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CORTISONE AND CORTICOTROPHIN IN ULCERATIVE COLITIS

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A large-scale therapeutic trial carried out by the co-operation of physicians in five hospital regions during the period 1952-5 showed that cortisone was useful in increasing the chance of the patient being in remission within six weeks of starting medical treatment (Truelove and Witts, 1954, 1955). 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, which are commonly severe and proved to be so in the control group. There were fewer patients who were treated by surgery because medical treatment was failing. However, a follow-up study showed that both cortisone-treated cases and control cases were subject to a high rate of recurrence during the next 18 months, and there was little to choose between the two groups in this respect.

These findings, although demonstrating beyond all reasonable doubt that cortisone by mouth is of some value in improving the chance of a fairly rapid clinical remission with medical treatment, left a number of questions unanswered. Consequently, as soon as the first trial was completed in 1955, a second therapeutic trial was set in train to settle some of the other issues which exist in the use of corticoids in ulcerative colitis. The number of questions which can be answered in a single therapeutic trial is limited, and we set ourselves the task of answering the following: (1) Do cortisone and corticotrophin differ in their efficacy in the acute attack of ulcerative colitis? (2) Will a small maintenance dose of cortisone by mouth keep a patient in clinical remission? (3) If a patient has once responded to corticoid therapy, is he particularly likely to respond again if he has a relapse?

The trial was divided into three parts, A, B, and C, corresponding to these three main objects.

As Part B was concerned with a study of maintenance therapy which lasted for one year, the conduct of the trial was confined to a limited number of physicians with a special interest in ulcerative colitis, because it is commonly found that any study involving maintenance treatment is difficult to operate.

Selection of Patients

Patients were selected on the same lines as in the previous trial, and were therefore straightforward cases

of active ulcerative colitis which might normally be expected to require some weeks of treatment in hospital. First attacks and relapses were kept separate in the design of the experiment because past experience had shown that first attacks are commonly more severe than relapses but at the same time more responsive to corticoid therapy. The total number of patients was 169, of whom 71 were in the first attack and 98 were in relapse. Our previous criteria of severity were used, and 32% of the cases were classified as severe, 55% moderate, and 12% mild.

Part A: Treatment of the Acute Attack

When a patient suitable for admission into the trial was found, the physician in charge sent a prescription on a special form to Mr. W. Trillwood, who acted as the central pharmacist of the trial. On receiving the prescription the central pharmacist would send six weeks' supply of either corticotrophin or cortisone tablets to the pharmacist of the hospital concerned. While awaiting the arrival of the corticotrophin or cortisone, the participating physician collected the data concerning the temperature, pulse rate, haemoglobin level, stools, etc., to cover a four-day period before the corticoid treatment was begun. During this period electrolyte disturbances could be corrected and a blood transfusion carried out if necessary. In urgent cases, when it might be thought advisable to start treatment with corticotrophin or cortisone immediately, the physician could telephone the central pharmacist to find out which treatment was to be given and could begin by using ordinary hospital supplies. In such cases the data for the state of the patient immediately before treatment were necessarily the data collected at the beginning of treatment.

Patients brought into the trial were then treated for six weeks with an initial dose of corticotrophin-gel, 80 units a day by intramuscular injection, or cortisone by mouth in a dose of 50 mg. q.d.s. This dose could be later reduced at the discretion of the physician in charge of the patient, if he judged that a smaller dose would be adequate or if there was evidence of over-dosage. The same batch of corticotrophin was used throughout. Potassium chloride, 1 g. q.d.s., was to be given throughout the whole course of treatment. Close watch was to be kept for electrolyte disturbances, which

may occur not only from the disease process but also from the action of cortisone and corticotrophin. At the end of the trial period it was advised that the dose should be tailed off rather than stopped abruptly.

In the event of a patient deteriorating during the six-weeks period, the physician was at liberty to abandon the use of corticoid treatment and to record the patient as having failed to respond. Likewise, if the physician in charge of a patient judged that emergency surgery was necessary, either because of the development of a complication or because of a general deterioration, he was at liberty to have surgery carried out. Once again, such a patient would be deemed to have failed on medical treatment.

General Principles of Treatment

In addition to cortisone or corticotrophin, patients were given full medical therapy along the lines thought best by the physicians in charge of them. The general principles of treatment have been discussed in our previous reports, but it should be noted that two particular forms of treatment—namely, salicylazosulphapyridine ("salazopyrin"*) and the local use of hydrocortisone in the colon—both of which have been used as specific forms of treatment in ulcerative colitis, were not employed in any patient in the present trial, at any rate during the trial period.

The response to treatment was assessed at the end of six weeks and the result recorded on a special data sheet which included such information as the temperature, pulse rate, number and character of the stools, haemoglobin level, E.S.R., sigmoidoscopic appearances, and barium-enema findings. If treatment with corticoid was abandoned prematurely—before the end of the six-weeks period of treatment—the patient's response was assessed at the time when the corticoid was given up.

Patients who were in complete clinical remission—that is, entirely symptom-free and with the general condition normal or returning to normal—were usually then admitted into the second part of the trial, which was designed to see whether they could be held in remission by cortisone.

