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CORTISONE IN ULCERATIVE COLITIS

FINAL REPORT ON A THERAPEUTIC TRIAL

BY

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In a preliminary report (Truelove and Witts, 1954) we have given the immediate results of a controlled trial of cortisone in the treatment of chronic ulcerative colitis. In the present paper it is intended to fill in some of the details about the immediate results and to report on the subsequent progress of the patients. The trial was confined to typical cases of chronic ulcerative colitis which would normally be expected to require at least six weeks' treatment in hospital, and patients with regional colitis, ileitis, or proctitis were not included. 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.

Diagnosis.—The diagnosis was established by the following criteria: (1) History. (2) Character of stools. (3) Sigmoidoscopy (in very ill patients, proctoscopy was regarded as sufficient). (4) Barium enema, except when the patient was gravely ill. (5) Absence of known pathogens in the stools.

First Attacks and Relapses.—First attacks and relapses 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 evidence of a specific infection such as bacillary dysentery. In patients with the chronic continuous form of the disease the illness was classified as a relapse if the symptoms had lasted more than two years.

General Principles of Treatment.—In addition to the special tablets, patients received full therapy along the lines thought best by the physician in charge of them. The following general principles of treatment were agreed upon: (1) High protein, low residue diet with vitamin supplements. (2) Maintenance of water and electrolyte balance, if necessary by intravenous infusion. (3) Blood transfusions to maintain haemoglobin above 70%. (4) Sulphonamides and antibiotics at the discretion of the physician in charge. (5) Rectal instillations, likewise at the discretion of the physician in charge. (6) Surgery should not normally be required during the period of trial, and would usually imply that the patient had failed on medical treatment. (7) Other forms of treatment at the discretion of the physician in charge of the patient.

Dosage.—The actual dosage of cortisone used in the 109 patients who received it 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 exceeding 100 mg. a day	17 „
Therapy for less than six weeks	16 „

The patients in whom therapy was stopped 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.

PART A: SHORT-TERM RESULTS

The effect of treatment was assessed by placing patients into three categories at the end of six weeks' treatment. In the majority this was 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 stopped before six weeks had passed, as noted above, and their condition has been assessed at the time when treatment was stopped. 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 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 Fig. 1 and Table I, 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.

The results of treatment have been further analysed to show the difference between first attacks and relapses, the effect of differences in severity of the disease, and the relative frequency of complications in patients treated with cortisone and not so treated. Fig. 2 and Table II show the results separately for patients admitted in their first attack of the disease and patients admitted in a relapse. In each

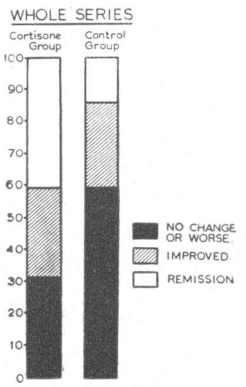

FIG. 1

FIG. 1.—Effect of treatment—whole series. FIG. 2.—Effect of treatment, showing first attacks and relapses separately.

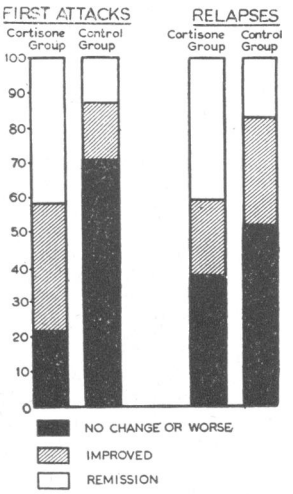

FIG. 2

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<0·001.

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<0·001		$\chi^2 = 8{\cdot}25$ n = 2 0·02>P>0·01	

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.

Effect of Treatment in Relation to the Initial Severity

As it has been found by analysing the data that the severity of the disease at the beginning of treatment has great bearing on the outcome of the illness it is worth while considering this item in detail. The severity of the illness at the beginning of treatment was assessed on the following criteria :

Severe.—Severe diarrhoea (six or more motions a day) with macroscopic blood in stools. Fever (mean evening temperature more than 99.5° F. (37.5° C.), *or* a temperature of 100° F. (37.8° C.), or more on at least two days out of four). Tachycardia (mean pulse rate more than 90 per minute). Anaemia (haemoglobin 75% or less—allowance made for recent transfusion). E.S.R. much raised (more than 30 mm. in one hour).

Mild.—Mild diarrhoea (four or less motions a day) with no more than small amounts of macroscopic blood in stools. No fever. No tachycardia. Anaemia not severe. E.S.R. not raised above 30 mm. in one hour.

Moderately Severe.—Intermediate between severe and mild.

TABLE III.—*Effect of Treatment in Relation to Initial Severity of the Illness*

Initial Severity	Cortisone Group			Control Group		
	No Change or Worse	Imp.	Remission	No Change or Worse	Imp.	Remission
			(*a*) *First Attacks*			
Severe ..	4	5	3	12	3	0
Moderate	6	10	8	12	2	2
Mild ..	0	1	8	3	1	3
Total	10	16	19	27	6	5
			(*b*) *Relapses*			
Severe ..	9	3	7	13	6	1
Moderate	13	8	9	12	9	6
Mild ..	2	3	10	8	4	4
Total	24	14	26	33	19	11

Table III sets out the results when patients in the various treatment groups are subdivided according to the severity of their illness at the beginning of treatment.

