

The electroencephalogram was repeated on October 3 and showed improvement. The 5 c/s waves were no longer present and the 22 c/s activity was limited to the anterior halves of the hemispheres.

Discussion

The first point of interest is the lesion in this artery. This was considered by the pathologist to be traumatic in origin, but there was no history of injury. One of us (C.R.) believes that this lesion was a localized plaque of atheroma, both because of its appearance and because of its situation at the common site near to the origin of the internal carotid artery.

The next and most striking finding was the immediate disappearance of well-marked pyramidal signs and symptoms once a normal flow through the internal carotid artery had been re-established. The explanation of this and of the temporary episodes of disturbance of function in the central nervous system which occurs in patients with a partial occlusion of the internal carotid artery is of interest. In our view the most likely explanation is that the narrowing of the lumen reduces the internal carotid blood flow. In our patient this, coupled with a greater reduction of flow due to haemorrhage into the arterial wall at the time of the onset of his major attack, was enough to maintain the symptoms and signs of pyramidal insufficiency but not enough to cause complete death of the cerebral cells.

The same type of explanation will account for the transitory attacks which occurred earlier in this patient, in the patient reported by Eastcott *et al.* (1954), and in those reported by other authors, including Chambers (1954) and Millikan and Siekert (1955). In these the narrowing of the carotid reduces the flow. Under ideal conditions this is sufficient to maintain normal cerebral function, but when the flow is further reduced by such events as a change of posture or a reduction of blood pressure transitory symptoms of cerebral ischaemia may result. Others have postulated that these attacks of transitory carotid ischaemia are due to spasm of the carotid vessels. It is possible that this may occur, but in the presence of an organic reduction in the size of the internal carotid artery a further reduction in flow by some general or local cause other than spasm is more likely. Another explanation is that thrombi may form on the narrowed part and peripheral emboli result, but this again is unlikely in view of the short duration and repeated occurrence of similar attacks.

We believe that the correct treatment of a patient with a partial occlusion of the internal carotid artery is surgical because of the disability it causes and because of the great risk of complete carotid occlusion; this view is shared by Denman, Ehni, and Duty (1955). By this means we have completely relieved three patients, greatly improved two others, and six patients with complete occlusions have been made no worse by exploration of this vessel; there has been no mortality. The alternative is to treat these patients with long-term anticoagulant therapy. We believe that this measure should be used after operation to reduce, if possible, the occurrence of further thrombosis in this vessel or elsewhere.

An important step in the diagnosis of this lesion is the correct interpretation of the carotid arteriogram. This should always show the bifurcation of the common carotid artery, and as much attention should be paid to this region as to the intracranial vessels.

The actual operation is aimed at restoring the flow through the internal carotid artery. This may be achieved by either a direct anastomosis, a thrombo-endarterectomy, or an arterial graft or transplant, depending on the type of abnormality which the surgeon encounters. We have employed each of these procedures with success in patients requiring reconstruction of the carotid arteries. In our view hypothermia is a valuable aid to this type of surgery, but the body temperature need not be reduced below 28° C. (oesophageal temperature).

Summary

The case of a man with a partial occlusion of the left internal carotid artery is reported; as a result he was unable to sign his name, suffered from difficulty in speaking, and had abnormal pyramidal signs and symptoms in his right upper and lower limbs. These neurological abnormalities had been present for eight weeks. Reconstruction of the internal carotid artery was followed by immediate and complete relief of his neurological abnormalities. We believe that this is the first report of the complete recovery of definite and persistent neurological symptoms and signs due to internal carotid obstruction. In 1954 a similar case was reported by Eastcott, Pickering, and Rob, but in this case the neurological abnormalities were intermittent and not persistent.

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TREATMENT OF ULCERATIVE COLITIS WITH LOCAL HYDROCORTISONE

BY

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A number of reports exist indicating that oral cortisone is a useful agent in the treatment of ulcerative colitis. In a controlled therapeutic trial carried out through the co-operation of many physicians, it was found that patients treated with oral cortisone were nearly three times as likely to be in clinical remission at the end of six weeks' treatment as patients in the control group (Truelove and Witts, 1955). In view of the fact that cortisone and, more particularly, hydrocortisone have been found useful when applied locally in several eye conditions, joint conditions, and skin diseases, it seemed worth while assessing the value of local treatment in ulcerative colitis.