Part B: Trial of Maintenance Therapy

This part of the trial was a fully controlled trial with patients allotted at random to treatment either with cortisone tablets or with inert tablets of similar appearance. Neither the physician nor the patient knew which form of treatment was being used in any particular case. The dose was 50 mg. of cortisone daily, given as one 25-mg. tablet twice a day. Patients on the inert preparation were likewise treated with a tablet twice a day. Patients in this maintenance part of the trial were seen at least once a month as out-patients by the physician in charge in order that progress could be assessed and for supplies of the maintenance tablets to be continued. Observations of the patient's clinical state were entered on a special data sheet.

A patient on maintenance therapy was classified as a failure if he developed either of the following symptoms: (a) diarrhoea, which was defined as an average of four or more stools a day for at least a week; and (b) passage of macroscopic blood with the stools for at least a week.

Positive sigmoidoscopic evidence of activity in addition to these symptoms was to be sought. It was of course appreciated that many patients in complete clinical remission may show positive sigmoidoscopic evidence of ulcerative colitis, but this was not to prevent physicians from recording the findings in patients who went into a relapse.

Part C: Effect of Known Cortisone Treatment on Patients Failing on Maintenance Therapy

When a patient had failed on maintenance therapy the effect of open therapy with known cortisone in a dose of 100–200 mg. a day in divided doses was to be assessed, unless there was some reason for not using this form of treatment.

Results in Part A

The effect of treatment was assessed by placing patients into three categories at the end of six weeks' treatment. In some patients corticoid treatment was stopped before six weeks had passed, as noted above, and their condition was then assessed at the time when this form of treatment 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, gaining weight. To be included in this category the patient was expected to show all the above features. *No change or worse*:—Self-explanatory. *Improved*:—All intermediate cases.

The results for the whole group are given in Table I, which shows that the patients receiving corticotrophin enjoyed a definite advantage over the patients treated

TABLE I.—Effect of Treatment on Whole Series

Clinical State at End of Treatment	Corticotrophin Group	Cortisone Group
Remission	51 (60.7%)	33 (38.8%)
Improved	12 (14.3%)	29 (34.1%)
Unchanged or worse	21 (25.0%)	23 (27.1%)
Total	84 (100%)	85 (100%)

$$\chi^2 = 11.0. \quad n = 2. \quad P < 0.01.$$

with oral cortisone. Thus, about two out of every three patients on corticotrophin therapy were in clinical remission at the end of six weeks' treatment, compared with about two out of five patients who were treated with oral cortisone. The present results with cortisone correspond to the results obtained in the first trial, and it may be mentioned that in the first trial only one out of every six patients in the control group was in remission at the end of six weeks.

One particular feature of these results is worth special comment. The proportion of patients left unchanged or actually becoming worse during the trial period was similar in the corticotrophin and cortisone groups. Similarly, there was no appreciable difference between the two treatment groups in terms of the number of patients who died, for there were five deaths in the corticotrophin group and seven in the cortisone group. In other words, where corticotrophin was superior to cortisone was not in the proportion of patients showing any degree of improvement but in the proportion who became entirely symptom-free.

When first attacks and relapses of the disease are considered separately an interesting result emerges. Table II shows that there is little difference in the results obtained with corticotrophin and cortisone for patients

*Salazopyrin is known as "asulfidine" in the U.S.A.

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

Clinical State at End of Treatment	First Attacks		Relapses	
	Cortico- trophin Group	Cortisone Group	Cortico- trophin Group	Cortisone Group
Remission ..	20 (50.0%)	13 (41.9%)	31 (70.5%)	20 (37.0%)
Improved ..	6 (15.0%)	9 (29.0%)	6 (13.6%)	20 (37.0%)
Unchanged or worse ..	14 (35.0%)	9 (29.1%)	7 (15.9%)	14 (26.0%)
Total ..	40 (100%)	31 (100%)	44 (100%)	54 (100%)
	$\chi^2=2.38$. $n=2$. $P>0.05$.		$\chi^2=11.3$. $n=2$. $P<0.01$.	

admitted in their first attack, whereas there is a marked difference between these two forms of treatment in patients admitted in a relapse. Taking the first attacks, it will be noted that the corticotrophin group had a somewhat higher proportion of patients symptom-free at the end of treatment, but it also had a slightly higher proportion of patients deriving no benefit from medical treatment; these differences from the cortisone group, however, are small, and would be expected to occur often by chance alone. Taking the relapses, the corticotrophin group fared conspicuously better than the cortisone group, there being nearly twice as big a proportion entirely symptom-free at the end of treatment. The differences between the two treatment groups so far as relapse cases are concerned are highly significant in a statistical sense, for they would occur by chance alone less than once in a hundred times.

Similarity of the Treatment Groups

It is, of course, essential to be certain that any difference in behaviour between the two groups is due to the specific treatment and not to other factors. The random allocation of patients to one or other treatment group is the main reason for concluding that the differences in clinical response to corticotrophin and cortisone represent genuine differences in the comparative efficacy of these two forms of treatment. The sex composition and the age composition of the two groups were closely similar, both for the series as a whole and when first attacks and relapses were considered separately. In any event, detailed analysis does not show that either age or sex makes any large contribution to the immediate prognosis of patients treated with corticoids. A more important factor to be considered is the severity of the illness when the patient was entered into the trial. Analysis showed that the two treatment groups were closely similar in the proportions of patients with severe, moderate, and mild attacks of the disease.