It can be seen that in each of the four main treatment groups patients who were severely ill at the beginning of treatment did much worse than patients who were only mildly ill—a finding which is not surprising. However, it can also be seen that at each level of severity, in both first attacks and relapses, the cortisone-treated patients had a more favourable outcome than the corresponding control patients. The results are more easily grasped by studying Fig. 3, which shows the results of Table III expressed as proportions. The numbers of patients in the individual sub-groups are small, so that random fluctuations are considerable, but the figure shows a general pattern which illustrates the two points of consequence —namely: (*a*) that in each of the four main treatment groups the severity of the illness at the beginning of the trial period influenced the outcome; (*b*) that at all levels of initial severity, in first attacks and relapses, the cortisone group compared favourably with its corresponding control group.

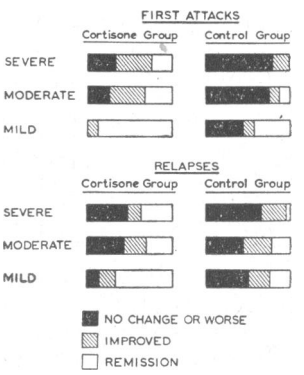

FIG. 3.—Effect of treatment in relation to the initial severity of the illness.

This is a finding of considerable importance, as there has been dispute on whether treatment with cortisone should be limited either to mild cases or to severe cases of the illness. It is evident from the present results that cortisone is worthy of trial in all patients suffering from ulcerative colitis, irrespective of the severity of the illness, unless there are special contraindications to its use. It is also clear that the ideal patient for cortisone therapy is one in his first attack while the disease is still mild. This is a policy of perfection which cannot be attained because many patients in their first attack

begin suddenly with severe symptoms, but in the remainder in whom the onset of the disease is gradual it is a policy that should be put into effect.

Sigmoidoscopy and Barium Enema

Unfortunately the data provided by 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 IV. Of the 120 patients, there were

TABLE IV.—*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≃0·02.

63 in the cortisone group and 57 in the control group; and these two samples were closely similar in respect of sigmoidoscopic findings before treatment. At the end of treatment the cortisone sample contained approximately three times as many patients whose sigmoidoscopic findings 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 regarded as 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.

Further information accrues if we relate the sigmoidoscopic appearances at the end of treatment with the clinical state. Table V sets out this information in the form of simple contingency tables separately for first attacks and relapses in both treated and control groups. It will be seen that there is an obvious correlation between the clinical

TABLE V.—*Sigmoidoscopic Appearances at the End of Six Weeks' Treatment Compared with the Clinical State*

Clinical State	Cortisone Group				Control Group			
	Sigmoidoscopic Findings			Total	Sigmoidoscopic Findings			Total
	Normal or Near-normal	Impd.	Unchd. or Worse		Normal or Near-normal	Impd.	Unchd. or Worse	
First Attacks								
Remission	7	2	3	12	1	2	—	3
Improved	2	2	4	8	—	1	3	4
Unchanged or worse	—	1	5	6	—	1	11	12
Total	9	5	12	26	1	4	14	19
Relapses								
Remission	10	7	4	21	3	2	5	10
Improved	—	1	6	7	1	4	8	13
Unchanged or worse	—	1	8	9	1	2	12	15
Total	10	9	18	37	5	8	25	38

state at the end of six weeks' treatment and the sigmoidoscopic appearances at that time. For example, the large majority of the patients who had normal or near-normal sigmoidoscopic findings at that time were patients who were in clinical remission. At the other end of the scale the majority of the patients who were unchanged clinically showed no improvement in the sigmoidoscopic appearances. However, the correlation is far from perfect, and in particular it may be noted that a considerable number of the patients who were in clinical remission still showed no improvement in the sigmoidoscopic appearances. In this connexion it is important to observe that this particular finding was true in the control group as well as in the treated group—a point that is worth making because a number of workers have concluded that cortisone may suppress the symptoms of ulcerative colitis while the disease remains active in the colon. The fact that not only the treated but also the control group had examples of patients in clinical remission with sigmoidoscopic evidence of marked activity is thus of much interest.

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

TABLE VI.—*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

in Table VI. Before treatment the 26 cortisone patients and 25 control patients had a similar range of barium enema findings. Only a small proportion of the sample show 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.

TABLE VII.—*Findings on Barium Enema Examination at the End of Treatment in Relation to the Clinical State*

Clinical State	Cortisone Group			Control Group		
	Barium Enema Findings		Total	Barium Enema Findings		Total
	Normal or Improved	Unchanged or Worse		Normal or Improved	Unchanged or Worse	
Remission ..	10	5	15	4	1	5
Improved ..	1	5	6	2	6	8
Unchanged or worse ..	1	4	5	—	12	12
Total ..	12	14	26	6	19	25

Once again, further information accrues if we relate the barium enema findings at the end of treatment to the clinical state. Table VII sets out this information in a more compressed form than that used for the sigmoidoscopic findings because of the small numbers involved. It will be seen that there is some correlation between the clinical state at the end of treatment and the findings on barium enema examination.

