

tiated glycogen-storage disease into a number of different types, and has revealed that the peripheral part of the glycogen molecule can undergo metabolic change independently of the central part. What light these new observations will throw on medicine will become clear early in the second century of glycogen. I believe that we can confidently assume that Claude Bernard would have given his interested approval to the many investigations into the structure and biosynthesis of glycogen which have taken place during the last twenty-five years of the first century of this substance.

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Courses for the training of matrons and assistant matrons for old people's homes are organized regularly by the National Old People's Welfare Council (in association with the National Council of Social Service). Each course lasts fourteen weeks. The next course will begin on September 9; there will be another early next spring. Applicants, who should be women of over 30 years of age, need have no special qualifications, although a practical knowledge of nursing and housekeeping is an advantage. Intending students may apply through their local education authorities for grants towards their training from the King George VI Social Service Scheme (Old People). Further details may be obtained from the secretary, National Old People's Welfare Council, 26, Bedford Square, London, W.C.1. There are over 1,400 homes for old people, provided either by voluntary organizations or by statutory authorities, and competent staff are constantly required.

TREATMENT OF ULCERATIVE COLITIS WITH LOCAL HYDROCORTISONE HEMISUCCINATE SODIUM

BY

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A previous article (Truelove, 1956) dealt with the treatment of mild and moderate cases of ulcerative colitis by means of a rectal drip of hydrocortisone. The result of 21 treatments was complete symptomatic relief within a few days in 14 instances, and it was concluded that this method was a useful addition to therapy. However, although clinical remission was accompanied by much-improved sigmoidoscopic appearances, it was found that the histological appearances of biopsy specimens of the colonic mucosa did not in general show a corresponding improvement.

Various possibilities which might have accounted for this discrepancy were considered. One was that the actual preparation of hydrocortisone used was not entirely harmless to the inflamed mucosa. Hydrocortisone in the form of its free alcohol is only slightly soluble in water, and it was therefore supplied by the manufacturers in solution in 50% ethyl alcohol. This concentrated solution was diluted 10 times in normal saline for actual instillation into the rectum, but nevertheless it seemed possible that even a 5% solution of ethyl alcohol might damage, or at least prevent from healing, a mucosa which was already diseased. This possible source of failure to induce mucosal healing can be eliminated if one uses a form of hydrocortisone which is freely soluble in water. Such a substance—hydrocortisone hemisuccinate sodium—has recently been synthesized, and Glaxo Laboratories kindly made supplies of it available for clinical trial.

Hydrocortisone Hemisuccinate Sodium

This is a white crystalline powder highly soluble in water, with which it forms a clear, colourless solution. There are as yet only scanty references in the literature to its use in man. The first account appears to be that of Orr *et al.* (1955), who used it intramuscularly to treat conditions such as disseminated lupus erythematosus, acute bronchial asthma, and the crisis of Addison's disease, and for replacement therapy after bilateral adrenalectomy; the results were comparable to those obtained by corresponding doses of hydrocortisone. The same authors also studied the effect of injecting it intravenously into a human being without adrenals and found evidence of an exponential decay curve characterized by a half-life of four to five hours, which agrees well with data obtained for hydrocortisone itself by Hellman *et al.* (1954), making use of a preparation labelled with radioactive carbon. These and other facts suggest that the two compounds are metabolized by the liver and excreted by the kidney in a closely similar fashion. Orr *et al.* suggested that the hemisuccinate would be valuable in the treatment of severe emergencies in which a "shock-like" state occurs, by virtue of its

high solubility in water, so that the equivalent of 100 mg. of hydrocortisone can be given in a volume of 2 ml. by simple intravenous injection from a syringe without the use of infusion apparatus. This use has also been suggested by the Council on Pharmacy and Chemistry (1956) in a brief account of the substance.

Its use for local application to the skin has been described by Robinson *et al.* (1956), who found it valuable in the treatment of those skin diseases, such as atopic dermatitis, contact dermatitis, seborrhoeic dermatitis, and pruritus ani, which are improved by local treatment with ordinary hydrocortisone. The hemisuccinate appeared to be efficient in a lower concentration than the preparations of less soluble hydrocortisone. Coste *et al.* (1955) have studied the action of hydrocortisone hemisuccinate sodium when injected into inflamed joints, and find that symptomatic relief is obtained comparable to that experienced with other preparations of hydrocortisone.

So far as is known, therefore, the biological actions of hydrocortisone hemisuccinate sodium are identical with those of hydrocortisone itself except in so far as they may be modified by the much greater water solubility of the hemisuccinate.

