within 36 hours. He continued on the same dose of iproniazid for a further five months, during which time he showed signs of increasing restlessness, euphoria, insomnia, and other mild toxic effects. He died in coma after an acute illness characterized by fever, coarse tremor, hallucinations, and "auditory delusions." At necropsy the brain showed that death was due to haemorrhagic encephalitis; since no other cause was apparent this was believed to be due to the toxic effect of iproniazid.

The toxic manifestations of the central nervous system caused by pethidine and iproniazid are similar: cerebral excitation, confusion, restlessness, and muscle twitchings are common to both. It is difficult to decide whether in our own and Mitchell's case cerebral symptoms were caused by the simple additive effect of the two drugs or by a more complex inhibition of the enzyme-detoxicating system in the liver. The problem, however, is of theoretical interest. It is of practical importance that the two drugs become incompatible once a certain level of iproniazid is reached in the tissues. This may take up to four weeks.

The response to chlorpromazine was remarkable and perhaps a life-saving measure in our patient. Barbiturates commonly invoked in the treatment of cerebral excitation did not help, and in larger doses could have done actual harm if, as we have suggested, the liver detoxicating system was affected by iproniazid.

Although the pharmacological action on the heart is not yet clearly established, the improvement in this case and in others still under observation suggests that iproniazid is a promising drug in the treatment of angina. Patients with decubital angina, however, need heavy sedation with morphine analogues and barbiturates; potentiation with iproniazid may give rise to toxic cerebral reactions as in our patient. It is because of such therapeutic implications that this case is reported.

Summary

A case of decubital angina treated with iproniazid is reported. Although the frequency of the attacks diminished, occasional pethidine injections were still needed for the relief of pain. During the fifth week of iproniazid treatment these injections were followed by signs of severe cerebral irritation and excitement which responded dramatically to chlorpromazine. Either the simple additive effect of the two drugs or more complex interference with the normal detoxication of pethidine in the liver by iproniazid is believed to have caused toxic cerebral damage. It is suggested that pethidine should be used with caution in patients on iproniazid treatment.

ADDENDUM.—Since this paper was submitted a different complication of iproniazid treatment has been encountered in a 63-year-old man suffering from incapacitating angina of effort. On a dose of 50 mg. twice daily, much improvement resulted. One month later, while still on the same dose, he complained of difficulty of micturition and giddiness, and his blood pressure had fallen from 140/80 to 110/75. Iproniazid was discontinued, and then resumed after one week. A fortnight later he developed a small cerebral thrombosis, from which he fortunately recovered. Hypotension caused by iproniazid may have precipitated this complication.

REFERENCES

Cesarman, T. (1958). *J. clin. exp. Psychopath.*, **19**, suppl. 1, p. 169.
Cossio, P. (1958). *Rev. méd. Chile*, **86**, 67.
Dally, P. J. (1958). *Brit. med. J.*, **1**, 1338.
Dundee, J. W., and Tinckler, L. F. (1952). Ibid., **2**, 703.
Fouts, J. R., and Brodie, B. B. (1956). *J. Pharmacol.*, **116**, 480.
Goodman, L. S., and Gilman, A. (1955). *The Pharmacological Basis of Therapeutics*, 2nd ed. Macmillan, New York.
Kline, N. S. (1958). *J. clin. exp. Psychopath.*, **19**, Suppl. 1, p. 72.
Mitchell, R. S. (1955). *Ann. intern. Med.*, **42**, 417.
Neefe, J. R., Gambescia, J. M., Kurtz, C. H., Smith, H. D., Beebe, G. W., Jablon, S., Reinhold, J. G., and Williams, S. C. (1955). Ibid., **43**, 1.
O'Connor, J. B., Howlett, K. S., jun., and Wagner, R. R. (1953). *Amer. Rev. Tuberc.*, **68**, 270.
Randall, L. O. (1958). *J. clin. exp. Psychopath.*, **19**, Suppl. 1, p. 178.
Scherbel, A. L. (1958). Ibid., **19**, Suppl. 1, p. 118.

