in view of the therapeutic advantage 40 mg. could perhaps be regarded as the most useful of the three doses tested.

This trial was conducted openly and withdrawals from it on account of worsening symptoms could have been influenced by knowledge of the dose given: the results at two weeks are largely unaffected by this factor because only two patients had been withdrawn by this time. Differences in composition of the treatment groups could have affected the results, particularly as the groups were small. The composition differed in three ways (Table I), but analysis of the results at the end of treatment suggests that these differences were not important. Thus, of the four patients with a first attack of colitis in the 20-mg. group, one was well at the end of treatment, one was unchanged, and two were worse; of the patients who had had other treatment without success in the 20-mg. group, two were well, one was unchanged, and three were worse; all but one of the nine patients with extensive disease involving the transverse colon downwards were well at the end of treatment.

The findings reported here using prednisone 60 and 40 mg. daily are very similar to those reported in two previous trials of out-patient treatment at this clinic using similar doses (Lennard-Jones *et al.*, 1960). In this trial 4 out of 20 patients given prednisone 20-mg. daily were in remission at two weeks compared with 14 out of 40 patients reported in an out-patient trial using prednisolone in the same dose for the same time (Truelove, 1960); part of this difference may be due to slight differences in the definition of "remission." The results using 20 mg. daily for five weeks are similar to those reported by Watkinson (1961a, 1961b) using the same dose for one month. It is difficult to compare results in different published series, as factors such as the severity of the disease (Truelove and Witts, 1959) greatly affect the results.

It has been pointed out that most patients who improved during this trial began to do so within two weeks. If improvement had begun by this time, the disease might pass into remission as treatment was continued. These observations may be compared with those of MacDougall (1959), who showed in a series of 115 patients with colitis treated with corticosteroids in hospital for up to six weeks that about two-thirds of those who improved began to do so within eight days. Conversely, two-thirds of those who showed no signs of improvement by the eighth day remained resistant to treatment.

Summary

The results of treatment with three doses of oral prednisone have been studied in an open randomized trial during 60 courses of treatment for out-patients with ulcerative colitis.

Symptomatic improvement during the first two weeks of treatment occurred more often among patients given prednisone 60 or 40 mg. daily than among those given 20 mg. daily. The remission rate was apparently twice as great among patients given 60 or 40 mg. daily as among those given 20 mg. daily.

Side-effects from treatment were most frequent among patients given 60 mg. daily, and thus prednisone 40 mg. daily appears the most useful of the three doses tested.

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RECURRENT MITRAL STENOSIS

AN ANALYSIS OF FINDINGS IN 32 CASES SUBMITTED TO REOPERATION

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It is more than ten years since mitral valvotomy became the accepted treatment for the majority of patients suffering from mitral stenosis. While many difficulties have been overcome some await solution, and among these the problem of restenosis seems to us to be the most important.

This paper describes the findings at 32 repeat valvotomies for recurrent stenosis.

Material and Incidence.—One of us (K.F.) carried out 270 valvotomies during the period 1951 to end of 1961. Of 231 survivors (1 not traced) 32 (29 females, 3 males) have required reoperation. All of these patients had had their primary valvotomy more than five years previously.

Details of First Operation

In all the cases requiring reoperation the primary valvotomy was carried out by the transatrial route and the "split" achieved with the finger or a Brock's knife. Table I shows the number of cases of restenosis in patients who have survived to the present time. The valve sizes before and after the first operation are shown in Table II.

Calcification of the valve was described as absent in 17 cases, slight in 9, moderate in 2, and severe in 4.

If one accepts the finding, on histological examination, of poorly or well-formed Aschoff bodies in the