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CORTISONE IN ULCERATIVE COLITIS

PRELIMINARY REPORT ON A THERAPEUTIC TRIAL

BY

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There are conflicting reports of the value of corticotrophin (A.C.T.H.) and cortisone in non-specific ulcerative colitis. The disease is so variable in its severity and course that a large-scale trial in which cortisone-treated and control groups are compared has been carried out to decide the issue. This therapeutic trial originally began in the Oxford region in March, 1952, with the help of the Medical Research Council, who agreed to supply cortisone. However, physicians in other regions were interested in the same subject, and the outcome was that four other regions arranged to take part in the trial, working to the same plan as had been evolved for the Oxford region. The other regions concerned were Leeds, North-west London, Birmingham, and Edinburgh.

The Plan

Full details of the plan will be given in the final report, and only some salient features are now mentioned. The trial was a "blind" one in that dummy treatment was given to approximately half the patients, and the physician in charge of the patient did not know whether cortisone or a dummy was issued. It was judged that if the physician proceeded on the assumption that every patient might be receiving potent cortisone, and if he also had the right to stop treatment at any time he considered it likely to be doing harm, such a blind trial was justified because of the greater value of its results. Other conventional forms of medical treatment could be used in addition to the specific therapy at the discretion of the physician in charge of the patient.

Dosage.—During the first half of the trial, covering 107 patients, cortisone was given orally for a period of six weeks. The dosage was 100 mg. a day, given as 25 mg. before each of the three main meals and 25 mg. at bedtime. This dosage could be reduced after two weeks to a lower maintenance dose of 50–75 mg. daily. The cortisone was tailed off to nothing in the final week of treatment. During the second half of the trial the physician in charge of a case could increase the dose up to 300 mg. a day and the course could be prolonged up to three months. Potassium citrate in a dose of 1 g. four times a day was given throughout the course of treatment. Close watch was kept for electrolyte disturbances which might occur both from the disease processes and from the action of cortisone. Blood electrolyte estimations and electrocardiograms were to be carried out on every patient.

Selection of Cases.—Patients in their first attack and those in a definite relapse were used for the trial. The physicians were instructed not to include patients in whom the disease was causing only very mild symptoms. In other words, the trial was to be confined to patients who would normally be expected to require at least six weeks' treatment in hospital. Patients with regional colitis or ileitis were not included. Patients who suffered from the following diseases in addition to ulcerative colitis were also not included: proved chronic peptic ulcer; hypertension; pulmonary tuberculosis; any other severe illness likely to influence the prognosis greatly. A chest *x*-ray examination was to be done in all cases to exclude pulmonary tuberculosis; and a barium-meal examination was to be made if the physician thought it desirable.

First Attacks and Relapses.—These were handled separately in the design of the master sheets because previous work suggested that their prognosis might be different. Physicians were asked to classify the illness as a relapse when the patient had previously had an attack of bloody diarrhoea without good evidence of its being due to a specific infection such as bacillary dysentery. In patients with the chronic continuous form of the disease the case was classified as a relapse if the symptoms had lasted more than two years.

Results

A total of 213 patients received treatment. Of these, three have been rejected from the analysis of results for the following reasons: one patient proved to be suffering from carcinoma of the colon, one had had a colostomy, and in the third the records were inadequate. Of the remaining 210 patients, 109 received cortisone and 101 received the dummy preparation.

Dosage

The actual dosage of cortisone used with the 109 patients who received a potent preparation was as follows:

100 mg. a day for six weeks	38	patients
100 mg. a day for two to three weeks, followed by smaller doses of 50–75 mg. a day	38	,,
Doses of 100 mg. and more	17	,,
Therapy abandoned before completion	16	,,

The patients in whom therapy was abandoned before completion of the six weeks period fell into two

categories: first, those who were deteriorating on treatment; secondly, some of the patients who went into a remission rapidly after beginning cortisone.