TREATMENT OF ULCERATIVE COLITIS WITH LOCAL HYDROCORTISONE HEMISUCCINATE SODIUM

A REPORT ON A CONTROLLED THERAPEUTIC TRIAL

BY

S. C. TRUELOVE, M.D., M.R.C.P.

Nuffield Department of Clinical Medicine, University of Oxford

(From the Radcliffe Infirmary, Oxford)

With an Appendix by M. H. HAMBLING, M.B., B.S.

Two previous studies have dealt with the use of hydrocortisone applied topically to the colon in ulcerative colitis by means of a nightly rectal drip (Truelove, 1956, 1957). In the first study, 21 mild or moderate attacks of the disease were treated with hydrocortisone in the form of the free alcohol, and there were 14 rapid remissions, these remissions usually occurring in the first few days of treatment. However, although the sigmoidoscopic findings showed improvement in parallel with the clinical response, the histological picture as judged by biopsy specimens was little altered. As hydrocortisone itself is poorly soluble in water, the actual solution used for the rectal drip was prepared by diluting hydrocortisone dissolved in 50% ethyl alcohol with 10 times its volume of saline. There was the possibility that the weak alcoholic solution used as the vehicle for the hydrocortisone prevented the mucosa from healing.

In the second study, a compound freely soluble in water, hydrocortisone hemisuccinate sodium, was used. The clinical response was similar to that obtained with hydrocortisone itself in that there were 11 rapid remissions out of 18 courses of treatment. However, the histological picture of the colonic mucosa showed a favourable response in those subjects enjoying clinical remission, and it was therefore decided that the hemisuccinate (or some other water-soluble compound) was the corticoid of choice for this form of treatment.

The view that hydrocortisone applied topically is a useful form of treatment in this disease could be only presumptive on the results so far mentioned. In other words, this view rested solely on a personal clinical judgment that no considerable proportion of patients with an attack of ulcerative colitis would go swiftly into remission unless the treatment was having some strongly positive effect. Any student of ulcerative colitis must view with scepticism the use of a treatment based upon personal impressions, for the history of the disease includes a large variety of treatments which in their turn were introduced with enthusiasm on the strength of a few favourable responses and then slowly abandoned when they were found to be ineffective. The disease is one which manifests itself by exacerbations and remissions which are often unpredictable. Furthermore, a large body of opinion regards it as a psychosomatic disorder, so that a new form of treatment might possibly be beneficial for reasons unconnected with the pharmacological actions of the therapeutic agent. It is therefore essential that new forms of treatment should be put to formal tests so that patients are not exposed unnecessarily to useless methods of treatment.

Objects of the Present Study.—The main object of the present study was to compare the effect of hydro-

cortisone hemisuccinate sodium used topically with an inert preparation which resembled it superficially. The second object was to form an impression whether the combined use of hydrocortisone and antibiotics was better than hydrocortisone used alone. The third object was to determine whether patients who went into remission with local treatment would remain relatively free from relapse if they received maintenance treatment on two nights a week.

Method

The study comprised three parts, corresponding to the three objects of the trial.

Part I. Blind Controlled Trial of Local Treatment Lasting One Week

Patients with active symptoms of ulcerative colitis were allotted in a random order to treatment with either preparation A or preparation B, one of which was actual hydrocortisone hemisuccinate sodium while the other was an inert replica. These preparations were made and labelled by Glaxo Laboratories, and their identity was unknown to all the other persons concerned in the trial until after its conclusion. Treatment was prescribed in the following form:

A. J. Smith
U. C. No. 23

℞ Special rectal drip nightly for seven nights.

Patients were numbered consecutively as they entered the trial, and the hospital pharmacist entered their names on a prepared list that showed which preparation a patient with any particular serial number was to have. Treatment consisted in dissolving the contents of one ampoule of A or B in 120 ml. of normal saline and dripping the solution into the rectum at night. No other treatment was used.

The inert preparation was made by the manufacturers by freeze-drying concentrated dextran solution put up for intravenous use. The resulting powder closely resembled the preparation of hydrocortisone hemisuccinate sodium used in the trial. Each ampoule of inert preparation consisted of 20–30 mg. of freeze-dried dextran, which corresponded in volume to 100 mg. of hydrocortisone in the form of the hemisuccinate sodium ester. On general principles we should expect this small amount of intravenous dextran in 120 ml. of saline to be harmless to the colonic mucosa, and practical tests on patients with ulcerative colitis immediately after going into remission support this view.

