tenance therapy with local hydrocortisone is therefore ineffective in reducing the chance of relapse.

The implications of these various findings are briefly discussed.

I am indebted to Glaxo Laboratories, who not only made a gift of the hydrocortisone hemisuccinate sodium and the inert preparation, but also packed and labelled them ready for use in this trial. I am also indebted to the Medical Research Council for a grant for technical assistance. I wish to thank the following colleagues: Dr. M. H. Hambling for conducting the bacteriological studies; Dr. R. L. Vollum and Dr. W. H. H. Jebb for advice on antibiotics and bacteriology; Miss H. Enser, who assisted me in the sigmoidoscopic examinations and prepared the histological specimens; Miss M. G. Craig and Miss S. V. James, who issued the various therapeutic agents according to the prepared plan; and Miss M. C. McLarty, who made the Charts.

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APPENDIX: BACTERIOLOGY OF THE COLONIC SWABS

BY

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Methods

At each examination the pelvic colon was swabbed through the sigmoidoscope. Bacteriological examination of the swab was made: (1) to exclude intestinal pathogens of the Salmonella and Shigella groups; and (2) to determine the antibiotic sensitivities of the predominant organisms in order to detect any marked increase of resistant strains following rectal antibiotic therapy.

Each swab was shaken with 5 ml. of digest heart broth, and a loopful of the broth was inoculated to each of the following media:—*Solid media:* Two blood-agar plates (one for anaerobic incubation), a deoxycholate citrate agar plate and a MacConkey agar plate. *Fluid media:* A Robertson's cooked-meat medium, and a Robertson's cooked-meat medium to which 10% NaCl had been added.

Finally 5 ml. of selenite F (Leifson, 1936) was added to the remainder of the broth and all cultures were incubated at 37° C. overnight.

The following day the plates were examined. The Robertson's cooked-meat medium was plated to two blood-agar plates (one for anaerobic incubation), one deoxycholate citrate agar plate, and one MacConkey agar plate; the Robertson's cooked-meat medium containing salt was sub-cultured to a plate of nutrient agar containing 7% salt and to a blood-agar plate (for aerobic incubation). The selenite F broth was plated to a deoxycholate citrate agar plate. All the plates were then incubated overnight at 37° C.

No special media were used in an attempt to isolate yeasts, lactobacilli, or anaerobic Gram-negative rods.

The organisms most frequently isolated were lactose-fermenting Gram-negative rods (L.F.s), *Streptococcus faecalis, Clostridium welchii, Staphylococcus aureus,* micrococci, Proteus, and paracolon organisms; and of these, L.F.s and *str. faecalis* were the most common.

The Gram-negative rods were examined for sensitivity to streptomycin and neomycin, while the Gram-positive organisms were tested against penicillin and neomycin.

Findings

1. No member of the Salmonella or Shigella groups was isolated from any of the 137 specimens examined.

2. Lactose-fermenting Gram-negative rods isolated from the 30 patients treated with rectal penicillin and streptomycin tended to show an increased resistance to streptomycin. Before treatment, 34 strains of L.F.s were isolated of which 4 were sensitive to 25 units of streptomycin per ml., and 30 sensitive to 12 or less units of streptomycin per ml.; whereas after treatment 24 strains were isolated, of which 7 were resistant to 100 units of streptomycin per ml., 1 was sensitive to 50 units of streptomycin per ml., 3 were sensitive to 25 units of streptomycin per ml., and the remaining 13 strains were sensitive to 12 or less units of streptomycin per ml. Strains of *Str. faecalis* isolated before and after treatment showed no increased resistance to penicillin.

3. Strains of *Staph. aureus* were isolated from eight patients, but in no case was a penicillin-sensitive strain replaced by a penicillin-resistant strain, and in only one patient (an in-patient) was *Staph. aureus* isolated from every specimen.

Colonic swabs from the smaller series of patients who were given neomycin rectally were subjected to the same culture routine as above, but in no case were neomycin-resistant organisms isolated.

Summary

Bacteriological examination of 137 colonic swabs failed to isolate any member of the salmonella or shigella groups.

Following rectal administration of streptomycin, penicillin, and neomycin it appeared that a few strains of lactose-fermenting Gram-negative rods showed increased resistance to streptomycin, but no Gram-positive organisms showed increased resistance to penicillin or neomycin.

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TREATMENT OF ULCERATIVE COLITIS WITH TOPICAL HYDROCORTISONE HEMISUCCINATE SODIUM

A CONTROLLED TRIAL EMPLOYING RESTRICTED SEQUENTIAL ANALYSIS

BY

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The many reports indicating that systemic corticoid therapy was of value in the treatment of ulcerative colitis, and the fact that topical hydrocortisone had been used successfully in various eye, joint, and skin diseases, made it possible that mild cases of colitis would respond to this method of treatment.