Sigmoidoscopy and Barium Enema

Unfortunately the data provided by sigmoidoscopy and barium enema are incomplete. All patients had both these investigations shortly before the beginning of treatment as part of the diagnostic criteria for admitting patients to the trial, but some did not have these

examinations repeated at the end of treatment. In a minority of cases this was because the patient had failed to respond to medical treatment, but in others because of a reluctance on the part of individual physicians to repeat the examinations in patients who were making satisfactory clinical progress.

In 136 patients sigmoidoscopy was carried out at the end of the trial period, so that comparison can be made with the findings before treatment. (Appearances were classified according to an agreed code.) Table III shows that patients treated with corticotrophin were somewhat more likely to show favourable sigmoidoscopic responses both in first attacks and in relapses of the disease. For the sample as a whole, the differences between the corticotrophin and cortisone groups reach conventional levels of statistical significance. If we assume that the sample is representative of the whole series, we can conclude that corticotrophin is more likely to bring about sigmoidoscopic improvement than is cortisone, although the difference is far from being a striking one.

So far as the barium-enema findings are concerned, our conclusions must be even more tentative, because only 92 patients underwent this examination at the end of the trial period. Many physicians are reluctant to carry out barium enema examinations more often than is strictly necessary for diagnosis or for assessment of the progress of the disease because they find that these examinations can be distressing to the patients and are occasionally followed by a frank clinical relapse. However, if we assume this sample of 92 patients to be representative of the whole group, Table IV shows that

TABLE IV.—*Barium-enema Findings in 92 Patients Examined at the End of Treatment*

	Corticotrophin Group	Cortisone Group
Normal	5	1
Improved	13	12
Unchanged or worse ..	29	32
Total	47	45

there was little difference between the corticotrophin and cortisone groups. In both, it is exceptional to find entirely normal appearances, although improvement is fairly common.

Complications in Part A

There are many complications of ulcerative colitis, some of which are extremely dangerous and help to account for the high fatality rate among the more severe examples of this illness. The corticoids themselves carry the risk of complications, no matter what the disease for which they are being used, when they are given systemically in the doses used in this part of the present study. An additional possibility is that they may increase the risk of complications of the disease itself. It is sometimes a knotty point to decide whether a particular complication is due directly to the disease, directly to the

TABLE III.—*Sigmoidoscopic Appearances in 136 Patients Examined at the End of Treatment of the Acute Attack*

Sigmoidoscopic Appearances	First Attacks		Relapses		Whole Series	
	Corticotrophin Group	Cortisone Group	Corticotrophin Group	Cortisone Group	Corticotrophin Group	Cortisone Group
Normal or near-normal ..	9 (31.0%)	2 (8.0%)	8 (21.6%)	5 (11.1%)	17 (25.8%)	7 (10.0%)
Improved	11 (38.0%)	15 (60.0%)	20 (54.1%)	21 (46.7%)	31 (46.9%)	36 (51.4%)
Unchanged or worse ..	9 (31.0%)	8 (32.0%)	9 (24.3%)	19 (42.2%)	18 (27.3%)	27 (38.6%)
Total	29 (100%)	25 (100%)	37 (100%)	45 (100%)	66 (100%)	70 (100%)
	$\chi^2=4.86$. $n=2$. $P>0.05$.		$\chi^2=3.54$. $n=2$. $P>0.05$.		$\chi^2=6.34$. $n=2$. $P<0.05$.	

treatment, or to the two acting in conjunction. We therefore think it essential to refer to our previous study of cortisone in ulcerative colitis, as there was then a control group of patients who were on no form of corticoid therapy. 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. So far as the dangerous complication of colonic perforation was concerned, the only two cases that occurred were both in the control group.

Table V shows the complications encountered in the present study. It will be appreciated that some individuals suffered from more than one of these

TABLE V.—Complications During the Trial Period

Complications	Corticotrophin Group	Cortisone Group
Hypercortisonism	11	2
Mental disturbances	5	3
Perforated peptic ulcer	1	0
Haemorrhage from peptic ulcer	1	0
Abscesses and fistulae about rectum	0	3
Perforation of colon	3	3
Massive haemorrhage from bowel	1	2
Moniliasis	6	3
Arthritis	0	1
Severe electrolyte disturbance (hypokalaemia)	1	1
Pyelonephritis	1	0
Skin rashes	0	2
Herpes zoster	1	0
Pneumonia	2	0
Staphylococcal abscesses of lung (multiple)	1	0
Prostatic obstruction	1	0
Deep leg-vein thrombosis	0	1
Sacral abscess at site of intramuscular injection of iron	0	1
Pulmonary embolism	0	1
Hepatitis (mild)	0	1

complications, either simultaneously or in succession. Some comments are worth making about the individual complications.