Effect of Treatment on Clinical State

The effect of treatment was assessed by placing patients into three categories at the end of six weeks' treatment. In the majority this was at the *conclusion* of their treatment; a minority during the second half of the trial received treatment for a longer period than six weeks, and for convenience in assessing the results their condition at the end of six weeks has likewise been taken. In some patients the specific therapy was abandoned before six weeks had passed, as noted above, and their condition has been assessed at the time when treatment was abandoned. The three clinical categories were as follows:

Clinical Remission.—One or two stools a day without blood. No fever. No tachycardia. Haemoglobin normal or returning towards normal. E.S.R. normal or returning towards normal. Gaining weight. (To be included in this category the patient was expected to show all the above features. In the great majority of the cases all these data were included in the records, but in some the data for haemoglobin, E.S.R., or weight were incomplete. In such cases all the available data had to conform to this schedule.)

No Change or Worse.—Self-explanatory.

Improved.—All intermediate cases.

The results for the whole group are shown in Table I and Fig. 1, which demonstrate that the patients receiving cortisone enjoyed a clear-cut advantage over the patients on a dummy preparation. Thus about two out of every five patients on cortisone therapy were in clinical remission at the end of six weeks' treatment, compared with less than one out of every six patients receiving the inert therapy.

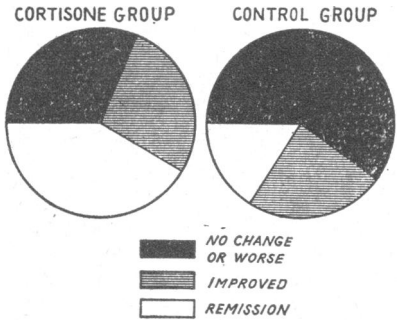

FIG. 1.—Effect of treatment — whole series.

TABLE I.—*Effect of Treatment on Whole Series*

Clinical State at End of Treatment	Cortisone Group	Control Group
Remission	45 (41·3%)	16 (15·8%)
Improved	30 (27·5%)	25 (24·8%)
No change or worse	34 (31·2%)	60 (59·4%)
Total	109 (100%)	101 (100%)

$\chi^2 = 21{\cdot}2$. n=2. $P < 0{\cdot}001$.

Table II and Fig. 2 show the results separately for patients admitted in their first attack of the disease and patients admitted in a relapse. In each case the cortisone group shows results which are significantly better than those of its control group. The beneficial effect of cortisone appears to be particularly well marked in first attacks of the disease. Past experience has shown that first attacks are in general more dangerous than relapses, and this relationship holds good for the control groups. By contrast, among the patients treated with cortisone those in their first attack have fared somewhat better than those in relapse.

TABLE II.—*Effect of Treatment in First Attacks and Relapses*

	First Attacks		Relapses	
	Cortisone Group	Control Group	Cortisone Group	Control Group
Remission	19 (42·2%)	5 (13·2%)	26 (40·6%)	11 (17·5%)
Improved	16 (35·6%)	6 (15·8%)	14 (21·9%)	19 (30·2%)
No change or worse	10 (22·2%)	27 (71·1%)	24 (37·5%)	33 (52·4%)
Total	45 (100%)	38 (100%)	64 (100%)	63 (100%)
	$\chi^2 = 20{\cdot}1$ n=2 $P < 0{\cdot}001$		$\chi^2 = 8{\cdot}25$ n=2 $0{\cdot}02 > P > 0{\cdot}01$	

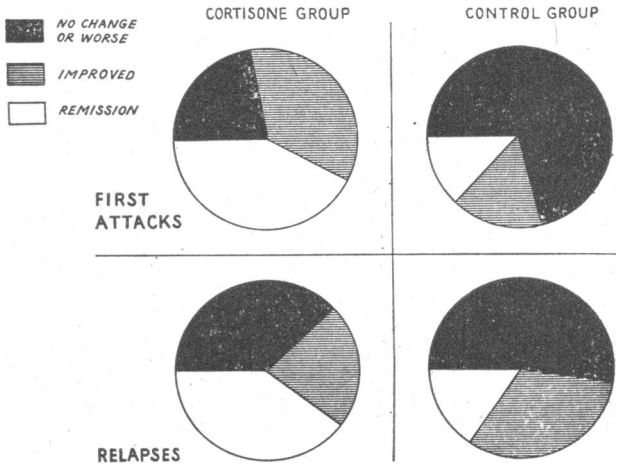

FIG. 2.—Effect of treatment, showing first attacks and relapses separately.