Part II. Open Use of Hydrocortisone and Antibiotics for Two Weeks

At the end of the first week all patients were given nightly rectal drips of known hydrocortisone and antibiotics. Penicillin, 1 mega unit, and streptomycin, 1 g., were added to the hydrocortisone solution, which contained the hemisuccinate in an amount equivalent to 100 mg. of hydrocortisone itself. In 10 instances neomycin in a dose of 250 mg. was used in place of penicillin and streptomycin.

Part III. Blind Controlled Trial of Maintenance Treatment Employing Rectal Drips Twice a Week Over the Course of Six Months

Patients who were in clinical remission at the end of Part II were admitted to the maintenance part of the trial. The practical arrangements were analogous to those used in Part I in that Glaxo Laboratories supplied preparations labelled X and Y, one of which was actual hydrocortisone and the other was inert. In the earlier stages of this part of the trial neomycin or an inert replica, labelled as antibiotic X or antibiotic Y, was used in combination with hydrocortisone or its "dummy," but this was later given up for reasons set out below.

Selection and Assessment of Cases

Only patients with active symptoms from ulcerative colitis were admitted to the trial. As in the previous studies, severe cases with much constitutional disturbance were excluded. Many of the patients were ambulant and were treated as out-patients, although some were in hospital.

Some patients who went into remission but who relapsed during or after maintenance therapy were readmitted to the trial, once again being allotted to treatment A or B at random.

The clinical condition immediately before treatment was recorded. All patients were examined by sigmoidoscopy on the day when treatment began, and the findings were recorded. During this examination a mucosal biopsy was performed by means of an improved version of an instrument devised for serial biopsy (Truelove *et al.*, 1955) and a swab was taken from the lower colonic mucosa for bacteriological study.

At the end of Part I and of Part II of the trial, exactly similar observations were made. They were also made during Part III (trial of maintenance therapy), although they might be limited to the final attendance six months after the conclusion of Part II.

Barium-enema studies were not made as a routine. In every patient at least one barium-enema examination had previously shown evidence of ulcerative colitis. This examination not infrequently causes an exacerbation of symptoms. The patients are usually young and suffer from a disease from which they are likely to have future attacks in the course of which further *x*-ray studies may be essential. Many of them are women in the reproductive years of life, and unnecessary gonadal exposure to *x*-radiation is to be avoided. For all these reasons, the barium enema should be used sparingly in ulcerative colitis.

Forty courses of treatment were given, it being arranged beforehand that 20 would be with preparation A and 20 with preparation B during Part I of the trial. In the interests of brevity, individual case histories are not recorded.

Part I. Controlled Trial of Local Hydrocortisone Treatment

Clinical Response.—The clinical response to the two preparations is given in Table I. It can be seen that there is a striking difference between the clinical response shown with inert treatment and that with actual hydrocortisone, only 1 in 20 treatments with a "dummy" resulting in clinical remission, compared with just over one-half with hydrocortisone. In statistical terms, the difference is highly significant, as it would occur by chance less than 1 in 100 times.

TABLE I.—*Clinical Results of One Week's Treatment With Hydrocortisone or an Inert Preparation*

Treatment Group	No. of Patients	No. Symptom-free	Test of Significance
A (Inert therapy)	20	1	$\chi^2_c = 9{\cdot}6$ n=1 P=0·01
B (Hydrocortisone hemisuccinate) ..	20	11	

χ^2 calculated with Yates's correction for continuity in view of the small numbers involved.

Sigmoidoscopic Responses.—The sigmoidoscopic findings resembled the clinical responses in showing a marked preponderance of favourable changes among the group receiving actual hydrocortisone. Once again the results are statistically highly significant (Table II). It is worth mentioning that there was almost perfect agreement between a good clinical response and a clear-cut sigmoidoscopic improvement. All the patients going into clinical remission showed improved sigmoidoscopic appearances. The only discrepancy was that one patient in each treatment group

TABLE II.—*Sigmoidoscopic Response to One Week's Treatment With Hydrocortisone or an Inert Preparation*

Treatment Group	No. of Patients	No. Showing Definite Improvement	Test of Significance
A (Inert)	20	2	$\chi^2_c = 8{\cdot}9$ n=1 P<0·01
B (Hydrocortisone)	20	12	

showed improved sigmoidoscopic appearances even though they were not in clinical remission. Both later became symptom-free.