Hydrocortisone is an active principle of the adrenal cortex and is the principal corticosteroid found in human plasma. Under ordinary conditions it is present in the blood and other body fluids at a concentration of about 5–10 µg. per 100 ml. Under conditions of stress, or following injection of corticotrophin, its concentration may rise to 50 µg. per 100 ml., or even higher. Hydrocortisone appears to act directly on the tissues of the body, where it is constantly being broken down into inert metabolites. When cortisone is given orally or by injection it acts because it is converted into hydrocortisone. For cortisone to be locally effective the appropriate enzyme for this conversion must be present in the tissues being treated. For local application hydrocortisone has the additional advantage over cortisone that it is water-soluble, though not to a high degree. (The foregoing paragraph is based on the findings presented in a number of scientific papers, such as those by Nelson *et al.* (1951), Nelson and Samuels (1952), Cote and Delbarre (1953), Hellman *et al.* (1954), Silber and Porter (1954), and Peterson *et al.* (1955). A good general account is included in an article by Cope (1955).)

TABLE I.—*Brief Clinical Details and Results of Treatment in the First Six Patients Treated With Local Hydrocortisone (Each Course of Treatment Lasted Three Weeks).*

Case No.	Previous History	Immediately Before Treatment	Response to Treatment	Progress During One Year Follow-up Period
1. Female aged 30	In 1951 began to pass blood and mucus per rectum, and had bouts of diarrhoea. In 1954, inflamed rectum and lower sigmoid colon up to 25 cm. found on sigmoidoscopy. Then treated with corticotrophin and went rapidly into remission, which lasted several months. Symptoms recurred; treated with oral cortisone, she again went into remission for several months; then began to pass blood per rectum, without diarrhoea	<i>Clinical:</i> Passing blood per rectum twice a day <i>Sigmoidoscopic:</i> Very active inflammation of rectum with less severe changes above recto-sigmoid junction	<i>Remission:</i> Excellent response. Rapidly became symptom-free. Much improved but not entirely normal	Remained almost entirely well. Occasional passage of trace of blood per rectum. Sigmoidoscopy showed mild inflammation up to 20 cm. from anal margin, thereafter shading off into normality
2. Female aged 38	In Feb., 1953, had a sudden attack of diarrhoea with blood in motions, lasting for 5 months. Thereafter fairly well, but would often pass blood and mucus per rectum, although without diarrhoea. In Sept., 1955, recurrence of diarrhoea, with 5 motions a day containing much blood. This settled down to two motions a day with blood and mucus present	<i>Clinical:</i> 2 motions a day with blood and mucus present <i>Sigmoidoscopic:</i> Marked changes in rectum up to 18 cm. from anal margin	<i>Remission:</i> Excellent response. Rapidly became normal. Much improved but not normal	Remained almost entirely normal, with mild inflammation in lower half of rectum only, for 8 months, when she suddenly relapsed with diarrhoea and gross blood in stools. After 5 weeks of these symptoms she was again treated with local hydrocortisone (see Treatment 20 in Table II)
3. Male aged 34	In March, 1955, gradual onset of diarrhoea with 5-10 motions a day, with occasional blood present. Symptoms had eased off somewhat before present treatment began	<i>Clinical:</i> 4 unformed motions a day with much mucus. Colicky abdominal pain preceding each motion. Barium enema showed involvement of transverse and descending colon <i>Sigmoidoscopic:</i> Moderate inflammation extending as far as could be seen	<i>Remission:</i> Excellent response. 2 stools a day, rather soft but otherwise normal Improved but not normal	Remained symptom-free regarding bowel action for 11 months, but with mild inflammation of colonic mucosa extending as far up as could be seen with a sigmoidoscope. 2 months after end of treatment developed ischio-rectal abscess, treated by surgical drainage; healed well. After 11 months bowel symptoms recurred, treated with local hydrocortisone hemisuccinate sodium (to be reported)
4. Female aged 30	In August, 1952, gradual onset of diarrhoea with 6 motions a day containing blood and mucus. After 1 year had a complete remission lasting 3 months, but symptoms then recurred. Admitted in Feb., 1954, with 6 motions a day containing blood; haemoglobin, 66%; and evidence, on barium enema, of ulcerative colitis affecting transverse and descending colon. Improved on general medical treatment, but diarrhoea recurred, and in 1955 was treated with oral cortisone with improvement but not complete relief. Barium enema showed widespread involvement of colon	<i>Clinical:</i> Intermittent diarrhoea with blood present in stools <i>Sigmoidoscopic:</i> Moderate inflammation extending as far up as could be seen	<i>Remission:</i> Excellent response. Entirely normal symptomatically. Much improved. Slight hyperaemia only	Remained well for 6 months, although sigmoidoscopic appearances were those of moderate activity. After 6 months had a sharp clinical relapse, which was treated with local hydrocortisone (see Treatment 15 in Table II)
5. Female aged 42	Since 1952 has passed large quantities of mucus and blood per rectum each time bowels were opened and at other times also. No diarrhoea. Barium enema showed evidence of ulcerative colitis affecting the rectum and sigmoid colon	<i>Clinical:</i> No diarrhoea but passing considerable amounts of blood and mucus with every motion, and also at other times <i>Sigmoidoscopic:</i> Severe inflammation extending as far up as could be seen	No change No change	Treated with corticotrophin gel by intramuscular injection; passed into complete clinical remission, with much improved sigmoidoscopic appearances. After 7 months' remission relapsed and was treated* with oral cortisone combined with "salazopyrin," with gradual remission
6. Female aged 35	In 1943 developed ulcerative colitis, for which she was discharged from the Women's Auxiliary Air Force. In remission from 1945 to 1949, when symptoms recurred and she was in hospital for 2 months. Fairly well until June, 1955, when diarrhoea recurred with up to 12 motions a day containing blood and pus. Barium enema showed involvement of descending and sigmoid colon. Treated with oral cortisone with slight improvement only	<i>Clinical:</i> 6 unformed motions a day with blood present, and also passing blood at other times <i>Sigmoidoscopic:</i> Moderate inflammation extending as far up as could be seen	No change No change	Treated with systemic corticotrophin gel with little effect. Then treated with salazopyrin with no effect. Subsequent slight improvement, but had 6 stools a day until 8 months after present study began, when she went gradually into remission and has since been symptom-free