Sigmoidoscopy and Barium Enema

Unfortunately the data with respect to sigmoidoscopy and barium enema findings are incomplete. All patients had one or other of these examinations made before treatment began, and the majority had both, as part of the diagnostic criteria for admitting patients to the trial, but a large number of patients did not have these examinations repeated at the end of treatment. Some physicians are reluctant to carry out these examinations once the diagnosis has been established for fear of provoking recurrence, and others may have failed to appreciate their desirability as part of the assessment of results.

With respect to sigmoidoscopic findings, there were 120 patients who were examined at the end of their course of treatment, so that comparison can be made with the sigmoidoscopic appearances at the beginning. The results are shown in Table III. Of the 120 patients, there were 63 in the cortisone group, and 57 in the control group. The cortisone sample contains approximately three times as many patients whose sigmoidoscopic findings at the end of treatment were normal or near normal. (The findings were classed as near normal when slight hyperaemia or slight granularity was the only abnormal finding.) Comparison of these two samples shows that the differences between them would be expected by chance about once in 50 times, so they may be deemed to be significantly different. If we make the assumption that these samples of the cortisone and control groups are equally representative of their parent groups we may conclude that the patients treated with cortisone were more likely to show sigmoidoscopic improvement than were the patients of the control group.

TABLE III.—*Sigmoidoscopic Appearances in 120 Patients Examined at the End of Treatment*

	Cortisone Group	Control Group
Normal or near normal	19	6
Improved	14	12
No change or worse	30	39
Total	63	57

$\chi^2 = 7{\cdot}81$. n=2. $P \simeq 0{\cdot}02$.

Data with respect to barium enema are even less adequate than those for sigmoidoscopy, because only 51 of the 210

patients had a barium enema examination carried out at the end of treatment. The results for this sample are shown in Table IV. Only a small proportion of the sample show

TABLE IV.—*Barium Enema Findings in 51 Patients Examined at the End of Treatment*

	Cortisone Group	Control Group
Normal	2	2
Improved	10	4
No change or worse ..	14	19
Total	26	25

normal findings at the end of treatment, which is not surprising, as it is common experience that the changes found on barium enema examination in this disease may persist long after a complete clinical remission. A bigger proportion of patients show some improvement in the barium enema findings, although these have not returned to normal; such improvement was more commonly found in the patients of the cortisone group. So far as we are able to deduce anything from such a small sample of the total number of patients, the changes in the barium enema findings are in the same direction as the clinical response—namely, that the cortisone group do better than the control group.

Recurrences after Stopping Therapy

A small number of patients treated with cortisone relapsed shortly after the end of treatment. For example, during the first half of the trial covering 107 patients there were 57 patients treated with cortisone; of 27 of these patients who were in remission at the end of treatment, 2 relapsed shortly afterwards; and of 18 who were "improved" during the treatment, there were 2 who had an exacerbation when it ended. By contrast there were no patients among the 50 control cases who went into a definite relapse when treatment stopped. (The liability to relapse at the end of treatment is less easy to determine for the patients in the second half of the trial, when treatment could be continued for longer than the six-weeks period at the discretion of the physician in charge.)

The following comments are worth making about this finding. The relapses among the cortisone-treated group suggest that the cortisone was holding the activity of the disease in check. It is likely that some patients will require continuous treatment to maintain their improvement, but this point has not been studied in the present trial. In any event, the frequency of relapse on stopping treatment is not high enough to alter the conclusion that cortisone is beneficial.

Complications

A variety of complications occurred during the trial; these will be dealt with in detail in the final report. For the moment it is worth recording that the only two cases of perforation of the bowel occurred among the patients of the control group. There was one case of massive haemorrhage from the bowel in a patient receiving large doses of cortisone.

Ileostomy

Twenty-three patients were submitted to ileostomy during or not long after their course of treatment, because of failure of medical measures. Among the cortisone group there were 9 patients (8.3%) who were treated by ileostomy during the trial period or within the next few weeks, compared with 14 patients (13.9%) of the control group.