Favourable reports of the use of topical hydrocortisone in colitis have already appeared (Truelove, 1956, 1957). These results were considered by him to be encouraging enough to merit a controlled trial of this form of treatment of colitis.

A controlled trial has therefore been undertaken where the relative merits of solutions of hydrocortisone hemisuccinate sodium and an inert preparation administered rectally to patients with haemorrhagic proctocolitis and ulcerative colitis have been assessed in a blind controlled trial. In order to obtain a significant answer as rapidly as possible a method of restricted sequential analysis devised by Dr. Peter Armitage has been used in the planning and control of the trial. A significant advantage in favour of the potent hydrocortisone has been demonstrated by 19 treatments in 16 patients with colitis where symptomatic remissions and sigmoidoscopic improvement occurred significantly more commonly in those receiving potent therapy. The

responses of patients receiving potent and dummy treatments are first contrasted and later the method of sequential analysis of the results obtained is detailed.

Method of Administration

Glaxo Laboratories were kind enough to provide potent and inert agents for the trial, labelled Y and X respectively. Treatment was administered to patients as follows: 100 mg. of hydrocortisone hemisuccinate sodium or the dummy preparation was dissolved in 100 ml. of normal saline. It is important that the solution be freshly prepared before use, as slow hydrolysis occurs and causes some of the hydrocortisone to precipitate out of the solution on standing. The patient lies on his left side, and the solution is then administered through an intravenous drip set attached to a rectal catheter at a fairly rapid drip rate of one to two drops per second over a period of 15 to 30 minutes. The rectal infusion is retained overnight and is repeated on 15 successive evenings. Usually the technique was rapidly mastered by the patients receiving it, and after two to three nights of treatment in hospital they returned home and continued nightly infusions there.

In more severely affected patients in whom nocturnal diarrhoea might prevent the retention of the infusion an intravenous injection of propantheline, 15–30 mg. half an hour before the infusion, was given to aid retention overnight.

Patients Treated

Sixteen patients with haemorrhagic proctocolitis or colitis were treated on 10 occasions with potent therapy and on nine with an inert preparation, three patients being treated twice. Treatments were allocated in random fashion to both groups, as is described later. All patients gave typical histories of recurrent diarrhoea and blood-stained stools, and showed mucosal changes on sigmoidoscopy which were consistent with the diagnosis. Barium-enema examinations were undertaken in each patient to assess the extent of colonic involvement. Precise clinical information on the age and sex, duration of history, and extent and severity of the disease is given in Tables I and II, and is summarized

TABLE I.—*Patients Receiving Hydrocortisone*

Treatment No.	Sex and Age	Duration of History	Extent of Disease*	Pre- and Post-treatment Assessments						Comment	Progress
				Hb	E.S.R.	Stools Daily	Blood	Mucus	Sig.†		
1	M 28	2 years	R.S.	—	—	6	++	++	3	Remission	Maintained for 6 months
				—	—	1	—	—	1		
2	M 59	2 ,,	R.S.D.	69	30	7	+++	+	4 (u)	Remission in severe acute colitis with associated ankylosing spondylitis. Mucosa restored to normal	Remission maintained clinically and sigmoidoscopically for 6 months
				98	20	1	—	—	1		
4	M 37	6 ,,	R.S.	90	—	6	++	+	2	Symptomatic remission without sigmoidoscopic improvement	Sigmoidoscopic appearances improved after 2 months. Clinical and sigmoidoscopic relapse at 6 months. Second course induced remission
				95	—	2	—	—	3		
6	F 28	4 ,,	R.S.	90	12	3	+	+	3	Symptomatic remission. Mucosal improvement	Remission maintained for 5 months
				95	8	2	—	—	2		
9	F 48	1 year	R.S.D.	79	15	8	+++	+	3	Failure—slight improvement	Relapse in 1 month. Received second course of dummy therapy
				70		5	+	+	2		
11	F 49	1 ,,	R.S.D.	85	6	2	+++	+	3	Clinical remission. Mucosal improvement. Associated duodenal ulcer	Remission maintained for 3 months
				90	6	1	—	—	1		
13	F 20	3 years	R.	93	15	5	++	+	3	Clinical remission. Mucosal improvement	Mild relapse after 3 months
				95	5	1	—	—	2		
15	F 53	25 ,,	R.S.	73	15	6	++	++	3	,, ,, ,,	Remission maintained for 6 months, when mucosa found to be normal
				85	5	1	—	—	2		
16	M 74	½ year	R.	74	—	5	+++	+	4 (u)	Clinical remission. Considerable mucosal improvement	Remission maintained for 6 months. Mucosa still remained improved (2)
				90	—	2	—	—	2		
18	F 44	7 years	R.S.	69	18	5	+	++	3	Clinical remission. Restoration of mucosal normality	Remission still maintained at 2 months
				87	12	1	—	—	1		