Present Investigation

With these considerations in mind it was decided to use hydrocortisone for the local treatment of ulcerative colitis. It was supplied for trial by Glaxo Laboratories in bottles containing 250 mg. of hydrocortisone (free alcohol) dissolved in 50 ml. of 50% ethyl alcohol, in which it is much more soluble than in water. For therapeutic use one of these bottles was emptied into a standard intravenous infusion bottle containing 500 ml. of normal saline. The hydrocortisone is soluble enough to be held in this dilution, and the resulting solution of 4.5% ethyl alcohol in saline was judged not to be an irritating fluid for the colonic mucosa. The infusion bottle containing hydrocortisone was suspended close to the patient's bed and the hydrocortisone dripped into the rectum through a standard blood transfusion giving-set, slightly modified to carry a rubber catheter for insertion into the rectum. The use of a controllable drip mechanism permits the solution to be run into the rectum at a slow and steady rate, so that the chance of its acting as an enema is much reduced. The method described was also easily mastered by those patients who

treated themselves in their own homes, and none of them experienced any difficulty in applying the treatment.

The patients now reported on were all mild or moderate cases of ulcerative colitis. Patients with the severe form may have much superadded infection with pyogenic bacteria. In view of the fact that cortisone encourages the spread of pyogenic infections, it was thought advisable to confine the local use of hydrocortisone, at any rate initially, to less severe cases. Although the hydrocortisone was used in low concentration compared with what has been found optimal in skin diseases, there are reasons to suppose that the concentration used would be adequate for local action in the colon. The mucosa of the colon is covered with a single layer of epithelial cells as opposed to the numerous layers of cornified cells covering the skin. The colon absorbs water and saline avidly, and hence the hydrocortisone would be drawn into contact with, or actually into, the mucosa in the process. (It has recently been shown by Liddle (1956) that $\Delta^9\alpha$ -fluorohydrocortisone (Δ FF) can be used to study the absorption of hydrocortisone by virtue of its capacity to suppress the normal secretion of corticotrophin and thus reduce blood levels of endogenous

hydrocorticoids to nearly zero. By this method, 26% of hydrocortisone was absorbed from the rectum compared with 2% from the skin, although Liddle specifically mentions that absorption across an inflamed mucosa has not been measured.) With these points in mind, a solution containing hydrocortisone at a concentration approximately 1,000 times that found in body fluids seems sufficient to have some local effect.

The treatment was given each night and was carried out with the patient in bed immediately before settling down for his night's sleep. On the first night one-quarter of a bottle was given—that is, approximately 125 ml. of liquid containing 60 mg. of hydrocortisone. During treatment the amount was increased up to half a bottle each night. The length of each course was originally three weeks, but later this was reduced to two weeks.