Deaths

There were 15 deaths during treatment or during the next few weeks. Five of these were among the cortisone-treated group, a mortality of 4.6%, and 10 among the control group (9.9%). Seven of the deaths occurred among the 23 patients who were submitted to ileostomy, 2 of them being in the cortisone-treated group and 5 in the control group.

Discussion

There are already many reports of the treatment of ulcerative colitis with cortisone and A.C.T.H. (Dearing and Brown, 1950; Elliott and others, 1951; Halsted and others, 1951; Kirsner and Palmer, 1951; Machella and Hollan, 1951; Rossmiller and others, 1951; Bekaert and Vuylsteek, 1952; Brown and McAuley, 1952; Gray and others, 1952). Most of the authors have noted considerable subjective improvement, with gain in appetite and reduction of diarrhoea. Objective improvement has been less often observed, but in those patients in whom the diarrhoea was most diminished sigmoidoscopic examination of the colon showed a decrease in inflammatory reaction. However, in none of these reports was there a formal trial in which some patients received therapy and some did not. In consequence it is difficult to judge from them how beneficial are the actions of A.C.T.H. and cortisone, particularly when it is borne in mind that ulcerative colitis is prone to show remissions even in the absence of specific therapy.

The present study deals with a considerable number of patients, who were allotted in a random order to treatment with cortisone or a dummy preparation without the physician in charge of the patient being informed of the nature of the treatment, unless such information became necessary as a result of a grave emergency. The results show that, as judged by ordinary clinical criteria, cortisone was undoubtedly beneficial in increasing the chance of remission. The effect was particularly striking in patients suffering from their first attack of the disease. It is known from previous observations (Rice-Oxley and Truelove, 1950) that first attacks are usually more serious than relapses, and this relationship holds true in the present study for the patients of the control group. By contrast, in the cortisone group, patients in their first attack fared somewhat better than those suffering from relapses.

It is unfortunate that a large number of patients were not examined again by sigmoidoscopy and barium enema at the end of treatment in order to permit comparison with the findings at the beginning. Sigmoidoscopy was carried out at the end of treatment in 63 patients in the cortisone group and 57 in the control group. Findings were significantly better in the cortisone group than in the control group, so that if we make the assumption that these samples were equally representative of the two parent groups we may conclude that cortisone exerts a beneficial influence on the disease when judged by sigmoidoscopy. The barium enema findings are less adequate, as this examination was made in only 51 of the 210 patients at the end of treatment, but within this small sample such differences as exist are in favour of the cortisone group.

The decision to submit a patient to ileostomy because medical treatment is failing constitutes a yardstick of the efficacy of medical measures. Likewise the number of patients dying during the trial period of treatment or within the next few weeks may be taken as a criterion. In each case the cortisone group compares favourably with the control group. Although the differences between the two groups are not statistically significant they may reasonably be regarded as reinforcing the previous conclusion that cortisone is beneficial.

Thus the criteria used—namely, the overall clinical picture, changes in sigmoidoscopic appearances, changes in the barium enema findings, resort to surgery because of failure of medical treatment, and early death—all point in the same direction, that cortisone confers benefit upon patients with an acute attack of ulcerative colitis.

Cortisone has its own dangers, which require evaluation. Halsted and others (1951), in treating 15 patients suffering from ulcerative colitis with A.C.T.H., had one patient who developed a perforated duodenal ulcer, one a coronary thrombosis, and one a massive haemorrhage followed by perforation. Tulin and others (1952) record that among 17 patients with ulcerative colitis treated with A.C.T.H. three developed peritonitis, from which one patient died; they believe that this agent is too dangerous to use in the acute

fulminating type of ulcerative colitis. Pessel and others (1953) report a fatal case of multiple bowel perforations and peritonitis occurring during treatment with A.C.T.H. It is therefore interesting to note that in the present study the only two cases of perforation of the bowel occurred in patients of the control group. One patient who was receiving large doses of cortisone had a massive haemorrhage from the bowel. Other less serious complications were fairly frequent in both the cortisone and the control group, and will be discussed in detail in the final report.