* *Extent of Radiological Changes:* R = Rectum only; no *x*-ray changes. R.S. = Rectum and sigmoid colon. R.S.D. = Rectum, sigmoid, and descending colon.
† *Sigmoidoscopic findings:* 1 = Normal mucosa. 2 = Mild granularity with minimal contact bleeding. 3 = Marked granularity and contact bleeding. 4 = Spontaneous rectal haemorrhage, ulceration (u).

TABLE II.—*Control Cases*

Treatment No.	Sex and Age	Duration of History	Extent of Disease*	Pre- and Post-treatment Assessments						Comment	Progress
				Hb	B.S.R.	Stools Daily	Blood	Mucus	Sig.†		
3	M 65	20 years	R.S.D.	80	10	3	++	+	3	Slight improvement	Relapse in 2 months
				85	10	2	+	—	3		
5	F 25	1 year	R.S.	65	15	10	++	++	3	Improved. Received second course dummy preparation	Relapse in 1 month
				76	9	5	+	+	2		
7	M 34	2 years	R.S.	88	12	3	++	+	3	Worse after treatment	Improved spontaneously in 3 months
				90	15	7	++	+	3		
8	F 48	25 ,,	R.	90	5	2	++	+	3	Slight improvement	Relapse in 2 months
				87	5	2	+	—	2		
10	F 25	1 year	R.S.	75	11	6	++	++	3	Failure	Relapse in 1 month. Given potent therapy
				80	10	6	++	++	3		
12	F 35	1 ,,	R.S.D.	82	25	6	++	+	4 (u)	,,	Some improvement followed systemic treatment with corticotrophin but condition still unsatisfactory and surgery undertaken
				74	30	6	++	++	4 (u)		
14	F 53	25 years	R.S.	85	—	6	+++	+	3	,,	Relapse in 2 months. Given potent therapy
				85	—	3	+	—	2		
17	F 66	6 mths	R.S.	89	20	7	++	+	3	Clinical remission. Mucosa unchanged	Remission maintained for 2 months
				90	20	2	—	—	3		
19	F 48	1 year	R.S.D.	75	35	10	++	+	3	Failure	Treatment abandoned after 5 infusions. Some improvement followed corticotrophin and "salazopyrin." Condition still unsatisfactory; surgery may be necessary
				70	30	15	++	++	3		

* † See footnotes to Table I.

in Table III, where those receiving potent and inert therapy are contrasted. It will be seen that the two groups of

TABLE III.—*Comparison of Effects of Topical Hydrocortisone with Dummy Preparation in Haemorrhagic Proctocolitis and in Ulcerative Colitis. Potent and Dummy Treatments Allocated in Random Manner to 16 Patients*

		Potent Therapy	Control Cases
No. of treatments		10	9
Ages		(4 males, 6 females) 20–74 years	(2 males, 7 females) 25–66 years
Extent of disease	Rectum	2	1
	Rectum and sigmoid colon	5	5
	Rectum, sigmoid, and descending colon	3	3
Duration of history	<1 year	1	1
	1–2 years	4	5
	3–4 ,,	2	0
	5 years+	3	3
Ulcerative lesions		2	1

patients treated are surprisingly similar in age, sex distribution, extent of disease, and duration of history. Two patients with more severe ulcerative lesions were treated with potent therapy and one with inert drug.

Method of Investigation

In all cases a clinical assessment of the patient's condition was made personally by an inquiry into the severity of diarrhoea and the blood content of the stools, the observer being unaware of the treatment given. A haemoglobin and an erythrocyte sedimentation rate were determined before and after treatment. Sigmoidoscopic examinations were performed before treatment and within two or three weeks of completion of the course of infusions. These examinations were made by an independent observer (Professor J. C. Goligher), who was also unaware whether potent or dummy treatment was being given. As will be seen, the clinical response of the patients receiving hydrocortisone (Table I) was strikingly better than those receiving inert therapy (Table II). In most patients receiving hydrocortisone the stools rapidly became normal; usually within two to three days of starting treatment blood disappeared from the stools and an improvement in the patient's general condition was shown by increased well-being and a rise in haemoglobin level and reduction in the erythrocyte sedimentation rates. The sigmoidoscopic appearances often returned to normal, but were improved in most of the cases going into clinical remission. Table II shows that inert therapy was strikingly ineffective: diarrhoea, if anything, was worse after treatment; haemoglobin and E.S.R. levels were unchanged or rather worse; and sigmoidoscopic appearances showed no change or a deterioration.