Histological Response.—Before treatment all the biopsy specimens taken at 15–20 cm. from the anal margin showed inflammatory changes of the type associated with ulcerative colitis. They have been classified as showing severe, moderate, or mild inflammation, according to the criteria employed by a pathologist colleague in a previous study (Truelove and Richards, 1956). Table III shows the histological picture as judged from biopsy specimens in each treatment group before and after the one week's controlled trial. Before treatment the two groups of patients were closely similar in respect of the histological changes. After treatment the histological picture in group A (inert therapy) was for all practical purposes identical with that before treatment. In group B (real therapy) there was a definite swing towards histological mildness. In statistical terms this group was significantly better histologically after treatment than it was before ($P<0.02$) and was also significantly better than group A after treatment ($P<0.05$). We may therefore justifiably conclude that topical hydrocortisone hemisuccinate exerts a favourable influence on the actual pathological picture of the colonic mucosa in ulcerative colitis (Fig. 1).

TABLE III.—*Histological Responses to One Week's Treatment With Hydrocortisone or Inert Preparation*

Treatment Group	Degree of Inflammation	Before Treatment	After Treatment	Significance of Differences Before and After Treatment
A (Inert therapy) ..	Severe	8	7	No significant difference
	Moderate	10	11	
	Mild	2	2	
B (Hydrocortisone hemisuccinate)	Severe	8	4	$\chi^2=8{\cdot}6$ n=2 P<0·02
	Moderate	11	7	
	Mild	1	9	
Significance of differences between A and B		No significant difference	$\chi^2=6{\cdot}2$ n=2 P<0·05	

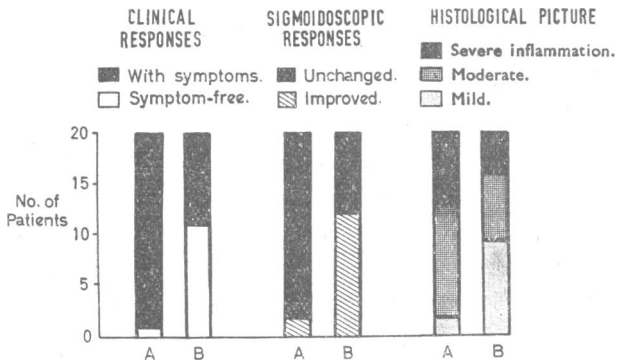

FIG. 1.—Position at end of Part I of trial, showing the differences in the clinical, sigmoidoscopic, and histological pictures after one week of topical treatment with either an inert preparation or real therapy. (A=Inert preparation. B=Hydrocortisone hemisuccinate sodium.)

Part II. Two Weeks' Treatment with Known Hydrocortisone and Antibiotics

Clinical Response.—At the end of another two weeks, when all patients had been treated with known hydrocortisone hemisuccinate and antibiotics used locally, the two treatment groups were closely similar in respect of their clinical state. In treatment group A, which began with only one patient in clinical remission, 12 patients went into remission during this period, making a total of 13 for the group. In treatment group B, which began this part of the trial with 11 patients in remission, another 5 became symptom-free, making a total of 16. The final difference between the two treatment groups is small, and would be expected to occur frequently by chance alone (Table IV).

TABLE IV.—*Clinical State at End of Part II of Trial, When All Patients Had Completed Two Weeks' Treatment With Known Hydrocortisone and Antibiotics*

Treatment Group	No. of Patients	No. Symptom-free	Test of Significance
A	20	13	$\chi^2=1{\cdot}1$ n=1 P>0·05
B	20	16	

Sigmoidoscopic Response.—Once again the sigmoidoscopic appearances moved in parallel with the clinical response. All of the 29 patients who were free of symptoms at the end of the third week showed sigmoidoscopic appearances which were decisively better than when they began treatment. Some residual inflammation (as judged by gross appearances) was present in a number of these 29 patients, but in 18 the appearances were judged to be "normal" or "near-normal," the latter term implying that the only abnormality was a fine pin-point granularity not accompanied by hyperaemia or by increased mucosal fragility. Three of the 11 patients still having bowel symptoms at the end of three weeks' treatment showed sigmoidoscopic improvement, and in all three there had been lessening of the bowel symptoms, although they were not yet symptom-free. Table V shows that the two treatment groups A and B were closely similar at the end of the second part of the trial.