We do not, as yet, know whether the patients treated with cortisone will show any lasting benefit over the subsequent course of time. A small number of the patients treated with cortisone relapsed shortly after the cessation of treatment, but not enough to alter materially the general picture of its beneficial effects. We are attempting to follow the long-term progress of all patients who have been included in the trial, so that this point may eventually become clear. It is already known that some patients may relapse and need further courses of treatment in the future. It seems likely that some patients will require continuous treatment with cortisone to maintain their improvement, but the efficacy of long-continued treatment remains to be determined.

Summary

Preliminary results are given of a therapeutic trial of cortisone in non-specific ulcerative colitis carried out by the co-operation of physicians in five hospital regions.

Of the 210 patients reported, 109 were treated with cortisone, the usual dose being up to 100 mg. a day for six weeks, and 101 received a dummy preparation.

As judged by the overall clinical response to treatment, the cortisone group enjoyed a clear advantage over the control group. Cortisone appeared to be particularly beneficial in first attacks of the disease.

Such data as exist on the changes in sigmoidoscopic and barium enema appearances between the beginning and end of treatment are in favour of the cortisone group.

Although neither difference is statistically significant, resort to ileostomy because medical treatment was failing, and death during the period of treatment or during the next few weeks, were both more common among the patients in the control group.

It is concluded that cortisone exerts a beneficial influence on the outcome of an acute attack of ulcerative colitis.

We wish to thank the many physicians who have taken part in the trial; their names will be published in the final report. The trial would have been impossible without the help of the Medical Research Council, who made available the cortisone used, met part of the clerical expenses, and provided facilities for meetings. Messrs. Merck kindly made a gift of cortisone and identical control tablets for a substantial part of the trial. We are indebted to the following pharmacists, who were responsible for the issue of cortisone and the dummy preparation within their regions: Mr. W. Trillwood (Oxford), Mr. N. W. Blacow (Leeds), Miss B. Boshell (N.W. London), Mr. E. Speakman (Birmingham), and Dr. G. Perrins (Edinburgh).

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SOME OBSERVATIONS ON THE TREATMENT OF ULCERATIVE COLITIS WITH A.C.T.H.

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Ulcerative colitis is a disease of unknown aetiology. Like many diseases the cause of which remains obscure, the aetiological factors are probably multiple, and the occurrence of the disease depends on their coincidental happening in a predisposed subject. Psychological factors undoubtedly play some part, while when the abnormal state of the mucous membrane is established, secondary infection is important. Little else can be said with certainty to be known of the cause of this disease. Treatment is confined either to general supportive measures with rest, diet, and blood transfusion, the correction of electrolyte balance in severe cases, and the treatment of secondary infection with antibiotics, on the one hand, or by ileostomy with or without colectomy on the other. Handling of psychological difficulties on common-sense lines is sometimes helpful, but formal psychotherapy is seldom indicated.

The Literature

The introduction of A.C.T.H. and cortisone has led to their trial by many workers in America on patients with ulcerative colitis. The fact that this disease is occasionally complicated by arthritis raised the question whether cortisone might have an effect whether or not joint changes were present (Dearing and Brown, 1950). Rather different conclusions have been reached by different workers, but the majority have found that A.C.T.H. and cortisone have some effect on this disease. Dearing and Brown treated one case with both ulcerative colitis and arthritis with cortisone, 50 mg. twice daily intramuscularly for 35 days, with complete symptomatic relief of the colitis after a few days and recovery of the joints after four weeks. This was not accompanied by any objective improvement in the bowel, but subjective relief persisted for seven months. Two further cases with ulcerative colitis showed no response at all, while a fourth case showed temporary improvement on two occasions with courses of cortisone, but no change later after a course of A.C.T.H. Rather more favourable results were recorded by DuToit and Bauer (1950) in two cases, by Gray *et al.* (1950) in one case, and by Kirsner *et al.* (1950) in 11 cases treated with A.C.T.H. of which 9 responded. In five cases treated with cortisone by Kirsner *et al.* (1950) four showed some change, but in two of these it produced less benefit than A.C.T.H. had done previously.

Gray *et al.* (1951) treated six severe chronic cases in an acute phase which had failed to respond to a control period of medical management over one to four months. Doses of 20 to 40 mg. of A.C.T.H. six-hourly for four to eight weeks were used, with gradual reduction over a period of five to seven days at the termination of treatment. Five of the six patients experienced a dramatic