The overall results obtained in 19 treatment periods are summarized in Table IV. Of 10 patients receiving potent therapy all but one went into clinical remission as compared with only one out of nine patients receiving inert treatment. Two, however, showed slight improvement after inert

TABLE IV.—*Topical Hydrocortisone in Ulcerative Colitis. Results of Treatment*

		Potent	Control
Clinical	Remission	9	1
	Improvement	—	3
	No change or worse	1	5
Mucosal appearances	Normal	3	—
	Improvement	6	3
	No change or worse	1	6
Remission maintained	1–2 months	2	2
	3–5 ,,	3	—
	6–9 ,,	4	—
Relapses		3	7

therapy. Mucosal appearances became normal in 3 and improved in 6 of the 10 patients receiving the potent agent, and contrasted markedly with those receiving the dummy treatment, where only three showed slight improvement. It has not been definitely established how long remission will be maintained after an initial course of treatment, but 4 of the 10 patients treated with hydrocortisone have remained in clinical remission for six to nine months. Three relapses have already occurred but have responded to further courses of treatment. The one patient showing remission on dummy therapy relapsed within a month of stopping treatment.

The response of three patients who were treated in the trial by both agents is of interest.

Case A: Courses 5 and 10.—A woman aged 25 gave a history of rectal bleeding, diarrhoea, and mucus discharge for one year, and sigmoidoscopy confirmed the presence of a haemorrhagic proctosigmoiditis. An initial course of dummy treatment effected a slight improvement with a reduction of the frequency of diarrhoea from ten to five stools daily and a lessening of rectal bleeding. Relapse occurred within one month and the patient re-entered the trial. She was unfortunate enough to be allocated a further course of dummy treatment, which had no effect upon her diarrhoea. She continued to pass six loose stools daily which contained more blood than before treatment was given. Mucosal appearances also worsened. Potent therapy was given outside the trial and induced a rapid clinical remission, with a reduction of stool frequency from six to two daily, a disappearance of blood from the stools, and an improvement in the mucosal appearance. A mild relapse has occurred in this patient after two months.

Case B: Courses 14 and 15.—A woman aged 53 gave a history of recurrent rectal bleeding, mucus discharge, and diarrhoea for 25 years. Sigmoidoscopy again confirmed the presence of a haemorrhagic proctosigmoiditis. An initial course of dummy treatment effected a slight improvement in the character of the stools and mucosal appearance, but relapse occurred within two months. A course of potent drug caused a striking clinical remission with a reduction of stool frequency from six to one daily and a disappearance of rectal bleeding. Mucosal appearances were improved.

Case C: Courses 9 and 19.—A woman aged 48 gave a history of ulcerative colitis for one year and severe mucosal inflammation, and ulceration was confirmed sigmoidoscopically. Treatment with the potent drug initially induced a slight improvement, with a reduction of bowel action from eight to five stools daily and a lessening of rectal bleeding. Mucosal inflammation was less marked after treatment. A severe relapse, however, occurred after one month, and treatment on a second occasion by dummy therapy considerably worsened the patient's diarrhoea and the appearances sigmoidoscopically. This patient showed some improvement with systemic corticotrophin, but required surgery to control her symptoms.

It will be seen that two of these patients serving as their own controls showed appreciable advantages in favour of potent therapy. The third patient did not seem particularly responsive to any form of corticoid treatment, but certainly fared better with potent than with dummy treatment. The successful outcome of potent therapy in the majority of patients treated is therefore clearly apparent. A method of sequential analysis used to demonstrate significant differences between the forms of treatment is now detailed.

Sequential Analysis

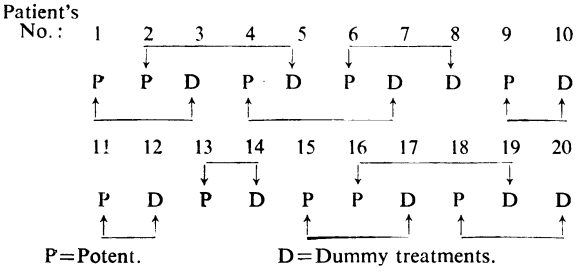
The statistical technique of restricted sequential analysis has been developed in particular relation to therapeutic trials by Dr. Peter Armitage, and formerly has been used to establish the relative merits of analgesics and cough-suppressive agents (Armitage, 1954, 1957; Newton and Tanner, 1956; Snell and Armitage, 1957). Treatments are allocated to pairs of patients in a random order, and the course of the trial is followed by accumulating the qualitative comparisons between treatments which are provided by each pair of patients. Results are recorded on a chart while the trial is in progress, the boundaries of which determine the minimum number of observations necessary to establish a significant advantage in favour of one treatment. Alternatively, other specified limits indicate that if no significant difference emerges when a certain number of pairs of patients have been treated the trial should be abandoned.