TABLE V.—*Sigmoidoscopic Appearances at End of Three Weeks' Treatment, the Last Two Weeks Having Been With Known Hydrocortisone and Antibiotics*

Treatment Group	No. of Patients	No. with Normal or Improved Sigmoidoscopic Appearances	Test of Significance
A	20	15	$\chi^2=0{\cdot}5$ n=1 P>0·05
B	20	17	

Histological Response.—The histological responses likewise showed improvement in both treatment groups after known therapy, and there was little difference between them at the end of this part of the trial. The small advantage maintained by group B is not statistically significant (Table VI, Fig. 2).

TABLE VI.—*Histological Picture at End of Part II of the Trial*

Treatment Group	Degree of Inflammation	No. of Patients	Test of Significance
A	Severe	3	$\chi^2=1{\cdot}2$ n=2 P>0·05
	Moderate	6	
	Mild .. Near-normal	11	
B	Severe	1	
	Moderate	6	
	Mild .. Near-normal	13	

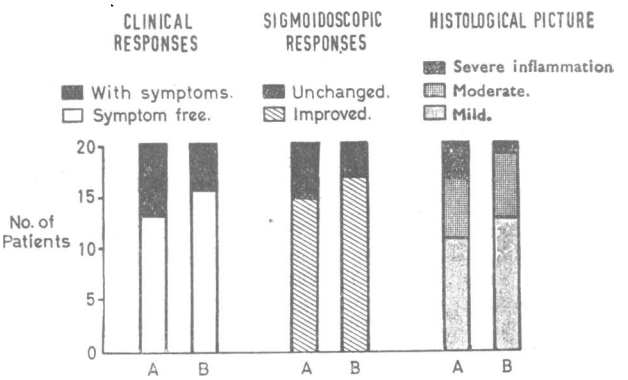

FIG. 2.—Position at end of Part II of trial, showing the similar clinical, sigmoidoscopic, and histological pictures after both treatment groups had received topical treatment with known hydrocortisone hemisuccinate sodium.

Action of Antibiotics Added to the Rectal Drip

The effect of antibiotics is not straightforward. The first thing to note is that in a few patients their use was attended by a sharp exacerbation of symptoms. In two of these cases it was known that the patients had previously had sensitivity reactions to penicillin given by injection, so that no great surprise was aroused when immediate symptomatic deterioration occurred. Both these patients had colonic biopsy specimens taken in the phase of flare-up, but the specimens showed only those changes which we associate with active ulcerative colitis; in other words, there was no specific recognizable change to be attributed to the penicillin. The antibiotics were stopped in these two patients, and they continued on the second part of the trial with hydrocortisone hemisuccinate alone; both went into clinical remission in this period. There were three other patients without known sensitivity reactions to any antibiotic who behaved in a similar manner. Two of these were among the 10 patients who were treated with neomycin in the drip instead of penicillin and streptomycin. One of them was already in remission when going into this second part of the trial, but she promptly relapsed on going on to known hydrocortisone and neomycin. On stopping the neomycin she rapidly became symptom-free, and remained so for some months. For this reason neomycin was discontinued for the remainder of the study.

On the other hand, there were some patients in whom it has been found that hydrocortisone alone did not have any appreciable effect during the first week of therapy but who improved rapidly when antibiotics were added to their treatment. (That such patients were on actual hydrocortisone during the first week has, of course, been known only since the study ended.) In parenthesis, it may also be added that similar favourable responses have been seen in a few instances among patients outside the present study who were being treated routinely with the rectal drip of hydrocortisone.