Hypercortisonism.—These patients showed one or several of the following features: retention of water with obvious oedema, hypertension, glycosuria (two cases), or the characteristic moon-face and hirsutism to a marked degree. It will be noticed that, in the doses used, corticotrophin was more liable to produce these effects than cortisone.

Mental Disturbances.—These could be included with hypercortisonism, for we have little doubt that the majority, if not all, were due to corticoid therapy. The clinical features varied from mania to stuporous depression. All the affected patients recovered without great delay when corticoid treatment was reduced or terminated. Corticotrophin was somewhat more apt than cortisone to produce mental disturbances.

Peptic Ulcer Complications.—The creation or activation of a peptic ulcer occurred in two patients, both of whom were receiving corticotrophin. One, who had a previous history of duodenal ulcer, died after a haematemesis, but this might well have been due to prostatic obstruction and ascending urinary infection. The other, in whom a bloody diarrhoea had been completely checked by corticotrophin in the course of a week, died from perforation of an ulcer on the greater curvature of the stomach.

Perforation of Colon.—This occurred in six patients, three in each group. Two of them died, the others being treated successfully by emergency colectomy.

Massive Haemorrhage from Bowel.—This occurred in three cases, but was not fatal in any.

Moniliasis.—This was a fairly common complication, being more frequent in the corticotrophin group. The two cases in which it was severe were likewise in the corticotrophin group. In one there was involvement of the upper gastro-intestinal tract, but the patient recovered. In the other the oesophagus was extensively invaded, and the

patient subsequently died from bronchopneumonia with multiple small abscesses in the lungs, although moniliae were not found in the sputum in life or in the lungs after death.

Electrolyte Disturbances.—Severe electrolyte disturbances after the beginning of treatment were unusual, presumably because physicians experienced in this disease take pains to correct any changes before they become severe.

Other Complications.—There were various other complications scattered between the two treatment groups, but they were individually few and no general conclusions can be drawn on their relationship to one or other form of treatment.

Ileostomy and Colectomy

Fourteen patients (8.3%) were treated by ileostomy combined with colectomy during or shortly after the trial period. Four elective operations were carried out after improvement on medical treatment, either because there was a complication such as recto-vaginal fistula or because surgery was judged to be the best definitive treatment; there was one death among this group. The remaining 10 patients underwent colectomy as an emergency operation. Five of these colectomies were done because of colonic perforation: one of these patients died. (The sixth patient with colonic perforation was judged unfit for surgery.) Another patient was operated on for suspected colonic perforation although no perforation was found. The remaining four colectomies were performed because of general deterioration of the patients' condition while under medical treatment, being carried out either during the trial period or at the end of it; there was one death following operation.

Deaths in Part A

There were 12 deaths in the acute attack, five being among the corticotrophin group and seven among the cortisone group, giving a fatality rate of 7.1%. Very brief details are given below.

Corticotrophin Group

First Attacks (4 deaths out of 40).

Case 1.—A man aged 76, an acute case of ulcerative colitis, failed to respond to six weeks' general medical treatment before admission to the trial. It was this fact, combined with the likelihood that he would die, which caused the physician in charge to ignore the past history of duodenal ulcer and arrange admission, taking "a calculated risk," to quote his own words. The patient's bowel symptoms responded well to corticotrophin, but four weeks after beginning this treatment he developed prostatic urinary obstruction, which terminated in fatal haematemesis and melaena. *Post-mortem examination:* (1) Haemorrhage from duodenal ulcer. (2) Prostatic obstruction, pyelonephritis, and renal calculus. (3) Colon completely healed.

Case 2.—A man aged 55, a moderately severe case, failed to respond to corticotrophin and developed bronchopneumonia, which proved fatal. *Post-mortem examination:*—(1) Bronchopneumonia. (2) Colon: healed scars of ulcers several inches long; satisfactory healing of the colon.

Case 3.—A man aged 57, a moderately severe case, rapidly became symptom-free with corticotrophin therapy, so that the dose was reduced to 40 units daily and he was allowed to go home at the end of four weeks to complete his trial period there. One week later he developed a respiratory infection and was brought to hospital in a moribund condition and died. *Post-mortem examination:*—(1) Acute bronchitis with early bronchopneumonia. (2) Colon: healing ulcerative colitis. (Note: This death occurred during the epidemic of Asian influenza, in which such rapid deaths were not excessively rare in individuals previously in good health.

The contribution of the corticotrophin must therefore remain problematical.)

Case 4.—A man aged 53, a severe case, with violent bloody diarrhoea and evidence of right-sided pulmonary infection, responded well and rapidly to corticotrophin so far as the bowel was concerned, so that he was passing one formed stool a day without blood. However, he then collapsed, dying with abdominal and chest symptoms. *Post-mortem examination*:—(1) Perforation of greater curve of stomach due to acute peptic ulcer; acute duodenal ulcer also present. (2) Extensive right-sided bronchopneumonia (non-tuberculous). (3) Colon: ulceration of caecum and ascending colon.

Relapses (1 death out of 44 cases).