Sequential analysis is therefore the method most economical of patients and of time in the comparison of two treatments, and seemed admirably suited to compare the relative merits of hydrocortisone and a dummy prepara-

tion in the treatment of colitis. By this method the significant advantage of potent treatment has been established in the strikingly small number of 19 treatment periods. Dr. Peter Armitage was kind enough to devise a chart suitable for the trial and to suggest the method of random allocation of the treatments given. Without his generous help the trial could not have been undertaken in this particular form.

Method of Random Allocation

A master sheet was prepared and held by the pharmacist dispensing the two forms of treatment. Pairs of patients, one receiving potent and one receiving dummy preparations, were first paired by the system of random numbers shown below, which is seen to be different for each group of 10 patients studied. The order of treatments given to each pair was determined by the spin of a coin, the next patient entering the trial receiving the alternative treatment and completing each pair. In this way a doubly randomized method of selection was ensured. Pairs of randomized treatments were as follows :



Both patient and physician were unaware of the nature of the treatments given until the course had been completed. Patients told that the relative merits of two unproved therapeutic agents in colitis were being compared, and that they stood even chances of receiving either, agreed willingly to participate in the trial.

Method of Sequential Analysis

The outcome of treatment in the pairs of patients studied is one of the four types indicated in Table V. Potent or inert therapy might be equally successful or ineffective; these are termed "tied" pairs and show no particular advantage for one agent and are not recorded on the chart. Pairs of subjects, where potent or inert therapy is effective in one instance and fails in the other, are termed "untied" pairs, and are recorded on the control chart as a point in favour of one form of treatment. The comparative frequencies of symptomatic remission and mucosal improvement assessed sigmoidoscopically are summarized in Table V, and provided information for separate control charts.

TABLE V

	"Tied" Pairs		"Untied" Pairs	
Potent	+	−	+	−
Dummy	+	−	−	+
Symptomatic remission ..	2	1	6	—
Sigmoidoscopic improvement	—	2	7	—
Method of recording on chart	Not used in investigation		Plot as point in favour of potent drug	Plot as point in favour of dummy preparation

Similar success or failure occurred in five pairs of patients which were not used in the investigation. The number of "tied" pairs is the only factor which cannot be predicted in advance in this type of trial. The frequency of "tied" pairs in this trial is remarkably small, as it might have been expected that similar numbers of pairs of patients might be "tied" or "untied." In six pairs of patients symptomatic remissions were induced by hydrocortisone, while in seven pairs mucosal appearances improved with the potent drug. Inert therapy in each pair of patients was uniformly unsuccessful. The number of untied pairs in favour of hydrocortisone was sufficient to establish a significant advantage when recorded on the control charts.

The outcome of treatment in each untied pair was completed on the chart shown in Fig. 1. Information is entered

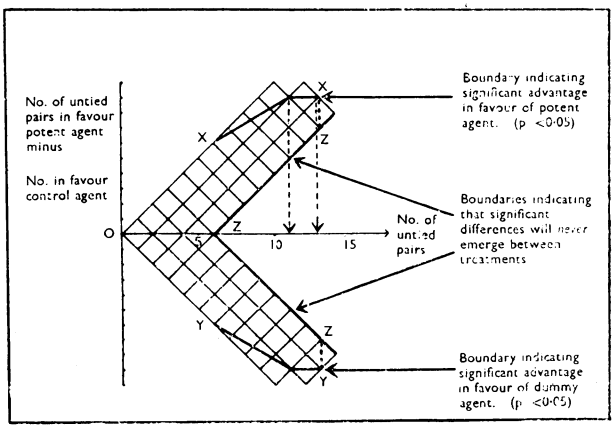


FIG. 1.—Sequential analysis chart comparing treatment of granular proctitis with dummy and that with hydrocortisone. Outcome of treatments in untied pairs, starting at point O. For each untied pair favouring hydrocortisone a point is drawn diagonally upwards towards the upper limit of the chart, XX, and for each untied pair favouring inert therapy diagonally downwards towards the lower limit, YY. As soon as one of these limits is intersected the significant advantage of one form of therapy is established. This will occur if 6 of 6, 10 of 11, or 11 of 13 untied pairs favoured one agent. If no significant differences are demonstrated between treatments the control line will oscillate up and down and eventually intersect the inner limits of the chart, ZZ, which might occur after as few as 6 or as many as 13 pairs of dissimilar responses had been entered on the chart. Intersection of these inner limits, ZZ, would indicate that the trial should be abandoned, as no significant advantage for a particular treatment would emerge.