Present Investigation

Hydrocortisone hemisuccinate sodium was supplied for trial by Glaxo Laboratories in bottles containing the molecular equivalent of 100 mg. of hydrocortisone. For therapeutic use the contents of one of these bottles was transferred to a standard blood-transfusion bottle and dissolved in 120 ml. of normal saline. (The volume of 120 ml. was selected purely because bottles of sterile normal saline of this size are prepared in this hospital for routine use and could therefore be supplied to the patients without the need of special arrangements. Any volume of saline up to about 250 ml. would appear to be suitable.) *The solution of hydrocortisone hemisuccinate sodium must be prepared shortly before its use* because slow hydrolysis of the hemisuccinate occurs with standing in solution, and the resulting free hydrocortisone goes out of solution.

The patients treated were all in a stage of mild or moderate symptoms. As in the previous study, patients severely ill with the disease have been excluded from this study and have been treated as in-patients along conventional lines. No other treatment was employed while the local hydrocortisone was in use. The patients carried out treatment entirely in their own homes, with the exception of two who were already in hospital and who began treatment as in-patients, going home after three days to complete it there. No difficulty has been experienced by the patients in carrying out the treatment.

The treatment is carried out nightly when the patient would normally be going to bed. The solution of hydrocortisone is prepared in the infusion bottle. The giving apparatus with its attached rubber catheter is plugged into the infusion bottle, which is then hung up close to the patient's bed. The patient lies in bed, inserts the catheter well into the rectum, turns on the screw-clip to start the solution running and adjusts the rate to 1-2 drops a second. As was found in the previous study, this slow rate prevents the instillation acting as an ordinary enema and causing defaecation. When the solution has run in, the catheter is removed and allowed to drop down into a bowl or basin beside the bed, where it is left until the next day. Thus the patient is able to settle down to his night's sleep as soon as the instillation is completed.

Treatment consisted at first of 10 nightly treatments, but later this was increased to 14 as the supplies of hydrocortisone hemisuccinate sodium increased.

Assessment of the Therapy

All patients were seen on the day on which treatment was to begin at night. Sigmoidoscopy was carried out and the appearances were recorded. In all cases a biopsy specimen was taken from the lower colon, between 15 and 20 cm. from the anal margin, by means of an improved version of a special colonic biopsy instrument (Truelove *et al.*, 1955). Specimens were taken for cytological examination by the Papanicolaou technique by means of a special instrument described previously (Boddington and Truelove, 1956).

The patients were examined again on the day after their last night of treatment and corresponding observations were made.

Results

Eighteen courses of treatment have been given to 15 patients, three of them having received two separate courses. The response to treatment of the individual patients is given in Table I, together with brief details of their previous history and their subsequent progress.

The clinical response to treatment was as follows: rapid remission, 11; improved, 1; no change, 6. This corresponds with what was found in the previous study, using ordinary hydrocortisone, when there were 14 remissions out of 21 treatments. Clinical remission was almost always very rapid in those patients who showed a favourable response, usually occurring in the first few days of the beginning of treatment; there was often marked improvement after the first night's treatment. In some patients the effect was dramatic in that the patient became symptom-free after the first instillation. For example, in Treatment No. 17, the patient had suffered from diarrhoea for the previous two weeks with six loose motions a day containing much blood. His haemoglobin value had fallen from 102% to 81% in that period and he felt ill. On the day following the first instillation he passed two formed stools not containing blood, and continued to do so.

Sigmoidoscopic Appearances

The sigmoidoscopic changes corresponded closely to the clinical response, all those patients going into clinical remission showing a marked improvement in the sigmoidoscopic picture. In these patients the abnormal fragility of the colonic mucosa, which manifests itself as "contact bleeding" and is largely or entirely responsible for loss of blood in this disease, was conspicuously absent. This was evident when taking "smears" from the colonic surface for cytological examination, because no obvious blood could be seen on the instrument when this was done and only a small quantity of mucoid material resulted. When the colonic mucosa is inflamed, as it is in an active phase of ulcerative colitis even when symptoms are very slight, the specimen must be taken with delicacy, for otherwise the epithelial cells are deluged by red blood corpuscles and the examination is rendered useless. By contrast, the special "smear-taking" instrument can be used with much more vigour on a normal mucosa without causing bleeding.