Complications

The complications of ulcerative colitis are numerous and diverse. Cortisone might be feared to increase the risk of some of them, notably perforation of the bowel, massive

TABLE VIII.—*Complications During the Trial Period*

Complications	Cortisone Group	Control Group
Perforation of the bowel leading to general peritonitis	0	2
Massive haemorrhage from the bowel	1	0
Local pyogenic complications around the rectum, such as ischio-rectal abscess and fistula-in-ano	6	2
Gangrenous appendix leading to pelvic abscess	0	1
Eye complications—namely, conjunctivitis, irido-cyclitis, and ulcerative keratitis	3	0
Polyposis	4	3
Thrombo-embolic complications	2	1
Aplastic blood disorder	1	1
Fibrotic stricture of rectum or sigmoid colon	0	2
Ulcerative stomatitis	1	1
Pneumonia	0	1
? Pyodermia gangrenosa (a large carbuncle yielding sterile pus)	1	0

haemorrhage, pyogenic complications, and electrolyte disturbances. Table VIII sets out the complications which occurred in the various treatment groups. Comparison is not easy, because of the multiplicity of complications, but some tentative conclusions are possible :

Perforation of the Bowel Leading to General Peritonitis.—This occurred in two patients, who were both in the control group. Both patients subsequently died. In this series, therefore, cortisone did not predispose to perforation.

Massive Haemorrhage.—One instance occurred in a patient receiving large doses of cortisone. She was treated with blood transfusion, and the cortisone was reduced. She recovered from the bleeding but died five weeks later.

Thrombo-embolic Complications.—Two patients of the cortisone group had venous thrombosis of the legs without serious effects. One patient in the control group died from a pulmonary embolus associated with thrombosis of the left iliac vein.

Pyogenic Complications.—These were more numerous among the cortisone group, who had six cases of ischio-rectal abscess, or related local complications, and one case diagnosed as pyodermia gangrenosa. Among the control group there were two cases of recto-vaginal fistula, one of which was accompanied by gross perianal infection, and one patient developed a gangrenous appendix going on to a pelvic abscess.

Eye Complications.—The cortisone group had three patients with ocular complications—namely, iridocyclitis, ulcerative keratitis, and conjunctivitis—whereas the control patients had none.

Some degree of *electrolyte disturbance* was fairly common in both cortisone and control patients, but seldom reached serious proportions. The following brief details of a case of hypokalaemia in a control patient serves to illustrate the point that electrolyte disturbance may be profound in ulcerative colitis irrespective of therapy, and that any patient with a severe attack of this disease should be treated in a hospital with good biochemical facilities.

The patient was a woman, aged 53, in her first attack. She was on inert tablets together with 1 g. of potassium citrate four times a day by mouth. On three occasions her serum potassium varied between 12.5 and 13.5 mg. per 100 ml., and finally fell to 11.3 mg. Repeated E.C.G.s showed changes in the S.T. segment compatible with hypokalaemia. At this stage the "cortisone" tablets were gradually reduced to nothing, and simultaneously the serum potassium level returned to normal values, this coinciding with a lessening of the patient's symptoms.

It is also of interest that some clinicians thought they could observe side-effects of cortisone in patients treated with inert tablets. For example, a patient in a sharp relapse of the disease was put on to inert therapy. There was a dramatic response, and she proceeded to a complete remission, which was still maintained at the end of the follow-up period two years later. She gained weight rapidly, and the clinician looking after her was convinced that she had developed a "moon-face" due to cortisone.

With the possible exceptions of pyogenic complications and eye complications, there is no evidence that the cortisone group was more liable to complications than the control group. There appears to be a prima facie case for combining cortisone with penicillin and sulphonamides to minimize the risk of pyogenic complications.

Ileostomy

Twenty-four patients were submitted to ileostomy, with or without colectomy, 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 six weeks, compared with 15 patients (14.9%) of the control group.

Early Deaths

There were 16 deaths during treatment or during the next two months. Five of these were among the cortisone-treated group (mortality 4.6%) and 11 among the control group (mortality 10.9%). Eight of the deaths occurred among the 24 patients who were submitted to ileostomy, 2 of them being in the cortisone-treated group and 6 in the control group. Brief details of the early deaths are given below.

First Attacks

(*a*) CORTISONE GROUP (2 DEATHS OUT OF 45 CASES)

(i) *Female Aged 28.*—A severe case with gross constitutional disturbances and 16 stools a day containing blood. While on cortisone she showed slight improvement, the number of stools falling to ten a day, but there was slow but steady deterioration after the cortisone was stopped. Twenty-five days after the cortisone treatment she was treated by ileostomy, which was followed by death three days later. *Post-mortem examination:* Ulcerative colitis.

(ii) *Female Aged 67.*—A severe case with faecal incontinence and gross blood in the stools, together with constitutional disturbances. She was treated with 100 mg. of cortisone daily for one week. Later the dose was increased to 200–300 mg. daily. After three weeks' treatment she developed a severe rectal haemorrhage which caused the clinician to withdraw the cortisone gradually. Thereafter she went slowly downhill and died five weeks later: *Post-mortem examination:* Cachexia; ulcerative colitis.

(*b*) CONTROL GROUP (6 DEATHS OUT OF 38 CASES)

(i) *Female Aged 8.*—Moderately ill on beginning treatment, which included repeated blood transfusions, chloramphenicol, and succinylsulphathiazole. She pursued a steady downward course, and ileostomy was carried out 18 days after stopping the control medication. She died 24 days after operation.

(ii) *Female Aged 50.*—A severe case on beginning treatment, with fever, tachycardia, anaemia (haemoglobin = 55%), and bloody diarrhoea. She deteriorated steadily during the trial period and afterwards, and the physician in charge remarked that "no treatment produced improvement." She died eight weeks after the end of the trial. *Post-mortem examination:* Extreme ulceration of the lower two-thirds of the colon with multiple polypi (non-malignant).