on the chart starting at point O. For each untied pair showing an advantage in favour of hydrocortisone a line is drawn one point diagonally upwards towards the upper limit of the chart XX and for each untied pair in favour of the dummy therapy one point diagonally downwards towards the lower limit YY. If the differences between treatment are great, successive points in favour of the potent remedy rapidly approach the upper limit XX, and once this margin is intersected a significant advantage for potent therapy to the 5% level has been demonstrated.

As will be seen from Fig. 1, this might be possible if six out of six untied pairs favour hydrocortisone when significant differences could be shown after 12 patients had been treated. If one untied pair of patients favoured inert therapy in the course of the investigation the outcome of the trial would be delayed until 10 or 11 untied pairs had favoured hydrocortisone and the upper margin of the chart had been intersected. Finally, if two pairs of patients favoured dummy preparation the outcome of the trial would be delayed until at least 13 untied pairs of patients had been obtained. A similar outcome would occur if dummy treatment was better than potent, when the progression of the line would be downwards to intersect the lower limit YY on the chart. If no significant difference existed between treatments the line would oscillate backwards and forwards and eventually intersect the inner limits of the chart labelled ZZ, which would indicate that even if the maximum number of 13 untied pairs were obtained no significant difference would emerge, indicating the limit to which the trial should be pursued.

The disadvantages of this type of analysis are that the number of tied pairs cannot be predicted precisely and that unless the difference between the agents compared is a great one a significant result will not emerge.

Special charts were used to record the frequency of symptomatic remission and sigmoidoscopic improvement.

The chart illustrating the occurrence of symptomatic remission in the pairs of patients treated is shown in Fig. 2, where it will be seen that remissions were induced in six of six untied pairs treated with hydrocortisone and that the control line favouring this agent rapidly approached the upper limit of the chart, demonstrating a significant advantage in favour of this agent.

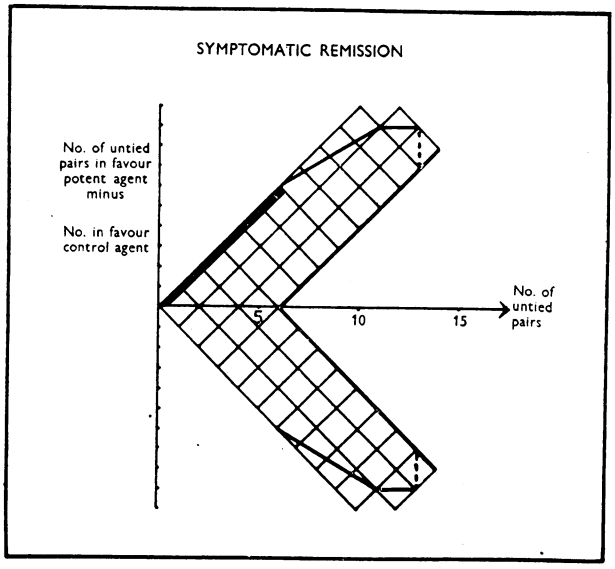


FIG. 2.—Sequential analysis chart illustrating the frequency of symptomatic remission in pairs of patients treated is here shown. As remissions were induced in six or six untied pairs treated with hydrocortisone the control line passed rapidly upwards and intersected the upper limit of the chart, demonstrating a significant advantage for hydrocortisone.

An almost exactly similar chart is shown in Fig. 3, where improvement in mucosal appearance assessed sigmoidoscopically has been recorded. Here again seven of seven untied pairs favoured hydrocortisone, and the control line uninterruptedly approached and intersected the upper limit of the chart, demonstrating again a significant advantage for the potent drug.

Hydrocortisone hemisuccinate sodium therefore was shown to be more effective than a dummy preparation after the small number of 19 treatments had been given and seems a valuable form of therapy for ulcerative colitis, particularly in mild cases where the inflammatory process is confined to the rectum and sigmoid colon. Its use in more severe cases of colitis is being further investigated. In these patients the intravenous administration of 15–30 mg. of propantheline half an hour before the rectal infusion reduces colonic motility overnight and enables the patients with nocturnal diarrhoea to retain the agent overnight. It might also be possible to incorporate the hydrocortisone hemisuccinate sodium in a suppository for use in patients with proctitis. This, too, is being investigated, as this method would prove far more convenient to patients with this disease.