Results

Two groups of patients are here reported on. First, a group of six patients who were treated in October, 1955, and who have been observed for one year since. These patients were studied with particular care, for at least one sigmoidoscopic examination with biopsy was carried out before treatment and further biopsy examinations were made at weekly intervals during treatment, and on isolated occasions during the period of follow-up, by means of a special biopsy instrument (Truelove *et al.*, 1955). Their

course of treatment lasted three weeks. Secondly, an additional 15 treatments, each of two weeks' duration, have been given to patients without such close study and with shorter periods of follow-up. These 15 treatments include four instances of repeat treatments on patients who had previously responded to this form of therapy but had subsequently relapsed.

The results for these two groups are shown in Tables I and II. It will be seen that the patients often went into clinical remission during treatment, the net result of the total of 21 treatments being clinical remission in 14 cases, improvement in 1 case, and no change in six cases.

Almost all the patients who went into clinical remission with the treatment did so with great rapidity, commonly during the first few days of treatment. It is well known that symptoms may rapidly abate in any patient with ulcerative colitis, but the occurrence of very rapid remission in two out of every three patients within a few days of starting a particular form of therapy is decidedly exceptional, even if we allow for the fact that most of the patients in the present study had only mild symptoms. Rapid clinical remission was not confined to those patients with mild symptoms. For example, the patient described under Treatment No. 15 was experiencing a sharp attack of symptoms with gross bloody diarrhoea, rapidly falling haemoglobin, general malaise, and a sigmoidoscopic picture of acute inflammation. She nevertheless had complete

TABLE II.—Results of Next 15 Courses of Treatment With Local Hydrocortisone (Each Course of Treatment Lasted Two Weeks).

Treatment No.	Previous History	Immediately Before Treatment	Response to Treatment	Subsequent Progress
7. Male aged 46	In October, 1955, developed dull abdominal pain with fever and sweating lasting about a week. Since then has been passing 2 stools a day, watery, with much mucus present and occasional blood. Barium enema shows evidence of ulcerative colitis in rectum and sigmoid colon	<i>Clinical:</i> 2 liquid motions a day, with much mucus and occasional blood <i>Sigmoidoscopic:</i> Marked hyperaemia, granularity, numerous petechiae and shallow erosions, as far up as could be seen. Mucosal fragility much increased	<i>Remission:</i> Excellent response. After a few days was passing one normal stool a day Much improved, but mild hyperaemia and granularity still present	Remained symptom-free for 3 months, then had relapse and was again treated with local hydrocortisone (see Treatment 14)
8. Female aged 28	In March, 1955, had one week's diarrhoea with 7-8 loose motions a day containing blood; gradual improvement followed. Aug., 1955, bloody diarrhoea recurred, then gradually cleared up. Recently has been constipated but passing much blood and mucus per rectum, with occasional diarrhoea	<i>Clinical:</i> Passing considerable amounts of blood and mucus per rectum. Much lower abdominal pain <i>Sigmoidoscopic:</i> Well-marked hyperaemia, granularity, and exudate with the mucosal fragility much increased. These changes extended beyond 23 cm. from the anal margin	<i>Remission:</i> Good response. Steady improvement and was normal after one week Greatly improved. Mild hyperaemia and granularity only	Remained well for 6 weeks, but developed acute sinusitis which was followed by relapse of ulcerative colitis with passage of blood per rectum, abdominal pain, and sigmoidoscopic evidence of activity. Oral cortisone brought good response. Remained almost symptom-free on oral cortisone at the end of study
9. Female aged 36	Two years' history of passing blood and mucus per rectum every few days. Usually constipated. Lower abdominal pain	<i>Clinical:</i> Passing blood and mucus per rectum, but without diarrhoea <i>Sigmoidoscopic:</i> Marked inflammation of the rectum, becoming mild above rectosigmoid junction	<i>Remission:</i> Symptom-free in a few days Much improved—nearly normal	Symptom-free (6 months' follow-up)
10. Male aged 28	In Jan., 1954, had diarrhoea with 6 motions a day containing blood and mucus. Diarrhoea stopped after 6 weeks, but intermittent rectal bleeding persisted. Sept., 1954, 7 weeks' diarrhoea. Dec., 1954, period of severe rectal bleeding. Feb., 1956, bleeding per rectum recurred followed by diarrhoea with up to 12 motions a day and loss of 1 stone (6.4 kg.) in weight. Barium enema showed evidence of ulcerative colitis from rectum to transverse colon	<i>Clinical:</i> Diarrhoea with blood and mucus present. Barium enema showed widespread involvement of colon <i>Sigmoidoscopic:</i> Hyperaemia and well-marked granularity of the mucosa extending up as far as could be seen	<i>Remission:</i> Became symptom-free in a few days. Gained 1 stone (6.4 kg.) in weight	Remained symptom-free for a month, then relapsed with 4 unformed stools daily containing small amounts of blood. Again treated with local hydrocortisone (see Treatment 21)
11. Female aged 57	Recurrent attacks of diarrhoea with blood and mucus since 1917. Recent attack began 2 months before present treatment, with diarrhoea of up to 18 stools a day with blood and mucus present. Anaemic and treated with blood transfusion before hydrocortisone therapy was begun. Also suffered from chronic pyelonephritis with hypertension	<i>Clinical:</i> Severe bloody diarrhoea as described in previous column <i>Sigmoidoscopic:</i> Marked hyperaemia and granularity of mucosa with numerous tiny erosions. Much purulent exudate. Mucosa very fragile with bleeding on slight trauma. These changes extended as far as could be seen	<i>Remission:</i> Rapid response to treatment; became symptom-free in a few days Greatly improved, but still showing hyperaemia with mildly increased fragility of mucosa	Recurrence of diarrhoea with blood in stools. These symptoms persisted until end of present study