(iii) *Male Aged 60.*—A severe case which was unchanged at the end of the trial period. Two days later the patient was treated with ileostomy, but he died six weeks later.

(iv) *Female Aged 30.*—A severe case on starting treatment. Ten days after starting the control medication there was a great increase in abdominal pain, and the next day laparotomy showed a gangrenous appendix and pelvic abscess. Seven days later control medication was stopped. The patient's condition gradually deteriorated, and five weeks later she was transferred to another hospital for total colectomy. She died post-operatively.

(v) *Female Aged 19.*—There was progressive deterioration with the control medication, which was stopped after 11 days. Four days later she perforated and developed peritonitis. This was treated with antibiotics, but fever and diarrhoea continued, and ileostomy was carried out after two more weeks. She died four days post-operatively.

(vi) *Female Aged 52.*—A moderately severe case which was unchanged at the end of the trial period. Two weeks later, on August 20, 1953, she was treated with ileostomy. She improved for a few weeks, but then deteriorated rapidly and died on September 28.

Relapses

(*a*) CORTISONE GROUP (3 DEATHS OUT OF 64 CASES)

(i) *Female Aged 30.*—A severe case with four years' history of recurrent diarrhoea and more recent anaemia resistant to iron

therapy. During treatment her general condition deteriorated, with progressive anaemia and leucopenia. She then developed agranulocytosis with sore throat and a purpuric rash. The white blood count was 900 per c.mm. and haemoglobin 33%. She died suddenly, presumably from a cerebral accident. Her case was diagnosed as ulcerative colitis complicated by aplastic anaemia which was possibly related to a course of chloramphenicol given during the previous year.

(ii) *Male Aged 46.*—A severe case which deteriorated steadily during the course of treatment. The patient was then treated with ileostomy and partial colectomy. He continued to deteriorate post-operatively, and died three weeks later. *Post-mortem examination:* Ulcerative colitis, pericardial effusion, and bronchopneumonia.

(iii) *Male Aged 61.*—A severe case with a 30 years' history of recurrent bloody diarrhoea. On the third day he died suddenly. *Post-mortem examination:* Generalized wasting due to ulcerative colitis of the whole colon, with gross polyposis. Brown atrophy of the heart. No evidence of coronary thrombosis or pulmonary embolus.

(*b*) CONTROL GROUP (5 DEATHS OUT OF 63 CASES)

(i) *Male Aged 43.*—A severe case in which the patient was improving on treatment but died suddenly one month after its beginning, because of a pulmonary embolus. *Post-mortem examination:* Thrombosis of left iliac vein with extensive pulmonary embolus. Ulcerative colitis affecting the whole colon with polyposis.

(ii) *Female Aged 21.*—A severe case which deteriorated during treatment. She discharged herself against advice, but died shortly after getting home.

(iii) *Female Aged 55.*—A severe case which went downhill rapidly, the patient dying seven days after beginning the control medication. *Post-mortem examination:* Severe ulcerative colitis affecting the distal two-thirds of the large bowel.

(iv) *Female Aged 22.*—Recurrent attacks of diarrhoea since the age of 11 years. She did not improve during treatment, which included penicillin, chlortetracycline, and succinylsulphathiazole. Subsequently developed thrombocytopenic purpura. Ileostomy performed, but she died five days post-operatively. *Post-mortem examination:* Pulmonary infarction; intestinal obstruction; widespread purpura; extensive ulcerative colitis with polyposis.

(v) *Female Aged 40.*—A severe case. Two days after starting treatment she developed colonic perforation leading to general peritonitis. This was attributed to the therapy, which was immediately stopped. She was treated with large doses of antibiotics, but failed to improve, and died three weeks later.

PART B: LONG-TERM RESULTS

We have attempted to follow the subsequent progress of all the subjects who were treated in this therapeutic trial. There are adequate follow-up data for a minimum period of nine months in respect of 205 patients out of the original 210. The few patients for whom we have no follow-up data have either refused to continue to attend hospital or have changed their address and been lost sight of. However, the follow-up is complete enough for us to take these data as representative of the whole series, because the error introduced by doing this is small.

Position Nine Months after the Trial

The picture presented by the various treatment groups at the end of nine months' follow-up is given in Table IX. Those classed as "symptom-free throughout" are patients who have remained in complete clinical remission since the trial period. By reference back to Table II it will be seen that the number of patients in the "symptom-free throughout" group appears to be unduly high in relation to those going into remission in the acute attack. This is because some patients who were much improved during the trial period went quickly on to a remission and then remained symptom-free, and such patients have been placed in the "symptom-free throughout" category. A considerable proportion of patients in all groups experienced symptoms during the nine months that followed the trial period. They have been divided into continuous and intermittent symptoms, a distinction which is easily made. Each of these categories has been further divided into severe or mild. The separation of symptoms into severe or mild has sometimes been difficult with the data at our disposal, but we

TABLE IX.—*Position at the End of Nine Months' Follow-up*

	First Attacks		Relapses	
	Cortisone Group	Control Group	Cortisone Group	Control Group
Symptom-free throughout	21	8	23	26
Alive with symptoms:				
(*a*) Mild (Intermittent)	5	3	10	4
(*a*) Mild (Continuous)	6 → 11	3 → 6	7 → 17	8 → 12
(*b*) Severe (Intermittent)	2	4	5	5
(*b*) Severe (Continuous)	3 → 5	4 → 8	4 → 9	6 → 11
Alive with ileostomy	3	7	11	5
Dead	3*	9†	4‡	6§
Totals	43	38	64	60

* Includes 2 deaths after ileostomy.
† Includes 7 deaths after ileostomy.
‡ 1 suicide, 1 death from haemolytic anaemia after blood transfusion and 2 after ileostomy.
§ Includes 2 deaths after ileostomy.

do not believe that the error is large, because most of the patients fall obviously into one or other group. We have classed as severe those symptoms which have been bad enough to cause another admission to hospital or complete invalidism at home, whether the symptoms have been continuous or intermittent. At the other end of the scale, many patients have short bouts of diarrhoea or passage of blood in the stools, or they may continuously have mild diarrhoea or slight rectal bleeding, without much ill effect upon their health. The "dead" category is obvious, and it includes all deaths from the beginning of the trial.