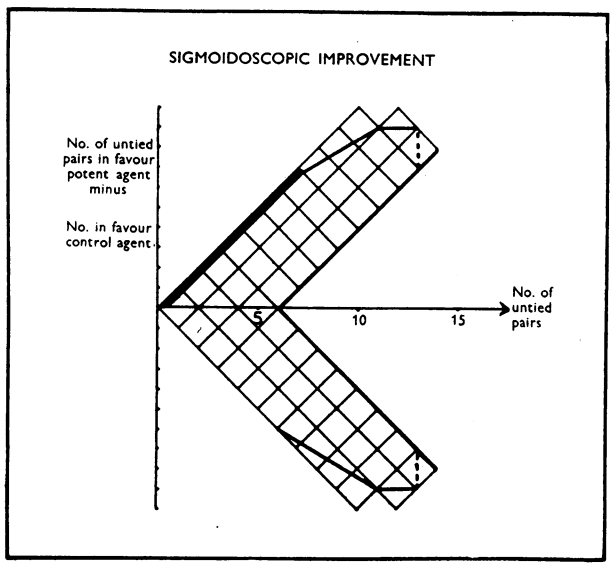


FIG. 3.—The frequency with which mucosal appearances improved sigmoidoscopically is entered on this chart, where again the significant advantage of potent therapy is demonstrated by an uninterrupted progression of the control line upwards to intersect the upper limit of the chart after seven pairs of patients had been treated.

Discussion

The favourable results reported by Truelove in 1956 and 1957 on the treatment of mild cases of colitis by the topical administration of hydrocortisone seemed to merit further inquiry, and for this reason the controlled trial into the value of this mode of treatment was undertaken and has been detailed above.

Truelove in 1956 treated a group of 17 patients with ulcerative colitis on 21 occasions by rectal infusions of a solution of hydrocortisone-free alcohol administered by slow rectal drip, and induced rapid clinical remissions in 14, accompanied in most instances by an improvement in the sigmoidoscopic appearances. A year later he reported a second series of 15 patients with colitis treated on 18 occasions by rectal injection of a solution of the more soluble derivative, hydrocortisone hemisuccinate sodium. Rapid clinical remissions were induced in 11 patients; sigmoidoscopic improvement was observed in every case in remission, accompanied in this instance by reductions in the severity of the inflammatory process judged histologically by serial colonic biopsies and by an improvement in cell morphology as judged by exfoliative studies.

The advantage of potent over dummy therapy has been demonstrated in three ways. Firstly, in the contrasting responses of patients treated in the two ways, where the majority of patients receiving hydrocortisone improved and those receiving dummy treatment worsened. Secondly, in the responses of two patients, serving as their own controls, who received both forms of treatment and who in both cases failed to respond to inert treatment and to undergo remission when potent therapy was given. Finally, by the use of sequential analysis, by which potent therapy was shown to induce symptomatic remission and sigmoidoscopic improvement significantly more commonly than the other form of treatment, the value of the rectal instillation of hydrocortisone hemisuccinate sodium was definitely established.

The new method of restricted sequential analysis designed by Armitage in 1957, modified from the method described by Bross in 1952, proved an extremely satisfactory method of demonstrating the differences, and a significant answer was obtained after 19 treatments had been administered.

Summary

An assessment of the value of rectal instillations of topical hydrocortisone hemisuccinate sodium in patients with ulcerative colitis has been undertaken.

The frequency with which symptomatic remission and sigmoidoscopic improvement were induced has been compared in pairs of patients receiving potent or dummy treatments.

The responses of the groups of patients receiving potent and inert therapy are contrasted. The majority of patients receiving potent hydrocortisone improved and those receiving inert therapy worsened.

In two patients serving as their own controls, dummy treatment failed to induce improvement while hydrocortisone caused a remission to occur.

Finally, comparison by sequential analysis showed that symptomatic remission and improvement in mucosal appearances were significantly more often induced by potent than by inert treatment.

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ANKYLOSING SPONDYLITIS

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In the spring of 1958 a questionary was sent to 343 patients with ankylosing spondylitis who had been seen, and the majority treated, at Westminster Hospital since the war. Answers were received from 209; most of the rest were returned by the Post Office, the present address of those patients being unknown. Many of the patients had been seen and treated while in the armed Forces, and the difficulty in tracing many lay in this fact. In the vast majority of cases, however, where the questionary was sent to the correct address an answer was received within three weeks, demonstrating once again the high degree of co-operation found in our previous study with this group of patients (Hart, Robinson, Allchin, and Maclagan, 1949). Questions were related particularly to the effects of treatment as assessed by the patient himself and the ability to do his work and earn his own living.