Continued overleaf

TABLE II.—Continued.

Treatment No.	Previous History	Immediately Before Treatment	Response to Treatment	Subsequent Progress
12. Female aged 51	Five months' history of passing blood and mucus per rectum but without diarrhoea	<i>Clinical:</i> Passing much blood and mucus per rectum up to 8 times a day <i>Sigmoidoscopic:</i> Marked hyperaemia of mucosa as far up as could be seen, with increased fragility and patchy exudate	<i>Remission:</i> One normal stool a day without blood or mucus Much improved. Slight hyperaemia and slightly increased fragility	Remained perfectly well (6 months' follow-up)
13. Female aged 30	In 1955 had a severe attack of ulcerative colitis associated with pregnancy, and was treated in hospital for 5 months with corticotrophin followed by oral cortisone, followed by salazopyrin. Was symptom-free on discharge in Dec., 1955. Remained in clinical remission and with sigmoidoscopic findings within normal limits (apart from some residual scarring) until April, 1956, when sharp relapse began possibly related to change of diet	<i>Clinical:</i> Three loose stools a day with much blood and mucus present <i>Sigmoidoscopic:</i> Marked hyperaemia and granularity with purulent exudate present. Numerous mucosal petechiae. Mucosal fragility much increased	No change Not done	Symptoms persisted in spite of variety of treatments, including oral cortisone, salazopyrin, and blood transfusion
14. Male aged 46	See Treatment No. 7	<i>Clinical:</i> For past two weeks had 3 loose stools a day with much mucus present <i>Sigmoidoscopic:</i> Hyperaemia and granularity with numerous petechiae present	<i>Remission:</i> Immediate response, to treatment with 1 normal stool a day after first instillation Much improved but residual hyperaemia and granularity present	Remained well for 3 months, then began to pass 3 loose stools a day with much mucus present. Treated with local hydrocortisone hemisuccinate sodium (to be reported)
15. Female aged 30	See Case 4 (Table I)	<i>Clinical:</i> Six unformed stools a day with much blood present. Hb has fallen from 95% to 75% in past fortnight <i>Sigmoidoscopic:</i> Marked hyperaemia with very extensive petechiae and purulent exudate. Extreme mucosal fragility	<i>Remission:</i> Immediate response to treatment. Diarrhoea less after 1 day. No bleeding after 2 days. One motion a day without blood after 3 days Much improved but still showed hyperaemia and granularity	Remained symptom-free (5 months' follow-up)
16. Male aged 46	Intermittent attacks of bloody diarrhoea since 1949. Three admissions to hospital. Two weeks before present treatment he had diarrhoea with small amounts of blood and pus present and with much lower abdominal pain	<i>Clinical:</i> Diarrhoea, with small amounts of blood and pus present in stools and lower abdominal pain <i>Sigmoidoscopic:</i> Well-marked hyperaemia, granularity, and mucosal fragility as far up as could be seen	<i>Remission:</i> Abdominal pain ceased after 2 days and diarrhoea after 5 days. Thereafter had entirely normal motions	Remained well (5 months' follow-up)
17. Male aged 46	Attacks of ulcerative colitis since 1953, for which was twice admitted to hospital. On second occasion in Dec., 1955, when he improved on treatment but continued to get 4-6 motions a day with occasional blood and mucus present. These symptoms persisted until present treatment began	<i>Clinical:</i> 4-6 loose motions a day with occasional blood and mucus present <i>Sigmoidoscopic:</i> Marked hyperaemia with numerous petechiae and purulent exudate. Mucosal fragility increased	<i>No change:</i> At first improved and became almost symptom-free, but symptoms recurred during treatment No change	Symptoms persisted in spite of a variety of treatments
18. Male aged 24	Developed first attack of ulcerative colitis in Dec., 1955. In Feb., 1956, was admitted to hospital with 15 motions a day containing much mucus and blood. Barium enema showed changes throughout the whole descending colon. Treated with corticotrophin with much improvement but without going symptom-free. Thereafter treated with oral cortisone as out-patient, but became rather worse with 6-7 motions a day containing small amounts of blood. Oral cortisone was tailed off at beginning of hydrocortisone treatment	<i>Clinical:</i> 6-7 motions a day with small amounts of blood present <i>Sigmoidoscopic:</i> Marked hyperaemia, granularity, and purulent exudate. Mucosal fragility much increased	<i>Improved:</i> One normal motion each morning; no further bowel action until evening, then he passed small amounts of mucus and a little blood No change	Mild symptoms persisted in spite of treatment, with salazopyrin, which was apparently beneficial
19. Female aged 62	Four months' passage of mucus per rectum with occasional blood and increasing frequency of defaecation	<i>Clinical:</i> 5 motions a day containing blood and mucus. Intermittent fever up to 101° F. (38.3° C.) <i>Sigmoidoscopic:</i> Well-marked hyperaemia and granularity	No change No change	Treated with systemic corticotrophin. Deteriorated. Developed severe fungus infection of mouth. Then gradually improved and was almost symptom-free at end of present study
20. Female aged 38	See Case 2 (Table I)	<i>Clinical:</i> Diarrhoea with gross blood and mucus in stools <i>Sigmoidoscopic:</i> Severe inflammation extending up to 20 cm. from anal margin and then shading off into normality	<i>Remission:</i> Symptom-free after a few days Much improved but not normal	Remained well for 2 months, then began to pass blood and mucus per rectum. Treated with local hydrocortisone hemisuccinate sodium (to be reported later)
21. Male aged 28	See Treatment No. 10	<i>Clinical:</i> Diarrhoea with 4 unformed motions a day, containing blood <i>Sigmoidoscopic:</i> Marked inflammation as far up as could be seen	No change No change	Treated with oral cortisone until end of present study, with improvement after 6 weeks