A more clear-cut picture emerges if we condense the data so that patients in each treatment group are placed in three categories: (i) Symptom-free throughout, (ii) alive but with symptoms, (iii) dead. Table X and Fig. 4 show these results.

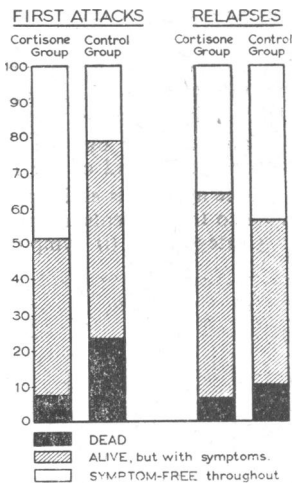

FIG. 4.—Position nine months after trial period.

It will be seen that the first attacks and the relapses have behaved differently from one another. In the first attacks the cortisone-treated group has maintained an advantage over its corresponding control group. The difference between these two groups is statistically significant. By contrast, the relapse group treated with cortisone has lost the advantage it enjoyed at the end of the trial period. The control group has slightly more patients in the "symptom-free throughout" category and slightly more deaths, but these differences are small and would be expected to arise by chance sampling errors about once in every three times. To summarize, therefore, by the end of nine months from the trial period the first attack and relapse groups are showing clear-cut differences. While patients in their first attack who were treated with cortisone maintain

TABLE X.—*Position in the Various Treatment Groups Nine Months After the Trial Period*

	First Attacks		Relapses	
	Cortisone Group	Control Group	Cortisone Group	Control Group
Symptom-free throughout	21 (48·8%)	8 (21·1%)	23 (35·9%)	26 (43·3%)
Alive with symptoms	19 (44·2%)	21 (55·3%)	37 (57·8%)	28 (46·7%)
Dead	3 (7·0%)	9 (23·7%)	4 (6·3%)	6 (10·0%)
Total	43 (100%)	38 (100%)	64 (100%)	60 (100%)
	$\chi^2 = 8·65$, $n = 2$, $0·01 < P < 0·02$		$\chi^2 = 1·70$, $n = 2$, $0·3 < P < 0·5$	

a clear-cut advantage over the corresponding control group, the initial advantage enjoyed by the relapse cases treated with cortisone has been lost.

Position at the End of the Follow-up

At the end of the follow-up there is information about the same 205 patients, but the period of follow-up varies from a minimum of nine months to more than two years. However, the distribution of length of follow-up is similar for the various treatment groups, so that comparison between them is valid. Approximately half the patients in each treatment group have been followed up for longer than 18 months from the trial period.

TABLE XI.—*Position at the End of Follow-up Period*

	First Attacks		Relapses	
	Cortisone Group	Control Group	Cortisone Group	Control Group
Symptom-free throughout ..	15	5	20	21
Alive with symptoms:				
(*a*) Mild Intermittent	7 } 13	6 } 7	11 } 17	6 } 10
(*a*) Mild Continuous	6 }	1 }	6 }	4 }
(*b*) Severe Intermittent	5 } 8	5 } 10	7 } 10	10 } 14
(*b*) Severe Continuous	3 }	5 }	3 }	4 }
Alive with ileostomy ..	4	7	11	8
Dead	3§	9†	6‡	7§
Totals	43	38	64	60

* Includes 2 deaths after ileostomy.
† Includes 7 deaths after ileostomy, and 1 from probable coronary thrombosis.
‡ Includes 1 suicide, 1 death from haemolytic anaemia after blood transfusion and 2 after ileostomy.
§ Includes 3 deaths after ileostomy.

Table XI sets out the position in the various treatment groups at the end of the follow-up.

Once again it is easier to compare them by condensing the data so that patients are placed into one of the three following categories : (i) Symptom-free throughout, (ii) alive but with symptoms, (iii) dead. These data are displayed in Table XII and Fig. 5. It will be seen that compared with the position at the end of nine months there is a general worsening of the picture, with a small increase in the number of deaths and a reduction in the number of patients who have remained symptom-free. However, the same distinction exists between first attacks and relapses as was noted nine months after the trial period—namely, that patients in their first attack treated with cortisone preserve an advantage over their controls, whereas the patients in relapse treated with cortisone present virtually the same picture as their corresponding control cases. Both at nine months and at the end of the follow-up it is the control group of patients in their first attack of the disease which presents the worst picture. This finding reinforces the conclusion we arrived at from the short-term results—that it is patients in their first attack of ulcerative colitis who are most conspicuously benefited by treatment with cortisone.