Duration of Disease.—Of the 209 who returned their questionaries, 23 had suffered from ankylosing spondylitis since before the onset of the second world war, in 58 the onset lay during 1940–4, in 75 during 1945–9, in 44 during 1950–4; in only 9 had it developed since that date.

Results

Work Capacity.—200 question sheets were returned fully completed. Of these, 21 were from women, 179 from men. This 8.5:1 ratio is an artificial one owing to the high number of Service men seen; it therefore does not reflect the true sex ratio in this disease. Of this number, 160 were working full time, and, if housewives, were doing their full duties in the home. Many stated that in addition to their ordinary duties they worked voluntarily in the evenings, and others did gardening and played games. 40 stated that they were incapable of full duties, but only 9 were incapable of any duties whatsoever. 19 were capable of modified duties and 12 of light or occasional duties. In addition the questionary had been returned by relatives of four patients, all male, who had died: one of amyloidosis, one of coronary thrombosis, one of carcinoma of the pancreas, and one of a neoplasm of uncertain nature. These figures—160 at full work, 19 at modified work, and only 21 capable of little or no duties—are typical of the group as a whole, and similar figures have been reported by Blumberg and Ragan (1956). Although working full time, many commented that the duties in their particular post were not physically hard and some that the post had been selected because of their disability. In four instances a regular paid post had been given up for full-time independent work where self-imposed duties could be varied to avoid the stiffness and discomfort attendant on too little mobility at work. Once again the well-known fact became evident that a stiff spine alone does not cripple, though stiff hips and peripheral joint involvement may.

General Health.—Of 191 patients who answered questions relating to their general health, 36 stated it was excellent, 74 good, 71 "fairly good," and 10 poor. Asked specifically about indigestion, 11 complained of severe recurrent or chronic dyspepsia, 38 of more moderate but annoying symptoms. Radiological investigation in 37 cases had revealed peptic ulcers in 10. Of these 191 cases, therefore, 49, or roughly 25%, have dyspepsia to the point of being a definite and occasionally a major complaint. Although some symptoms were obviously related to or aggravated by therapy, this was clearly not so in all cases. This group of spondylitic dyspeptic patients remains a major therapeutic hazard, for almost all current forms of therapy may aggravate gastro-duodenal symptoms or cause complications. Of other disabilities, the next most common was iritis. Although no specific question was asked and although the eye was not mentioned on the questionary, 35 patients mentioned iridocyclitis when asked for general comments about their health. One was registered as a blind person from this disability. Three patients were under treatment for pulmonary tuberculosis; one had had a thoracoplasty. Vertigo was mentioned by 7, headaches by 4, anaemia by 4, and recurrent bronchitis by only 4, although 8 made major complaints regarding stiffness of the chest wall and inability to breathe deeply.

Analgesics.—To the question, "What medicines have you found to be most helpful for your spondylitis?" 43 answered none, 49 aspirin in some form, 54 compound codeine tables, 56 phenylbutazone, and 9 steroid therapy. This last is a small group, as only a small minority had been offered steroid therapy. No other drug was mentioned more than once.

Radiotherapy

One of the main reasons for the follow-up was to learn what the patients thought of the long-term results of deep *x*-ray therapy and to find out what blood disorders had occurred, if any. The large majority of these patients were treated at Westminster Hospital by Dr. F. M. Allchin, Mr. Tom Prossor, and Dr. Kenneth Newton in the conservative dosage reported by us previously (Hart *et al.*, 1949); only a few treated elsewhere received a total dosage above 1,500 r to any part of the spine, and the majority received under 1,200 r. Of 143 patients who had received therapy to the spine, 114 (80%) stated they had received some benefit, 29 (20%) that they had not. Of those who stated that they had received benefit, 41 (28.7% of all patients treated with deep *x* rays) stated that some benefit still persisted, after follow-up periods varying from 2 months to 17 years since therapy was given; 27 of these 41 patients had received therapy more than four years previously. 30 patients had had symptomatic relief for six months or less, 18 for seven months to five years, 3 for periods over five years, the effect then completely wearing off. In 22 cases details of duration of relief were not adequately given.

While some of this improvement may be psychogenic and reflect the high optimism of the patients as a group, the stories given fall into fairly regular patterns, and suggest more than "therapeutic persuasion." In some cases the question of introduction of a natural remission has to be considered where for many years after therapy the condition appears to have remained largely or completely quiescent. On these figures it seems that 20% of irradiated spondylitics will derive no benefit whatsoever, 20% a temporary symptomatic improvement for a period of up to six months, the remaining 60% some degree of relief for periods varying from seven months to many years.