Case 5.—A man aged 76, a moderately severe case, responded well to corticotrophin so far as the bowel was concerned, as the stools were normal after four weeks. He, however, had developed a monilial infection of the mouth, which became severe and spread into the oesophagus. Corticotrophin was reduced in dosage and then stopped, but he remained extremely ill. Treatment with nystatin and local gentian violet had little effect. Pulmonary symptoms developed, but moniliae were not found in the sputum; however, death occurred from the respiratory infection. *Post-mortem examination*:—(1) Bronchopneumonia with multiple small abscesses; moniliae not isolated. (2) Moniliasis of mouth, pharynx, and entire oesophagus. (3) Colon: ascending colon showed congestion and inflammation, transverse colon was normal, sigmoid and descending colon showed congestion and some ulceration.

Cortisone Group

First Attacks (2 deaths out of 31 cases).

Case 6.—A woman aged 22, a severe case, with marked constitutional disturbance and faecal incontinence of grossly bloody stools, had failed to respond to one month of vigorous general medical treatment. With cortisone she was much improved, the fever subsided, and the stools fell to about four a day with only small amounts of blood present. She was getting up and about when, during the third week, she developed abdominal pain and tachycardia, for which no cause could be found. For the next few days she improved, but then, during the night, she developed severe pain in the chest accompanied by peripheral circulatory failure. Attempts to overcome this failed, and the next day, following a second attack of severe chest pain, she died. The clinical diagnosis was pulmonary embolism. Permission for a post-mortem examination was refused.

Case 7.—A young man of 19, a severe case with fever, tachycardia, anaemia, and much raised E.S.R., had 20 loose bloody motions a day. On cortisone he gradually deteriorated, and after 2½ weeks a monilial infection of the throat developed. Four days later he suffered a perforation of the anterior wall of the caecum. Ileostomy and colectomy were carried out. The immediate post-operative course was uneventful, but a few days later pain in the left side of the chest developed and he was found to have a small sterile effusion. The white blood count was 46,000. It was thought likely that a subphrenic abscess was developing, and he was treated with tetracycline. Blood culture yielded a growth of non-haemolytic streptococci sensitive to chloramphenicol which was then used as treatment but without effect. The pathological report on the operation specimen stated: terminal ileum normal; mucosa of caecum severely diseased, with several deep ulcers, one of which had perforated; most of the rest of the colon showed severe ulcerative colitis. *Post-mortem examination*:—(1) General emaciation. (2) Ileostomy appeared satisfactory. (3) Abdomen: low-grade peritonitis and small pelvic abscess, no subphrenic abscess. (4) Infarcts in both lungs with a small effusion of the left side. Pathologist's opinion of the cause of death: general blood-stream infection with non-haemolytic streptococci, together with chronic low-grade peritonitis and pleurisy.

Relapses (5 deaths out of 54 cases).

Case 8.—A boy aged 16, a severe case with gross constitutional disturbance, showed no response to cortisone after four weeks' trial. He was therefore treated by ileostomy. The post-operative course was at first uneventful, but 10 days after the operation he suddenly collapsed and died. Permission for a post-mortem examination was refused.

Case 9.—A woman aged 34, a severe case with gross constitutional disturbance, showed little change during the six-weeks trial with cortisone. She was then given a short course of corticotrophin, which improved her, and was treated by colectomy. However, she died after this operation. A pathological report on the operation specimen stated: "Whole colon affected by ulcerative colitis; sigmoid colon and caecum grossly ulcerated, but remainder showing healing with pseudopolypoid changes." *Post-mortem examination*: Marked fatty degeneration of the liver.

Case 10.—A woman aged 79 had a three-years history of ulcerative colitis, the present attack not being extremely severe so far as the bowels were concerned, but there was gross constitutional disturbance. She continued to lose weight, went downhill, and died. *Post-mortem examination*:—Proctocolitis. No obvious immediate cause of death.

Case 11.—A woman aged 36, a severe case with profuse bloody diarrhoea and gross constitutional disturbance, showed no response to cortisone therapy, and after one week a colonic perforation was suspected and laparotomy was carried out. No perforation was found, but emergency total colectomy and ileostomy were performed. The patient died post-operatively. The report on the operation specimen stated that the colon showed areas of narrowing and thinning of walls, with congested mucosa interspersed with hyperplastic polypoid areas and with ulceration at many points; the terminal ileum showed a roughened haemorrhagic mucosa. *Post-mortem examination*:—(1) Proctocolectomy and ileostomy. (2) Focal necrosis of liver. (3) Severe hypokalaemia (serum potassium, 3.2 mEq).

Case 12.—A man aged 71, a moderately severe case, progressed reasonably well until he collapsed with signs of perforation 21 days after starting treatment. He was thought not fit enough to undergo emergency surgery. *Post-mortem examination*:—Ulcerative colitis affecting the descending and sigmoid colon and the rectum, with perforation of three ulcers in the sigmoid colon. Generalized peritonitis.

Results in Part B

Of the patients who were symptom-free at the end of Part A of the study, 68 were admitted to the trial of maintenance. This group of 68 patients was composed of four subgroups according to whether the preceding attack of ulcerative colitis had been a first attack or a relapse and whether it had been treated with corticotrophin or cortisone. Patients in each of these subgroups were allotted at random to maintenance therapy with oral cortisone, 25 mg. b.d., or with inert tablets, and their progress was observed for one year.