Consequently, there appear to be two conflicting factors at work. On the one hand, the inflamed colonic mucosa may sometimes react badly to the topical application of antibiotics in high concentration. On the other hand, some patients who are not responding to local hydrocortisone alone appear to do so promptly when antibiotics are added to the rectal drip. The net effect of these two opposing influences seems to be a small gain in the number of remissions achieved, if one can go on a comparison of the results obtained in the present study with those of the two previous studies of local hydrocortisone in ulcerative colitis (Table VII). The differences are not statistically significant, and

TABLE VII.—*Comparison of Results Obtained When Antibiotics are Added to the Rectal Drip of Hydrocortisone with Those Obtained with Hydrocortisone Alone*

	No. of Patients	Remissions		Test of Significance
		No.	%	
(I) Hydrocortisone (free alcohol) for 2–3 weeks (Truelove, 1956)	12	14	66·6	$\chi^2=0·8$
(II) Hydrocortisone hemisuccinate sodium for 2 weeks (Truelove, 1957)	18	11	61·1	n=2
(III) Hydrocortisone hemisuccinate sodium plus antibiotics (present study)	40	29	72·5	P>0·05

inspection of the figures is sufficient to discount any idea that the addition of antibiotics makes any major difference to the success of this form of treatment. Nevertheless, one can tentatively suggest the following working rules: (1) Antibiotics should not be used as a routine addition to a rectal drip of hydrocortisone hemisuccinate. (2) If no response is obtained with hydrocortisone alone in one week, it is worth trying the effect of adding antibiotics, and a mixture of penicillin and streptomycin seems preferable to neomycin. If the addition of antibiotics causes symptomatic exacerbation they should be stopped immediately. If the response is good, antibiotics can be continued for a week or 10 days, being then discontinued even if treatment with local hydrocortisone is to be maintained.

Of course, this opinion refers only to the use of high concentrations of antibiotics. It is possible that the use of lower concentrations might not cause exacerbations, but further work will be necessary to decide this.

Bacteriological Findings

Colonic swabs taken serially from the patients were examined bacteriologically by Dr. M. H. Hambling, who has summarized his findings in an Appendix to this article. The main object of this part of the study was to see whether the use of antibiotics frequently gave rise to colonic organisms insensitive to the antibiotics used, and, if so, whether this circumstance influenced the response to treatment. In brief, it can be said that resistant organisms sometimes appeared in the bowel, but their presence seemed to have no influence on the clinical response to local hydrocortisone.

Part III. Controlled Trial of Week-end Maintenance Therapy with Local Hydrocortisone for a Period of Six Months

Twenty-six of the patients who were symptom-free at the end of Part II of the trial were put on to maintenance treatment consisting of a rectal drip on two consecutive nights each week (week-end maintenance therapy). Of these, 13 received treatment with hydrocortisone hemisuccinate sodium (preparation Y) and 13 with the inert preparation (preparation X).

These two treatment groups did not differ in their liability to clinical relapse during the six months covered by this part of the trial. In each group of 13 patients there were five who suffered from clinical relapse accompanied by sigmoidoscopic and histological deterioration (Fig. 3). It has therefore been shown that week-end maintenance therapy with local hydrocortisone does not protect against relapse occurring.

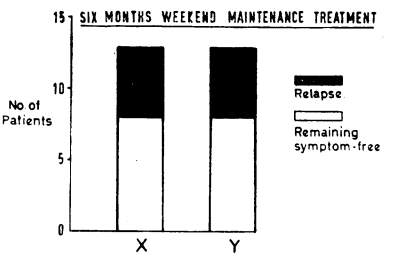

FIG. 3.—Position at end of Part III of trial, showing the similar state of patients given week-end maintenance therapy with either an inert preparation or real therapy. (X=Inert preparation. Y=Hydrocortisone hemisuccinate solution.)

However, it must be mentioned that among the 10 patients who relapsed during the maintenance part of the trial 9 rapidly became symptom-free with nightly rectal drips of hydrocortisone; the tenth did not respond to topical hydrocortisone alone, but did so promptly when oral prednisolone, 5 mg. four times a day, was given in addition.