symptomatic relief in three days from the onset of therapy, which was self-administered at home.

The sigmoidoscopic changes throughout treatment corresponded roughly to the clinical response, in that all the patients experiencing a clinical remission showed an improved sigmoidoscopic picture, which the others did not. However, in only one patient did the sigmoidoscopic appearances become entirely normal, although in some of the others the abnormal changes were slight at the end of treatment.

By contrast, the histological appearances of biopsy specimens taken throughout treatment showed no such corresponding improvement. In general, the mucosal changes appeared much the same at the end of treatment as at the beginning, even among those patients experiencing complete symptomatic relief and with greatly improved sigmoidoscopic appearances. In some cases the surface epithelium appeared more gravely disturbed during treatment than before it. Whether this was due to the effects of the hydrocortisone itself or whether the vehicle of 4½% ethyl alcohol was exerting a noxious influence is at present uncertain.

The patients who passed into clinical remission were liable to suffer from recurrence of symptoms during the follow-up period, although a relapse during the first few weeks after stopping treatment was not common. Among those who responded well to the treatment the sigmoidoscopic picture often showed some worsening after treatment was stopped, but this might occur without simultaneous clinical relapse. Four patients who relapsed clinically some months after a successful first treatment were treated a second time. In the case of the first three patients so treated, the second course of treatment was rapidly effective in suppressing symptoms, but the fourth patient showed no response to the second course.

It might be supposed that local treatment applied by a rectal drip would be effective only in patients in whom the disease was limited to the rectum or lower colon. In other words, the treatment might be efficacious only in those varieties of ulcerative colitis which have been labelled "haemorrhagic proctitis" and "recto-sigmoiditis." Many of the patients fell into these categories, as was to be expected in view of the fact that severely ill patients were excluded from the study. However, not all these patients with limited disease responded to the treatment, and, by contrast, there were other patients with radiological evidence of widespread involvement of the colon who did respond. The geographical extent of the disease is therefore not the important element in determining response to treatment. The reason for this becomes plain when we consider the extent to which substances dripped into the rectum will spread through the colon.