In this respect the patients in remission after hydrocortisone hemisuccinate sodium were normal or close to it. The patients who were classified as showing "near-normal" appearances at the end of treatment displayed a particular type of fine granularity of the mucosa as the only abnormal finding. The abnormality revealed itself as the reflection of numerous "pin-heads" of light. It is believed that each point of light arises where the mucosa has a tiny bulge on its surface due to the presence of a large lymphoid follicle in the substance of the mucosa itself. Lumb and Protheroe (1955) described the frequent occurrence of these big follicles in the mucosa of ulcerative colitis as occurring during a phase of healing, a view from which I have no reason to dissent. In any event, large lymphoid follicles were commonly found in the biopsy specimens taken from patients who showed this special form of granularity.

TABLE I.—*Summary of Clinical History and the Response to Treatment with Local Hydrocortisone Hemisuccinate Sodium. (The length of treatment was 10 days for the first three patients and 14 days for the remainder)*

Treatment No.	Previous History	Immediately Before Treatment	Response to Treatment	Subsequent Progress
1. Female aged 46	Attacks of blood and mucus per rectum with diarrhoea since 1944, admitted 4 times, the last occasion being in 1948. During admissions sigmoidoscopy showed inflamed mucosa of rectum and lower colon and barium-enema examination showed appearances of ulcerative colitis affecting rectum and sigmoid colon. After last admission remained comparatively well, although subject to mild attacks of passing blood and mucus for a few days at a time. Two weeks ago suddenly developed abdominal pain and diarrhoea with 4 loose motions a day containing blood. These symptoms persisted and she felt unwell	<i>Clinical:</i> 4 loose motions a day with much blood and mucus present. Hb 79%. General malaise <i>Sigmoidoscopic:</i> Hyperaemia and granularity of rectum with increased fragility. These appearances become less severe above the recto-sigmoid junction	<i>Remission:</i> Immediate response. No diarrhoea after 1 day. No discharge of blood after 2 days. Thereafter passed 2 formed motions a day. Feeling of malaise disappeared <i>Sigmoidoscopic:</i> Near-normal. Slight granularity only. No increase in fragility, no hyperaemia	Remained symptom-free (10 months' follow-up)
2. Female aged 31	Developed ulcerative colitis in Feb., 1954. Admitted May, 1954, because symptoms had become worse and 8-10 loose bloody motions a day were passed. Barium enema showed evidence of ulcerative colitis affecting sigmoid colon. Sigmoidoscopy showed sharp inflammation of colonic mucosa. Treated with systemic corticotrophin and made excellent response. After a year became subject to intermittent diarrhoea with occasional gross blood, but was not badly affected until 1956, when attacks became more severe with 7-8 loose stools a day containing blood and with symptoms becoming more or less continuous	<i>Clinical:</i> 7-8 loose stools a day containing small amounts of blood. Hb 71%. E.S.R. 37 mm. <i>Sigmoidoscopic:</i> Marked hyperaemia and granularity with free bleeding on contact. Much purulent exudate present	<i>Little change:</i> Some improvement but not symptom-free. Bleeding almost ceased, but still had 4 stools a day, rather loose. Hb 76%. E.S.R. 32 mm. <i>Sigmoidoscopic:</i> Improved, but mild hyperaemia and granularity persisted	Gradual improvement but mild symptoms persisted
3. Female aged 34	In 1953 suddenly began to pass blood and mucus in motions and then developed diarrhoea with 4-5 motions a day. These symptoms lasted for 2 months. Thereafter stayed well until June, 1956, when diarrhoea suddenly developed with 5-6 motions a day, loose and with some blood present. Felt ill	<i>Clinical:</i> 6 loose motions daily with small amounts of blood present. Barium enema showed evidence of ulcerative colitis in descending and sigmoid colon <i>Sigmoidoscopic:</i> Marked hyperaemia and granularity with greatly increased mucosal fragility. These changes extended as far up as could be seen	<i>Remission:</i> Immediate response to treatment with one motion not containing blood on day following first rectal drip <i>Sigmoidoscopic:</i> Much improved. Mild hyperaemia and granularity up to 12 cm. from anal margin, with normal appearances above that	Remained symptom-free and was sigmoidoscopically normal at end of study. Hb 93%. E.S.R. 14 mm. (9 months' follow-up)