Discussion

The present study has shown beyond all reasonable doubt that hydrocortisone hemisuccinate sodium administered in a rectal drip produces rapid clinical remissions in a considerable proportion of patients with mild to moderate attacks of ulcerative colitis. These clinical remissions are accompanied by improvement in the sigmoidoscopic appearances and by lessening of the inflammatory changes seen in colonic biopsy specimens. The experimental design of the trial permits the conclusion that the beneficial effect is a pharmacological one, because a control group receiving a placebo given under identical conditions showed a negligible number of favourable responses.

It is probable that the hydrocortisone hemisuccinate sodium acts chiefly by some direct effect upon the actual mucosa of the colon. In the first place, the beneficial effect commonly appears to be much more rapid than that observed with cortisone and its analogues used systemically. Secondly, some patients outside the present study have been maintained on nightly rectal drips of hydrocortisone hemisuccinate sodium for periods of several months without any clinical evidence of cortisonism. Thirdly, the preliminary

results of my colleague Dr. I. E. Bush suggest that only a comparatively small fraction of the hydrocortisone hemisuccinate sodium reaches the systemic circulation. Finally, and perhaps most convincingly, favourable clinical, sigmoidoscopic, and histological responses have been observed in patients with ulcerative colitis limited to the rectum and recto-sigmoid region by the use, once or twice a day, of suppositories containing only 10 mg. of hydrocortisone as the hemisuccinate. As some of these patients had previously suffered from attacks of classical ulcerative colitis involving a substantial part or the whole of the colon, there is no need to consider the possibility that they were not true examples of ulcerative colitis.

The therapeutic action would appear to resemble what happens in those skin diseases, such as atopic dermatitis, which respond favourably to topical application of hydrocortisone in a lotion or ointment. Absorption through the skin is very small, being of the order of 2%, so that the systemic effect is negligible, but the favourable results can be impressive, and have been shown by properly controlled studies (Sulzberger and Witten, 1954) to be directly due to the hydrocortisone. An analogous improvement of the buccal mucosa has been observed in patients with severe recurrent aphthous stomatitis who were receiving amounts of hydrocortisone hemisuccinate sodium too small to have any appreciable systemic effects (Truelove and Morris-Owen, 1958).

The addition of antibiotics to the rectal drip has turned out on balance to be beneficial in only a small proportion of patients. Although the weight of evidence is heavily against ulcerative colitis being a bacterial disease, there is little doubt that secondary bacterial infection is responsible for many of its most unpleasant complications. It seemed possible that the presence of bacterial infection might be the reason for some patients failing to respond to local hydrocortisone treatment. As it has been shown by elegant experiments that an infected atopic dermatitis may respond neither to local hydrocortisone alone nor to local antibiotics alone but will respond when the two are used together (Robinson *et al.*, 1956), it was hoped that an analogous response might be obtained in ulcerative colitis. In the event, the gain from adding antibiotics to the rectal drip of hydrocortisone has appeared to be small, and sharp exacerbations have occurred in a few patients from the direct application of antibiotics to the inflamed colon.

Although some patients enjoy a prolonged remission after a short course of local hydrocortisone, about two-fifths of the patients have a recurrence of symptoms in the course of the next six months and require further treatment. This fact illustrates the major problem in the management of ulcerative colitis to-day. By one method or another most attacks of ulcerative colitis can be brought under control by medical methods and the patient rendered symptom-free. However, once a patient has suffered from an attack of ulcerative colitis he is extremely liable to have subsequent attacks, and we know of no method to prevent them. The part of the present study which concerned maintenance therapy was designed to see whether, once a patient had been brought into clinical remission with local hydrocortisone, he could be held in remission by means of local treatment given on two consecutive nights a week only (week-end maintenance treatment). The answer is a decisive " No." A more fruitful approach to the problem may be to give a much more prolonged initial course of local treatment in those patients who respond well to it, in the hope that the colon will become more permanently improved by this means.

Outside the present study, a number of patients have been on prolonged treatment with nightly rectal drips of hydrocortisone, and the results so far appear to be very favourable, not only as regards the immediate benefits but also with respect to the production of a long-lasting remission. However, more patients need to be treated and to be observed for longer periods before this important question can be answered with any degree of assurance. Alternatively, the liability to recurrent attacks can be accepted and each one can be treated as it arises. When a patient has once responded well to local hydrocortisone it is likely that he will do so in subsequent attacks, and a number of patients have now been kept free of any major disability by intermittent courses of treatment given whenever clinical relapse occurred.