All the essential information for judging the effect of maintenance therapy is given in Table VI, upon which are based Tables VII and VIII, which deal with individual points. Table VII shows that maintenance treatment with cortisone had no beneficial effect upon the course of the disease during the year of observation. Indeed, the patients receiving cortisone tablets suffered from relapse somewhat more frequently than did the patients in the control group, although the difference is not statistically significant. However, the direction of the difference makes it possible for us to conclude with a high measure of assurance that cortisone in a dose of 25 mg. b.d. had no beneficial effect.

Table VIII shows that the relapse rate was appreciably higher (more than half as great again) among the patients who had originally been treated with corticotrophin as against those who had received cortisone in the acute attack. The difference is just at the borderline of the conventional level of statistical significance. This is an important finding because it bears on the comparative value of these two agents in ulcerative

TABLE VI.—*Relapses Occurring During the Course of One Year of Maintenance Therapy*

		Time after Beginning Maintenance Therapy (Months)								Total No. of Relapses	Total No. of Patients
		1	2	3	4	6	7	9	10		
<i>Maintenance Therapy with Cortisone Tablets</i>											
Corticotrophin group	{ 1st attack	1					2			6	10
	{ Relapse	1	1	2	1	1	1	—	1	8	12
Cortisone group	{ 1st attack	2	—	—	—	—	—	—	—	2	8
	{ Relapse	1	—	1	—	—	—	—	—	2	7
Total ..		5	2	3	2	1	3	—	2	18	37
<i>Maintenance Therapy with Inert Tablets</i>											
Corticotrophin group	{ 1st attack	1	2	—	1	—	—	—	—	4	6
	{ Relapse	2	1	—	—	—	—	—	1	4	12
Cortisone group	{ 1st attack	1	—	—	—	—	—	—	—	1	3
	{ Relapse	2	—	1	—	—	—	1	—	4	10
Total ..		6	3	1	1	—	—	1	1	13	31
Grand Total ..		11	5	4	3	1	3	1	3	31	68

No relapses occurred during the fifth, eighth, eleventh, and twelfth month.

TABLE VII.—*Relapse Rate Among Patients Treated with Cortisone and Inert Tablets (Whole Series)*

Maintenance Treatment	No. of Patients	Relapses		Significance of Difference
		No.	%	
Cortisone ..	37	18	48.6	$\chi^2 = 0.3$, $n = 1$, $P > 0.05$
Inert tablets ..	31	13	41.9	

TABLE VIII.—*Comparison of Relapse Rate in Patients Originally Treated Either with Corticotrophin or with Cortisone*

Original Treatment	No. of Patients	Relapsing on Maintenance Treatment		Significance of Difference
		No.	%	
Corticotrophin	40	22	55.0	$\chi^2 = 3.46$, $n = 1$, $P \approx 0.05$
Cortisone ..	28	9	32.1	

colitis. Corticotrophin has been shown to be the more effective in bringing about clinical remission in the acute attack, at any rate so far as patients in a relapse (as opposed to a first attack) are concerned. On the other hand, this beneficial effect is largely offset by the increased relapse rate during the succeeding year.

Results in Part C

It is of some importance to know whether a good clinical response to corticoid treatment in one attack of ulcerative colitis means that such patients are likely to respond favourably if they suffer from a subsequent attack.

Of the patients who suffered from a frank clinical relapse during the course of maintenance therapy, 15 were treated with cortisone in an initial dose of 50 mg. q.d.s. The clinical response to this form of treatment is given in Table IX. It will be seen that the response was much the same as was obtained for the whole cortisone group in the initial acute attack (see Table I). This finding disposes of the possibility that one good

TABLE IX.—*Response to Treatment with Known Cortisone in 15 Patients who Relapsed While on Maintenance Therapy*

Response to Cortisone Treatment	No. of Patients	%
Remission ..	6	40
Improved ..	3	20
Unchanged or worse ..	6	40
Total ..	15	100

response to corticoid therapy is a favourable sign indicating that subsequent attacks will also respond. On the other hand, there is no suggestion that patients become unduly refractory to cortisone.

It is also worth mentioning that it made no difference whether the maintenance treatment had been with cortisone or inert tablets. Although the numbers are small, the exact similarity between the response of patients who had been on "real" and "dummy" maintenance tablets, respectively, makes us conclude that a maintenance dose of cortisone of 50 mg. a day did not influence the response to a larger dose if a frank relapse was being treated (Table X).

TABLE X.—*Response to Treatment with Known Cortisone in Patients who Relapsed while on Maintenance Treatment with "Real" or "Dummy" Cortisone Tablets*

Clinical Response to Cortisone Treatment	Type of Maintenance Treatment Preceding Relapse	
	Cortisone	Inert Tablets
Remission ..	4	2
Improved ..	2	1
Unchanged or worse ..	4	2
Total ..	10	5

Discussion

Our previous controlled therapeutic trial disclosed that oral cortisone was a useful addition to the standard medical treatment of ulcerative colitis in increasing the chance of remission. This conclusion finds support in the work of others, such as that carried out in the University of Chicago (Kirsner and Palmer, 1954; Sklar *et al.*, 1957; Kirsner *et al.*, 1957a, 1957b) and in Toronto (Maltby *et al.*, 1956). However, the beneficial effect of cortisone was far from universal, and only a little more than 40% of the patients were symptom-free after six weeks' treatment, even though this was a much higher proportion than occurred in the control group. An additional limitation was shown to be that the chance of relapse during the next 18 months was much the same for the cortisone as for the control group. In the present study the results with cortisone were practically identical with those in the first trial, even though the dosage was on the average twice as large.