Extent of Spread of Rectal Drip

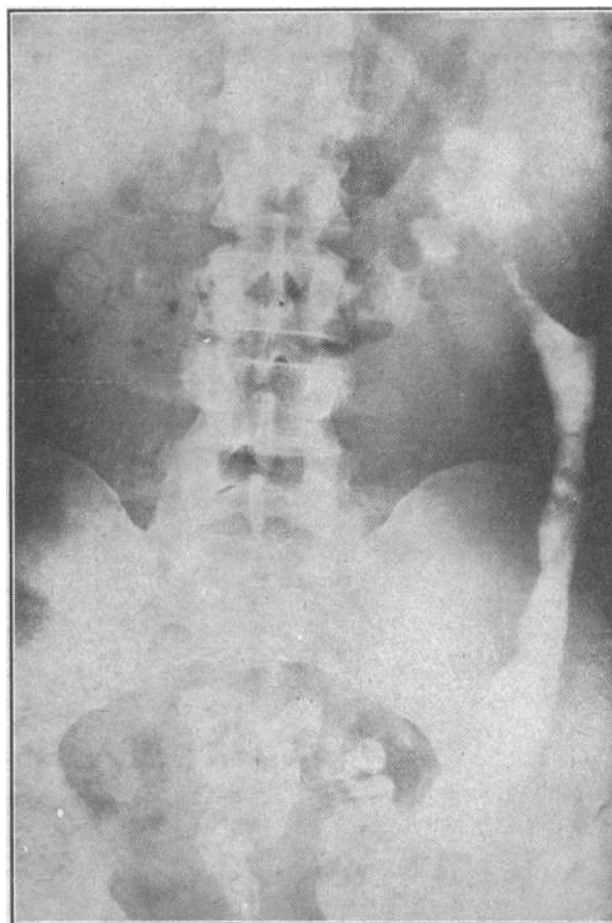
In order to determine how far along the colon the hydrocortisone solution travels when it is dripped into the rectum with the patient supine, each of the first six patients treated was examined radiologically after a dilute suspension of barium sulphate had been dripped into the rectum under similar conditions. It was found that a suspension of 15 g. of barium sulphate in 250 ml. of normal saline was sufficient to yield clear radiographs. The patient set up the rectal drip with the dilute barium suspension while lying on the x-ray table and remained there until the radiological examination was completed some three and a half hours later. The barium sulphate suspension was dripped into the rectum at the usual rate, and radiographs were taken at the end of the administration, followed by additional radiographs at intervals of one hour, two hours, and three hours after its completion.

The barium sulphate suspension was found to travel extensively through the colon, in all cases travelling as far up at least as the splenic flexure and, in some, across the transverse colon and into the ascending colon. A typical

radiograph taken one hour after the conclusion of the rectal drip is shown in the accompanying illustration. This wide spread is presumably due to the occurrence of non-propulsive contractions of the colon such as have been demonstrated both in animals and in man (Templeton and Lawson, 1931; Adler *et al.*, 1941). It demands only the application of simple physical principles to see that if the anal sphincters remain closed during such contractions any liquid contents are likely to be widely dispersed through the colon. It is clear that if a local treatment can be found which is efficacious against ulcerative colitis it can be applied effectively by rectal drip over the bulk of the colonic mucosal surface, provided the patient is not rectally incontinent.

Discussion

The present study has shown that about two out of every three patients with mild or moderate symptoms of ulcerative colitis experience complete symptomatic relief when treated with nightly instillations of hydrocortisone into the rectum. The clinical response has shown a well-marked pattern. Either the patient responds swiftly to the treatment so that symptomatic relief is obtained in the first few days or he is left unchanged by it. Whether this difference reflects any fundamental difference in the nature of the disease in different patients is entirely uncertain. However, it is a pattern of response which has commonly been observed when hydrocortisone has been employed as a local treatment on the skin, in the eyes, and in joints. For example, Sulzberger and Witten (1954) reported a study of the effect of hydrocortisone in 252 patients with skin diseases, in many of whom the lesions were symmetrically bilateral, so that one side of the body could be treated with an inert



Radiographic appearances one hour after dripping a weak suspension of barium sulphate into the rectum with the patient supine.

ointment and used as a control. In those patients who showed a good response to hydrocortisone the effect was quickly apparent, visible improvement occurring in 24 to 48 hours.

Although the sigmoidoscopic picture showed improvement during therapy in all those patients going into clinical remission, only one patient had entirely normal sigmoidoscopic findings at the end of treatment. A more marked discrepancy was seen in the case of the histological picture of the mucosa as judged by examination of small specimens taken for biopsy from the neighbourhood of the recto-sigmoid junction, for it was exceptional to find improvement. This finding emphasizes that this form of treatment can be regarded only as a means of symptomatic relief and that the disease continues in those who pass into complete clinical remission. However, this is probably true of all forms of medical treatment in present use, and Truelove and Richards (1956) have reported that more than half of the biopsy specimens taken from patients in clinical remission show evidence of inflammation.