Although the present study has shown topical hydrocortisone hemisuccinate sodium to have a genuinely favourable effect in ulcerative colitis, it remains to be seen whether this form of treatment is superior to others which have been shown to be of value in cutting short attacks of the disease, such as corticoids used systemically. My impression is that local hydrocortisone hemisuccinate sodium scores over corticoids used systemically by the rapidity with which favourable responses are obtained and by the absence of any evidence of systemic side-effects of therapy. At present, my experience of this form of treatment extends to its use in about 100 patients, a number of whom have had more than one course of treatment, while some others have been on treatment for periods of several months consecutively. There have been no side-effects discernible clinically and no complications. In my own experience, therefore, the method has proved entirely safe.

Although this and the two previously published studies have been concerned with the less severe attacks of ulcerative colitis, it should not be thought that local hydrocortisone hemisuccinate sodium is valueless in the severe attacks. A number have been treated, and the results have been most encouraging. However, the local treatment of severe attacks raises certain problems, one of which concerns methods of ensuring that the therapeutic agent is retained in the colon. Propantheline bromide, given intravenously, is one agent which has been used to assist in retention. Heavy sedation of the patient and elevation of the foot of the bed also help. But these are issues which lie outside the province of the present study, which is concerned mainly with a formal demonstration that topical hydrocortisone hemisuccinate sodium is an effective form of treatment for a large proportion of patients with mild or moderate attacks of ulcerative colitis.

Summary

A formal therapeutic trial has been conducted to show whether topical hydrocortisone hemisuccinate sodium has a genuinely beneficial action in ulcerative colitis.

In the first part of the trial a controlled comparison was made of hydrocortisone and an inert preparation which resembled it in appearance. At the end of one week of treatment the patients receiving hydrocortisone therapy showed a striking advantage over those on the inert preparation, not only in respect of the clinical state but also as regards the sigmoidoscopic appearances and the histological appearances of colonic biopsy specimens.

All patients were then given open therapy with topical hydrocortisone and antibiotics used in conjunction for two weeks. About three-quarters of the patients were in clinical remission at the end of this period. By comparison with other studies in which antibiotics were not used, the addition of antibiotics seems to confer a small gain in the number of successes with topical hydrocortisone therapy, although at the price of a few patients developing exacerbation of symptoms.

Twenty-six of the patients who were in clinical remission after open therapy were entered for a trial week-end maintenance therapy lasting six months. Thirteen of the patients received hydrocortisone and the other 13 an inert preparation. The clinical course of the two groups was identical, each having five patients who relapsed during the six-months period. Week-end main-

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.

REFERENCES

Robinson, H. M., Robinson, R. C. V., Strahan, J. F., and Cohen, M. M. (1956). *U.S. armed Forces med. J.*, 7, 963.
Sulzberger, M. B., and Witten, V. H. (1954). *Med. Clin. N. Amer.*, **38**, 321.
Truelove, S. C. (1956). *Brit. med. J.*, **2**, 1267.
—— (1957). Ibid., **1**, 1437.
—— Horler, A. R., and Richards, W. C. D. (1955). Ibid., **2**, 1590.
—— and Morris-Owen, R. M. (1958). Ibid., **1**, 603.
—— and Richards, W. C. D. (1956). Ibid., **1**, 1315.

APPENDIX: BACTERIOLOGY OF THE COLONIC SWABS

BY

M. H. HAMBLING, M.B., B.S.

Department of Bacteriology, the Radcliffe Infirmary, Oxford

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.

REFERENCE

Leifson, E. (1936). *Amer. J. Hyg.*, **24**, 423.

TREATMENT OF ULCERATIVE COLITIS WITH TOPICAL HYDROCORTISONE HEMISUCCINATE SODIUM

A CONTROLLED TRIAL EMPLOYING RESTRICTED SEQUENTIAL ANALYSIS

BY

GEOFFREY WATKINSON, M.D., M.R.C.P.

Senior Lecturer in Medicine, Department of Medicine, University of Leeds

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