The comparison between corticotrophin and cortisone in the acute attack has shown that there is little to choose between these two agents in the treatment of a first attack but that corticotrophin is more efficient in bringing about clinical remission in patients suffering from a relapse of established ulcerative colitis. We realized that the actual comparison has been between 80 units of corticotrophin and 200 mg. of cortisone a day, but the former is probably a maximum effective dose, and it seems unlikely that much would be gained by giving a larger dose of cortisone in view of the fact that 200 mg. produced much the same effects as 100 mg.

The use of corticotrophin in the doses employed in the present study carries the price of a higher risk of complications due to therapy, which chiefly take the

usual form of hypercortisonism, with a clinical picture resembling that of Cushing's syndrome, but which also include a greater liability to mental disturbance, to moniliasis, and to serious complications of peptic ulcer. It has also been shown that the patients treated successfully with corticotrophin are more prone to suffer from a relapse during the next year, and this circumstance offsets to some extent the greater potency of corticotrophin in treating an actual relapse. For these reasons we judge that corticotrophin should not normally be used in treating an attack of ulcerative colitis until cortisone, hydrocortisone, or one of the synthetic adrenal steroids (prednisone, prednisolone, or triamcinolone) has been tried without favourable response. An exception may be made in those patients in a severe relapse who are judged to be so ill that the most potent remedy should be immediately used.

One of the disadvantages of carrying out a long-term therapeutic trial is that new remedies may be introduced while the trial is in progress. Thus prednisone, prednisolone, and triamcinolone have come into use since the present trial started. It is believed by some workers that hydrocortisone and prednisone are more effective than cortisone in chronic ulcerative colitis although not as effective as corticotrophin (Fierst *et al.*, 1957). It may well be that all corticoids which are given by mouth and have to pass the barrier of the liver are at a disadvantage compared with agents which are given parenterally, but this could be decided only by further trials on similar lines. Trials are also required of the relative merits of corticoids by mouth, corticotrophin by subcutaneous injections, and water-soluble preparations of hydrocortisone applied topically to the colon by means of a rectal drip (Truelove, 1958; Watkinson, 1958). Finally, the hormones might be compared with salicylazosulphapyridine, which has been claimed to have a specific action in chronic ulcerative colitis (Svartz, 1942, 1948, 1954, 1956; Morrison, 1952, 1953; Bagen, 1955).

The most important finding in our present study is a negative one. It has often been considered that when an attack of ulcerative colitis has been brought under control by the use of cortisone the dose can be reduced to quite a small maintenance level and the patient will be held in remission. We have now found that a maintenance dose of 50 mg. of cortisone daily has no effect upon the relapse rate. We can only conclude that those workers who have judged a maintenance dose of this size to be of use have been attributing to the treatment an effect which is really due to the natural history of the disease. When a disease presents in the form of attacks interspersed by periods of freedom from symptoms, clinical judgment is inadequate in deciding whether a maintenance treatment is effective and a fully controlled trial is essential.

Of course, our negative finding in respect of cortisone maintenance therapy when used in a dose of 50 mg. daily cannot be applied to different dosages. We do not have any information on whether a larger dose would be more effective or whether, if this were so, the benefits would outweigh the risks of long-term treatment with such higher doses. What is plain is that if a patient remains symptom-free when the dose of cortisone is reduced to 50 mg. a day the cortisone might as well be stopped, because there is no evidence that it helps to prevent relapse, and this dose is still sufficient to bring about harmful effects.

The final part of our study shows that a patient who has once responded successfully to treatment with corticotrophin or cortisone has much the same chance of responding in a subsequent attack as the general run of patients. On the one hand, there is no suggestion that a favourable response to this form of treatment in one attack means that the chance of responding well in a later attack is specially good. On the other, there is no evidence that such patients are unduly refractory to cortisone treatment.

It is sometimes said that no medical treatment has any appreciable effect on the long-term results in ulcerative colitis, but, although maintenance treatment has proved unsuccessful, the ability to relieve the acute attacks with cortisone and corticotrophin throws doubt on this statement. It is also stated that treatment with cortisone and corticotrophin may prejudice future surgical treatment. The present trial affords no evidence on this point, but in our previous study the patients treated by cortisone not only came less often to surgery than the control patients but also survived it better when they did. We know of no unequivocal evidence that adrenal hormones increase the ulceration or friability of the colon, and we see no reason why their use should increase operative mortality provided steps are taken to combat possible hypoadrenalism at the time of operation and in the early post-operative period. This is readily done by seeing that surgery is performed under cover of hydrocortisone, which can be given intravenously if necessary.

Summary

A therapeutic trial of corticosteroid therapy in non-specific ulcerative colitis has been carried out in ten hospital centres.