4. Female aged 45	20 years ago had severe attack of ulcerative colitis, in hospital 3 months. Attack lasted for more than a year. Thereafter was entirely symptom-free until 1955, when diarrhoea developed with much blood in stools. Barium enema showed changes of ulcerative colitis in descending and sigmoid colon. Sigmoidoscopy showed evidence of mild ulcerative colitis. Treated with cortisone as out-patient, becoming symptom-free in 3 weeks. Sigmoidoscopic appearances became normal. Thereafter remained in clinical remission, although E.S.R. was raised, until June, 1956, when she again began to pass blood in motions. After 3 weeks of these symptoms local hydrocortisone hemisuccinate started	<i>Clinical:</i> 2 poorly formed motions a day with blood present <i>Sigmoidoscopic:</i> Marked hyperaemia and granularity as far as could be seen, with many petechiae and increased mucosal fragility	<i>Little change:</i> 3 formed motions a day still containing a little blood <i>Sigmoidoscopic:</i> Little change	Treated with oral cortisone and rapidly became symptom-free with near-normal sigmoidoscopic appearances (9 months' follow-up)
5. Female aged 30	For past 5 years has had bouts of diarrhoea with as many as 10-12 stools a day which are loose, offensive, and contain blood and mucus. Has felt tired and has lost weight. In May, 1956, admitted to hospital because of a severe attack. At that time had gross bloody diarrhoea. Hb 81%. Barium enema showed changes of ulcerative colitis extending from middle of transverse colon to rectum. Sigmoidoscopy showed evidence of severe ulcerative colitis. Treated with systemic corticotrophin and went into remission. However, soon relapsed and began to get diarrhoea with blood in stools. These symptoms continued and by Aug., 1956, was having gross bloody diarrhoea. Local treatment then begun	<i>Clinical:</i> Bloody diarrhoea with 7-8 loose stools a day containing moderate or large amounts of blood <i>Sigmoidoscopic:</i> Marked hyperaemia and granularity. Fragility greatly increased. Purulent exudate present and ulceration. These changes extend up as far as could be seen	<i>Little change:</i> Noticed slight improvement but nothing marked <i>Sigmoidoscopic:</i> No change	Treated with oral cortisone but she became worse and this was stopped. Then treated with "salazopyrin" with slight improvement; but symptoms, though less severe, persisted at end of follow-up
6. Female aged 39	In Feb., 1955, had sudden attack of diarrhoea with blood, lasting 5 months. Thereafter was fairly well but would often pass blood and mucus per rectum although without diarrhoea. In Sept., 1955, diarrhoea recurred with 5 motions a day containing blood. This settled down to 2 motions a day with blood and mucus. In Oct., 1955, treated with local hydrocortisone and rapidly became symptom-free. Remained symptom-free for 8 months, then suddenly relapsed with diarrhoea and gross blood in stools. After 5 weeks of these symptoms, again treated with local hydrocortisone, becoming symptom-free in a few days. Remained well for 2 months, but then began to pass much blood and mucus per rectum several times a day	<i>Clinical:</i> Passing much blood and mucus per rectum several times a day <i>Sigmoidoscopic:</i> Marked inflammation as far up as could be seen	<i>Remission:</i> Blood stopped after 2 days. Passed some mucus for a few more days and then became entirely normal <i>Sigmoidoscopic:</i> Near normal	Remained symptom-free for 3 weeks, then began to pass blood and mucus. After one week of these symptoms she was again treated with local hydrocortisone hemisuccinate (see Treatment No. 10)
7. Male aged 43	In Oct., 1955, first noticed blood in stools, then symptoms gradually became worse. At first had 2-3 motions a day, always with blood present; he gradually worsened, and was admitted to hospital in Sept., 1956, with 4-5 motions a day containing blood. Barium enema showed mild changes of ulcerative colitis	<i>Clinical:</i> 3-5 motions a day with much mucus and blood present <i>Sigmoidoscopic:</i> Marked hyperaemia and granularity of mucosa as far up as could be seen. Fragility increased. Purulent exudate present. No gross ulceration seen	<i>Remission:</i> Immediate response to treatment and was symptom-free in 3 days <i>Sigmoidoscopic:</i> Much improved. Mild inflammation only	Remained in clinical remission, but sigmoidoscopically showed some relapse after one month. At end of study was still symptom-free, but sigmoidoscopy showed definite inflammation. Hb 97%. E.S.R. 5 mm. (7 months' follow-up)

(continued overleaf)