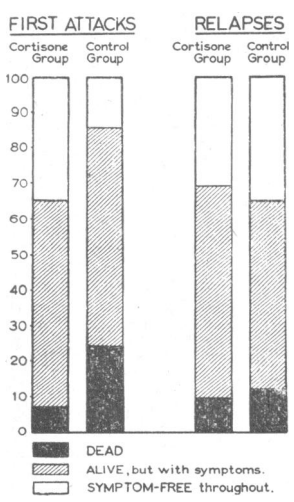

FIG. 5.—Position at end of follow-up period.

TABLE XII.—*Position in the Various Treatment Groups at the End of Follow-up*

	First Attacks		Relapses	
	Cortisone Group	Control Group	Cortisone Group	Control Group
Symptom-free throughout ..	15 (34·9%)	5 (13·2%)	20 (31·2%)	21 (35·0%)
Alive with symptoms	25 (58·1%)	24 (63·2%)	38 (59·4%)	32 (53·3%)
Dead	3 (7·0%)	9 (23·7%)	6 (9·4%)	7 (11·7%)
Total ..	43 (100%)	38 (100%)	64 (100%)	60 (100%)
	$\chi^2=7·74$ n = 2 P ≃ 0·02		$\chi^2=0·489$ n = 2 P ≃ 0·8	

Surgery

It was mentioned in Part A that 24 patients were treated by ileostomy (with or without colectomy) during the trial period or shortly afterwards. Another 20 patients were treated by ileostomy during the period of follow-up, making a total of 44 patients in all. Of these, 14 (31.8%) were dead by the end of the follow-up period. The majority of the deaths in the surgically treated patients occurred shortly after the initial operation, but some followed a later operation (for example, a colectomy after an earlier ileostomy), and in a few the ileostomy later gave rise to complications which were fatal. These findings demonstrate the widespread use of surgery to-day, for more than one-fifth of the original group of cases have been treated surgically in the course of a comparatively short period. The high mortality in the surgical group does not appear to have been due to postponement of operation by the therapeutic trial. In the selection of cases it was advised that patients likely to require early surgery should not be admitted to the trial.

Late Deaths

In addition to the 16 deaths which occurred during the trial period or shortly afterwards, there were 9 deaths during the period of follow-up, making a total of 25, or 11.9% of the original 210 patients. Brief details of the later deaths are given below.

First Attacks

(*a*) CORTISONE GROUP (1 DEATH OUT OF 43 PATIENTS FOLLOWED UP)

(i) *Female Aged 24.*—A severe case which went into remission on cortisone therapy but relapsed immediately it was stopped. Cortisone was recommenced, and she again went into remission although sigmoidoscopy and barium enema showed evidence of disease. It was decided to treat her with ileostomy, which was carried out on January 30, 1953, with simultaneous right hemicolectomy. On March 6, 1953, left hemicolectomy was performed. Thereafter she improved well, but on May 22, 1953, she was admitted to hospital with acute intestinal obstruction, from which she died. *Post-mortem examination* confirmed the cause of death.

(*b*) CONTROL GROUP (3 DEATHS OUT OF 38 PATIENTS FOLLOWED UP)

(i) *Female Aged 19.*—A very severe case that was unchanged at the end of the trial period. She continued to suffer from severe diarrhoea, anaemia, and loss of weight, and four months later, in December, 1952, ileostomy was carried out. In January, 1953, she was readmitted with a septic arthritis and total colectomy was carried out on March 31, 1953. There was gradual deterioration in her condition post-operatively, with breaking down of her wounds, and she died on April 23, 1954. *Post-mortem examination:* Cachexia. Chronic peritonitis, with retroperitoneal abscesses following total colectomy.

(ii) *Male Aged 63.*—A moderately severe case that went into remission. He remained symptom-free until his sudden death one year after the trial period, which was attributed to coronary thrombosis.

(iii) *Female Aged 28.*—A severe case that showed some improvement during the trial period. She continued to improve, and was discharged home at the end of January, 1953. A severe relapse occurred and she was readmitted at the end of February. She gradually improved, and it was decided to carry out ileostomy and total colectomy, which was done on May 27, 1953. She died six days post-operatively. *Post-mortem examination:* Gross generalized peritonitis and paralytic ileus.

Relapses

(*a*) CORTISONE GROUP (3 DEATHS OUT OF 64 PATIENTS FOLLOWED UP)

(i) *Male Aged 64.*—A patient with a 33-years history of ulcerative colitis who was admitted in relapse. At the time of beginning cortisone treatment he was classed as a mild case.

Sigmoidoscopy showed polyposis, which was confirmed by biopsy, but no evidence of malignancy was seen in the biopsy specimen. Two months after the trial period he was readmitted with a recurrence of bloody diarrhoea. Three months later he developed jaundice, and the liver gradually increased in size and showed irregularity due to secondary deposits. He died two months after the onset of jaundice. *Post-mortem examination:* Entire colon almost denuded of mucosa except for pseudo-polyps. Numerous areas of thickening of the colon, not necessarily in relation to the polypi, which on section showed carcinomatous infiltration. Secondary deposits in liver.

(ii) *Female Aged 47.*—A moderately severe case with a six-years history of intermittent symptoms. She improved on cortisone therapy, and was discharged with mild diarrhoea but with no blood in the stools; eight months after discharge, however, she committed suicide.

(iii) *Female Aged 39.*—A moderately severe case that went into remission on cortisone therapy. Two months later she had a ? perforation with development of a pelvic abscess. She was admitted to another hospital for total colectomy; it was then found that the perforation had been of the appendix. Following the colectomy she developed acute haemolytic jaundice attributed to blood transfusion and died.