In the first part of the trial, which involved 169 patients admitted to hospital with a frank attack of ulcerative colitis, a comparison was made between the effect of oral cortisone in a dose of 50 mg. q.d.s. and that of intramuscular corticotrophin in a daily dose of 80 units of the gel.

For the group as a whole, corticotrophin proved to be more effective than cortisone in bringing about complete clinical remission in the course of six weeks' treatment. Further analysis showed that corticotrophin and cortisone gave closely similar results in patients admitted in first attacks of the disease. Among patients admitted in a relapse of established disease, corticotrophin was much superior to cortisone, there being twice as big a proportion of patients rendered symptom-free during the trial period.

Complications were numerous and some were attributable to corticosteroid therapy. Corticotrophin-treated patients were more liable to show hypercortisonism, mental disturbance, peptic ulcer complications, and monilial infections.

Deaths during the trial period or shortly after were roughly equal in the two treatment groups, there being five deaths among those patients treated with corticotrophin and seven among those treated with cortisone. Brief details of the fatal cases are given.

In the second part of the trial, patients who were symptom-free at the end of the trial period of treatment with corticotrophin or cortisone were put on maintenance treatment, which lasted for a year unless a relapse of the disease supervened. This part of the trial was a

"double-blind" study in which some patients were treated with cortisone tablets, 25 mg. b.d., while the remainder received inert tablets.

Cortisone, in the dose used, proved to have no effect on the liability to relapse of the disease during the year of observation.

The other important finding during this period was that patients treated in the acute attack with corticotrophin were more liable to relapse than patients who had been treated with cortisone. The superiority of corticotrophin in bringing about clinical remission in the acute attack is therefore partly offset by the greater chance of subsequent relapse.

In the third part of the trial a number of the patients who relapsed during the year of maintenance were treated openly with cortisone. The results were similar to those obtained with cortisone in the original attack. In other words, patients who have previously responded well to corticosteroid therapy are neither specially likely to respond well when a subsequent attack of the disease occurs nor likely to be unduly refractory to corticosteroids.

The essential conclusions are: (1) There is little to choose between corticotrophin and cortisone in the treatment of a first attack of ulcerative colitis. (2) In a frank relapse of established ulcerative colitis corticotrophin is superior to cortisone in bringing about a fairly speedy clinical remission, but at the price of a greater risk of complications and of a higher risk of subsequent relapse. Consequently it may normally be best to begin with cortisone and to hold corticotrophin in reserve for use in patients who do not respond well. (3) Maintenance treatment with cortisone in a dosage of 25 mg. b.d. is totally ineffective in reducing the liability to relapse.

The findings are discussed in relation to new corticosteroids which have been developed since this study began and to other forms of treatment which have been used to induce remission of an attack. The need for organized therapeutic trials to compare the efficacy of these various agents is stressed.

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FALL OF BLOOD PRESSURE AFTER A NORADRENALINE INFUSION AND ITS TREATMENT BY PRESSOR AGENTS

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In circumstances in which the blood pressure has fallen low, noradrenaline is often given by intravenous drip in order to restore it; for this purpose noradrenaline is preferred to adrenaline because it is a more effective pressor agent and because under its influence the heart rate does not rise. The observation has often been made, however, that when the drip of noradrenaline is stopped the blood pressure falls to a low level and that the drip has to be started again to maintain the pressure at a reasonable height. Anaesthetists and others accustomed to using a noradrenaline drip know that the drip should not be stopped suddenly but should be reduced gradually, and some speak of "weaning" the patient from the drip.

Recent observations which we have made have enabled us to offer an explanation of the fall in blood pressure which occurs on stopping a noradrenaline drip, and to suggest measures for dealing with it.

Methods

The observations have been made in spinal cats prepared by Dale's method. The cat was anaesthetized with ether and the cord was exposed and cut at the level of the second cervical vertebra. The brain was then destroyed by a probe passed through the foramen magnum, after which artificial respiration was given and ether was discontinued. Noradrenaline was infused at a constant rate by using a motor-driven syringe (C. F. Palmer (London) Ltd.). Cats were given reserpine dissolved in 20% ascorbic acid by intraperitoneal injections of 3 mg./kg. on two successive days. The cats were then used for experiment on the third day. In some experiments the volume of the spleen was recorded by drawing it outside the body wall and enclosing it in a plethysmograph.

Results

Noradrenaline is ordinarily thought of as the substance released at the terminations of the post-ganglionic sympathetic fibres, and also released, together with adrenaline, from the adrenal medulla. This view is, however, incomplete. Noradrenaline is present in all organs innervated by sympathetic nerves, and can be extracted from them. This was shown by Schmiterlw (1948) for the large vessels of the ox, the horse, the dog, and the pig; and also by Euler and Purkhold (1951) for the spleen, the kidney, the liver, and the salivary glands; and by Goodall (1951) for the heart. Furthermore, Adams-Ray and Nordenstam (1956) have shown that chromaffin cells, which are known to contain adrenaline and noradrenaline, are present in human skin, and our colleague, Mr. E. H. Leach, has also found them adjoining the vessels in the skin of the rabbit ear. We were able to extract