TABLE I.—Continued

Treatment No.	Previous History	Immediately Before Treatment	Response to Treatment	Subsequent Progress
8. Male aged 35	In March, 1955, gradual onset of diarrhoea with 5-10 motions a day, occasionally containing blood. In Oct., 1955, was treated with local hydrocortisone, with rapid remission. Remained symptom-free regarding bowel action for 11 months, although 2 months after end of treatment ischio-rectal abscess developed; this was treated by surgical drainage and healed well. After 11 months bowel symptoms returned and after one week hydrocortisone hemisuccinate was given	<i>Clinical</i> : 6 unformed motions a day containing small amounts of blood <i>Sigmoidoscopic</i> : Well-marked hyperaemia and granularity extending as far as could be seen	<i>Remission</i> : Became symptom-free in 1 week <i>Sigmoidoscopic</i> : Much improved. Mucosa still rather hyperaemic but no increased fragility	Remained symptom-free for 2 months, then symptoms recurred with 6 loose motions containing gross blood and with fall of Hb from 102% to 81%. Treated again with hydrocortisone hemisuccinate (see Treatment No. 17)
9. Male aged 47	In Oct., 1955, had dull abdominal pain with fever and sweating for about a week. He then passed 2 stools a day, watery with much mucus and occasional blood. Barium enema showed evidence of ulcerative colitis in rectum and sigmoid colon. Sigmoidoscopy showed ulcerative colitis of marked severity. In Jan., 1956, had local hydrocortisone, with rapid remission. Remained symptom-free for 3 months, then relapsed and was again treated with local hydrocortisone, with excellent response, becoming symptom-free after first instillation. Remained well for 3 months, then began to pass 3 loose stools a day containing much mucus. At this stage local hydrocortisone hemisuccinate given	<i>Clinical</i> : 2 liquid motions a day with much mucus present <i>Sigmoidoscopic</i> : Marked hyperaemia and granularity stretching up as far as could be seen. Fragility increased	<i>Remission</i> : Immediate response to treatment with 1 formed normal motion a day after the first instillation <i>Sigmoidoscopic</i> : Very mild hyperaemia only. No increase in fragility	Remained symptom-free for 2 weeks and then again developed very loose motions with much mucus and small amounts of blood present and was again treated with hydrocortisone hemisuccinate (see Treatment No. 14)
10. Female aged 39	See Treatment No. 6	<i>Clinical</i> : Passing blood and mucus per rectum several times a day <i>Sigmoidoscopic</i> : Severe inflammation up to 15 cm. from anal margin, mucosa becoming normal above this. Rectal mucosa very hyperaemic and granular, with mucopus present. Mucosa oozes blood with slight trauma	<i>Remission</i> : Bleeding stopped after first night. Normal motions after second night. Thereafter symptom-free <i>Sigmoidoscopic</i> : Near normal	Remained symptom-free with normal haemoglobin and E.S.R. (6 months' follow-up)
11. Female aged 44	In 1953 developed bouts of diarrhoea lasting 2-3 weeks. In 1955 had severe attack of diarrhoea with 8-12 liquid motions a day containing much blood and mucus. Lost 5 kg. in weight and was anaemic. Barium enema showed changes of ulcerative colitis throughout almost whole colon. Sigmoidoscopy showed typical changes of ulcerative colitis. Treated in hospital with cortisone and general medical measures. Treatment complicated by deep vein thrombosis, first of right leg and later of left, for which anticoagulant therapy given. However, colitis responded and she was in clinical remission on discharge. After 2 months' remission colitis recurred, and as an out-patient she was given oral cortisone, again went into remission. On stopping cortisone diarrhoea recurred with 6 loose motions a day though with very little blood. Further course of oral cortisone as out-patient brought improvement without her being entirely symptom-free. Reasonably well until Oct., 1956, when diarrhoea returned with 10-12 liquid motions a day containing small amounts of blood. At this stage local treatment given	<i>Clinical</i> : 10-12 liquid motions a day with small amounts of blood present. Much abdominal pain <i>Sigmoidoscopic</i> : Severe inflammation. Fragility greatly increased. Exudate present. Ulceration	<i>Little change</i> : 10 unformed motions a day, although with no blood present, and with abdominal pain <i>Sigmoidoscopic</i> : Improved. Fragility normal but still hyperaemic	Treated with salazopyrin; response being excellent. One normal formed motion a day after 4 days' treatment (6 months' follow-up)
12. Male aged 31	In 1950 developed diarrhoea, with bowels usually open 3-5 times daily; occasionally more severe bouts, when bowels were opened 8-10 times daily. Small amounts of blood and mucus present. Symptoms were continuous. In 1954 admitted to hospital without much benefit. In 1955 readmitted with 8 motions a day containing blood. Barium enema showed evidence of mucosal damage throughout whole of colon and terminal ileum. Sigmoidoscopy showed appearances of ulcerative colitis. Moderately anaemic. Treated with oral cortisone with much improvement. Thereafter continued on cortisone as out-patient but still had moderate diarrhoea. In Nov., 1956, symptoms became worse while still on cortisone, with 6-8 loose motions a day but without blood. At this stage local treatment given	<i>Clinical</i> : 6-8 loose motions a day not containing blood <i>Sigmoidoscopic</i> : Moderate inflammation stretching up as far as could be seen	<i>No change</i> <i>Sigmoidoscopic</i> : No change	Treated with oral cortisone combined with salazopyrin with gradual improvement
*13. Female aged 40	In Aug., 1956, developed diarrhoea with up to 10 loose stools a day containing blood and mucus. In Oct., 1956, seen as out-patient at Radcliffe Infirmary by colleague. Hb 92%. Barium enema showed changes suggesting ulceration in rectum only. Following barium enema had exacerbation of symptoms with 18 or more loose stools a day containing blood, with generalized abdominal pain. Hb fell to 79%. At this stage transferred to me and local treatment started	<i>Clinical</i> : 18 or more loose motions a day with blood and mucus present. Hb 79%. Generalized abdominal pain <i>Sigmoidoscopic</i> : Severe inflammation extending as far up as could be seen	<i>Remission</i> : Immediate improvement, but had mild symptoms for 18 days, when she became entirely symptom-free with 1 formed stool a day; no abdominal pain and feeling well. Hb had risen to 91% <i>Sigmoidoscopic</i> : Slight hyperaemia and granularity affecting rectum only. Normal appearances above 5 in. (12.5 cm.) from anal margin. Mucosal fragility not increased	Remained symptom-free with normal sigmoidoscopic appearances (6 months' follow-up)