(*b*) Control Group (2 Cases out of 60 Patients Followed Up)

(i) *Female Aged 38.*—A moderately severe case that was improved on control medication. She was discharged with mild diarrhoea though without blood in the motions, but developed a severe relapse and was readmitted for surgery. Ileostomy and total colectomy were carried out four months after the trial period. She made good progress, but four months later developed obstruction of her ileostomy This settled on conservative treatment, but then recurred. Operation was carried out with relief of the abdominal distension, but peritonitis occurred with subphrenic abscess and the patient died. *Post-mortem examination:* Subphrenic abscess and generalized peritonitis following perforation of the ileum.

(ii) *Female Aged 71.*—A moderately severe case which did not benefit from medical treatment during the trial period, but which later improved until her discharge from hospital in November, 1952, with mild diarrhoea and with small amounts of blood in the motions. She was readmitted in February, 1953, with a right hemiparesis due to cerebral thrombosis and with evidence of active ulcerative colitis persisting. The hemiparesis cleared up well and she was discharged in March, 1953. She was readmitted later in that month for rectal incontinence, which did not respond to medical treatment. Three months later ileostomy and colectomy were carried out, with initial improvement, but she then developed generalized oedema and fever which led to death. *Post-mortem examination:* Peritonitis.

DISCUSSION

In our preliminary report it was demonstrated that cortisone greatly increases the chances of remission or improvement in chronic ulcerative colitis. This is particularly true of first attacks of the disease, but it is also true of relapses. It can now be added that it is true of all grades of severity of the disease. Nevertheless, cortisone is not a specific remedy for ulcerative colitis, and much the best results are obtained in early cases in which the disease is only moderately severe. Cortisone does not increase the risk of severe complications such as haemorrhage and perforation, and the mortality is lower in treated cases. There is a possibility that cortisone may increase the local and remote infectious complications, such as ischio-rectal abscess and iritis, and on this account it would seem wise to supplement it by antibiotics or sulphonamides.

The duration of treatment in the present trial was limited to periods of from six weeks to three months. The follow-up examinations have shown that the effects of such a course of treatment are likely to be temporary. This is especially true of chronic cases of the disease, which have lost the advantage they gained over the control group by the end of nine months. It is also true of the first attacks, though here the advantage is longer preserved and is still evident at the end of two years. It is highly desirable to carry out a controlled trial of maintenance therapy with cortisone to see if the beneficial effects can be maintained or if the patient eventually becomes resistant to the treatment. This we are in process of doing.

In the meantime there seem to be good grounds for advising that early cases of ulcerative colitis should promptly be brought under treatment with cortisone, which should, if necessary, be given in considerably higher dosage than has been used in the present trial. When treatment is successful, as it is likely to be in a substantial proportion of cases, they should be kept under careful supervision so that treatment can be promptly resumed if symptoms recur.

The trial has given us an opportunity to follow 205 cases of ulcerative colitis for an average period of eighteen months. From the circumstances of the trial their progress can be assumed to be at least as good as, and probably better than, the average for the country as a whole at the present time. Of these patients 61 are symptom-free, 119 have symptoms, and 25 are dead. Ileostomy, with or without colectomy, has been carried out on 44 patients, and of these 14 are dead. One patient has died of carcinoma of the colon, but the risk of carcinoma has not loomed large in the present series of cases. The position is that, of a fairly representative sample of cases of ulcerative colitis admitted to hospital at the present time, 12% are dead and a further 15% have a permanent ileostomy at the end of an average of eighteen months.

It is now generally agreed that, once irreversible damage has been done to the colon and the patient has persistent troublesome symptoms, it is wisest for him to submit to ileostomy, which is nowadays usually combined with colectomy. In skilled hands, the mortality for these procedures can be reduced to a reasonable level and the results are good. The results of surgery in this series compare unfavourably with those obtained in centres where a special interest has been taken in the surgical treatment of ulcerative colitis. This does not appear to have been due to postponement of operation by the therapeutic trial, for it was advised that patients likely to require early surgery should not be admitted to the trial. Nor is it due to any ill effect of the cortisone, as the mortality was higher in patients who had not had cortisone than in those who had. A relatively high mortality is not uncommon in the development of new operative procedures, and it is likely that the mortality of surgical treatment of ulcerative colitis over the country as a whole will fall. Nevertheless, it would seem that more attention should be devoted to getting cases of ulcerative colitis to hospital at the earliest possible stage. Resolute medical treatment for the first few weeks, supplemented with cortisone and followed by attentive supervision, might prevent the irremediable damage to the colon which nowadays so often leads to invalidism and, unless treated by ileostomy and colectomy, is likely to prove fatal.

SUMMARY

A therapeutic trial of cortisone in non-specific ulcerative colitis has been carried out 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 an inert preparation of similar appearance. Physicians were not informed which preparation the patient was receiving.

At every stage of severity of the illness, and in both first attacks and relapses, the cortisone-treated patients did better than the corresponding control patients. Cortisone was particularly beneficial in first attacks of the disease.

Patients treated with cortisone were somewhat more likely to suffer from pyogenic complications than patients not so treated, but the two groups did not differ appreciably in other complications. When patients are treated with cortisone it is probably wise to employ penicillin or sulphonamides in addition.

Sigmoidoscopy was carried out at the end of treatment on 120 patients so that comparison could be made with

the sigmoidoscopic appearances before treatment. Normal or improved sigmoidoscopic appearances were more frequent in the cortisone group. Similarly, for 51 patients examined by barium enema at the end of treatment, improvement in the radiological appearances was more common in the cortisone-treated patients.