The fact that the present form of treatment is in no sense a cure of the disease should not be taken to mean that it is useless. If symptoms can be promptly checked in a considerable proportion of patients, particularly by the use of a method which they can carry out in their own homes, it is a valuable addition to therapy. So far, there has not been sufficient opportunity to see whether repeated short courses of local hydrocortisone administered as soon as symptoms recur will keep patients in a good state of general health for a prolonged period. Four patients in the present study who relapsed some months after a successful course of treatment were treated a second time, with rapid relief of symptoms in three of them. It is highly desirable that further experience along these lines be gained.

Although the results now reported seem reasonably favourable, it is not claimed that the form of hydrocortisone used is necessarily the best for local treatment. Hydrocortisone (free alcohol) has a very limited solubility in water and was therefore supplied by the manufacturers in solution in 50% ethyl alcohol. This was diluted 10 times with saline, but, even so, it is conceivable that the resulting weak alcohol solution which acted as a vehicle for the hydrocortisone was not entirely innocuous to the inflamed mucosa. A form of hydrocortisone which is freely soluble in water may therefore prove to be superior for local use in ulcerative colitis. One such preparation, hydrocortisone hemisuccinate sodium, is being tried at present.

It will be appreciated that the opinion expressed that the present study has shown local hydrocortisone to be frequently effective in bringing about symptomatic relief in mild attacks of ulcerative colitis is no more than a presumption based on clinical judgment. It is conceivable that the rectal drip might aid in the relief of symptoms merely by lubricating the colon and thus minimizing the damage caused by defaecation, just as preparations such as "isogel" and "normacol" may be useful in mild cases of ulcerative colitis. Alternatively, those who believe ulcerative colitis to be a psychosomatic disorder will find a ready explanation of the apparent benefit in the use of any treatment which is novel. Yet a third possibility is that a rectal drip of hydrocortisone is no more than an inconvenient and expensive way of allowing hydrocortisone to be absorbed to exert its systemic effects. These possibilities could be assessed by a properly designed therapeutic trial. Such a trial may be advisable, but at present it seems best to form clinical judgments on various preparations of hydrocortisone so that the one found to be most efficient can be put to a formal test in due course.

Summary

A group of patients suffering from ulcerative colitis in a stage of mild or moderate severity have been treated by the introduction of a solution of hydrocortisone into the rectum by means of a slow drip. Those who were

severely ill were not included. Treatment was given nightly, originally for three weeks, latterly for two weeks.

Twenty-one courses of treatment have been given to 17 patients, four having been treated twice.

In 14 instances rapid clinical remission occurred, this change occurring in the first few days after starting treatment. In one instance the patient was much improved but not in complete clinical remission. In the remaining six instances the treatment had no effect.

The sigmoidoscopic changes roughly corresponded with the change in clinical state, for all those patients going into clinical remission showed an improved sigmoidoscopic picture, although in only one instance did the sigmoidoscopic findings become entirely normal.

By contrast, the histological findings met with in small biopsy specimens did not in general show a corresponding improvement.

The effect of the treatment is not permanent, although a successful immediate outcome may be followed by a period of clinical remission lasting at least for several months. In the case of four patients who suffered clinical relapse some months after an excellent response to treatment, the institution of a second course of treatment brought about clinical remission in a few days in three of them, so that repeated courses of treatment whenever symptoms recur may prove to be effective in some of those patients who respond to the first course of treatment.

This method of treatment appears to be a useful addition to the treatment of ulcerative colitis, particularly as it can be carried out by patients in their own homes.

I am grateful to Glaxo Laboratories for making a gift of the hydrocortisone; to Miss Shirley Thomas, who assisted at the sigmoidoscopic examinations and in other ways; to Mr. D. Jerrome, of the Dunn School of Pathology, who prepared some of the histological specimens through the courtesy of Professor Sir Howard Florey; to Dr. M. A. Jennings, of the Dunn School of Pathology, who examined some of the specimens; and to my radiologist colleague, Dr. K. Lumsden, who arranged for the special barium enema examinations to be carried out. It is a pleasure to record my appreciation of the first six patients treated. They were plainly told that the treatment was experimental and that if they took part they would undergo repeated sigmoidoscopy with biopsy; none refused treatment.

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The West London Medico-Chirurgical Society has decided to discontinue the *West London Medical Journal* and to revert to an annual volume of proceedings, the first issue of which will appear in January, 1958. The *West London Medical Journal* first appeared in 1896, succeeding the *Proceedings of the West London Medico-Chirurgical Society* (1882-96).