Deaths were less frequent among the cortisone group than among the controls; brief details are given of the fatal cases.

Follow-up information is available for an average period of eighteen months in respect of 205 patients out of the original 210.

Nine months after the trial period patients treated with cortisone in the first attack preserved a clear advantage over the corresponding control group. By contrast, relapse cases treated with cortisone had lost the initial advantage they showed at the end of the trial period.

At the end of the follow-up period, essentially the same pattern existed as at nine months, but with a slight worsening of the general picture.

About one-fifth of the original group had been treated by ileostomy by the end of the study. Of these 44 patients, 14 (31.8%) were dead at the end of the study.

Cortisone is a valuable addition to the medical treatment of ulcerative colitis. We think it likely that better short-term results than we have obtained in the present trial could be achieved by the use of higher doses when necessary. However, its effect is far from permanent, particularly in the established disease, though it is possible that more prolonged treatment than we have so far used will give better long-term results.

ACKNOWLEDGMENTS

We wish to thank the many physicians who have taken part in the trial; their names are given below. We also thank those physicians who referred cases for inclusion. 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 control tablets for the earlier part of the trial, and Roussel Laboratories Limited generously gave the control tablets for the latter part of the trial.

Physicians taking part in the trial.—Birmingham Region: Drs. J. McD. Holmes, Bruce Maclean, Kenneth May, A. M. Nussey, W. M. Priest, C. R. St. Johnston, R. E. Smith, J. A. Wakes-Miller, and S. R. F. Whittaker. *Edinburgh Region:* Sir Alexander Biggam, Dr. W. I. Card, Professor D. M. Dunlop, Dr. Ian Easton, Professors H. W. Fullerton, I. W. Hill, R. B. Hunter, Drs. Lindsay Lamb, G. L. Malcolm Smith, and A. W. Wright. *Leeds Region:* Drs. A. M. Affleck, D. R. Cameron, C. C. Cobb, C. L. Davidson, G. M. Din, R. Fletcher, J. H. Fellows, J. R. Fountain, L. Glick, D. Laing, A. Leese, F. W. G. Marson, R. D. Miller, D. C. Muir, H. P. O'Clunide, J. A. Price, J. W. Rae, T. G. Reah, J. K. Rennie, L. W. Smith, Professor R. E. Tunbridge, Drs. J. Walker-Hirst, G. Watkinson, L. Watson, and C. E. Woodrow. *North-west London Region:* Drs. F. Avery Jones, C. A. Birch, N. Coghill, E. D. H. Cowen, C. M. Fletcher, Thomas Hunt, E. B. Jackson, G. H. Jennings, K. D. Keele, T. D. Kellock, A. R. Kelsall, M. D. Milne, and T. Simpson. *Oxford Region:* Drs. J. G. Bird, E. M. Buzzard, A. M. Cooke, P. H. Denton, M. S. Good, W. Hausmann, F. G. Hobson, L. M. Jennings, H. S. Le Marquand, V. E. Lloyd Hart, D. H. G. MacQuaide, P. Mallam, W. Stokes, J. R. Tasker, S. C. Truelove, and Professor L. J. Witts.

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SUPPURATIVE LYMPHADENITIS FOLLOWING INTRADERMAL B.C.G. VACCINATION OF THE NEWBORN

A PRELIMINARY REPORT

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Suppurative lymphadenitis is generally regarded as the most critical local complication of B.C.G. vaccination and has been shown by numerous workers (de Bruijne *et al.*, 1952; Mande and Huët, 1952; Biering-Sørensen, 1953; Gaisford and Griffiths, 1954; W.H.O. Tuberculosis Research Office, 1955) to vary in frequency and severity with the age of the child and the dose of vaccine. In general, the younger the child and the stronger the dose of B.C.G., the higher the frequency of enlarged or perforated glands—and this seems to be true whether vaccination is made by intradermal injection, multiple puncture, or scarification (Mande, 1954). Few studies have, however, been made on the relation between the dose of vaccine and the degree of B.C.G.-induced tuberculin sensitivity in newborn infants.

The present paper is a preliminary report of an investigation being carried out in the newborn. It was designed to study the frequency and severity of glandular involvement (and of the local vaccinal lesion) and the degree of tuberculin sensitivity after intradermal B.C.G. vaccination in relation to the dose of vaccine and the vaccination procedure. For this purpose more than 1,500 newborn babies have been vaccinated with various doses of B.C.G., either by a single injection or by dividing the dose into two, giving 0.1 ml. into each shoulder. The first babies to enter the study were born (and vaccinated) in November, 1953, and each week thereafter for the following 14 months (up to and including January, 1955) newborn babies have been added to the study. A one-year follow-up of all vaccinated babies will be completed in January, 1956.

The study is a joint effort of the Public Health Nurses Agency of Copenhagen (Københavns Sundhedsplejerske Institution), the B.C.G. Department of the State Serum Institute of Denmark (Statens Seruminstitut), and the W.H.O. Tuberculosis Research Office (T.R.O.). The work is being carried out in co-operation with the two municipal maternity hospitals of Copenhagen. A preliminary report of the findings, together with a broad outline of how the work is being done, seemed warranted at the present time because of the immediate practical implications of the results obtained so far.

Material and Methods

Babies born in the two maternity hospitals during the period November, 1953, to January, 1955, inclusive, and for whom permission for B.C.G. vaccination had been