* This patient immediately showed marked improvement, but she still had mild symptoms at the end of 14 days' treatment. Treatment was therefore continued for a further seven days, in the course of which she became entirely symptom-free.

TABLE I.—Continued

Treatment No.	Previous History	Immediately Before Treatment	Response to Treatment	Subsequent Progress
14. Male aged 46	See Treatment No. 9	<i>Clinical:</i> 2 very loose motions a day with small amounts of blood and much mucus present <i>Sigmoidoscopic:</i> Severe inflammation extending as far as could be seen, with much increased mucosal fragility causing free bleeding on contact	<i>Remission:</i> 1 normal stool a day after 3 days' treatment <i>Sigmoidoscopic:</i> Mild hyperaemia and slightly increased fragility of mucosa	Remaining symptom-free (6 months' follow-up)
15. Male aged 28	In 1949 had left pleural effusion followed by iridocyclitis. In 1951 tuberculous pulmonary lesion of left upper lobe found on x-ray examination. Treated in sanatorium. June, 1951, early tuberculous caries of spine. Thereafter well until in Jan., 1956, he had short episodes of diarrhoea with blood and mucus. In Aug. developed severe bloody diarrhoea with constitutional disturbance. Attack became very severe. Treated with systemic corticotrophin, salazopyrin, and antituberculous drugs. On this regime improved but developed toxic anaemia with Heinz bodies. By Dec., 1956, was improved but still getting 6-7 motions in 24 hours, loose and sometimes liquid but without gross blood. At this stage given local treatment	<i>Clinical:</i> 6-7 loose or liquid motions a day with mucus present but no gross blood <i>Sigmoidoscopic:</i> Well-marked hyperaemia and granularity extending up as far as could be seen. No gross ulceration. Fragility moderately increased. Mild polypoid changes at 15 cm. from anal margin	<i>Slight improvement:</i> 5 partly formed motions a day not containing blood or mucus. Gaining weight <i>Sigmoidoscopic:</i> Improved, but still hyperaemic and slightly granular	Gradual improvement; and became symptom-free (6 months' follow-up)
16. Male aged 23	In 1954 began to pass bright red blood per rectum and much mucus. Bowel action usually regular but occasional diarrhoea. Barium enema normal, but following this had diarrhoea with 6 unformed stools a day containing blood. Transferred to me for treatment, by which time diarrhoea was easing off with 2 loose stools a day containing blood and mucus	<i>Clinical:</i> 2 loose stools a day containing blood and mucus <i>Sigmoidoscopic:</i> Marked hyperaemia and granularity with much increased mucosal fragility. These changes extended up to 17 cm. from anal margin and had become mild	<i>Remission:</i> Symptom-free after 4 days <i>Sigmoidoscopic:</i> Mild hyperaemia and granularity in lower half of rectum only. Within normal limits above	Remaining symptom-free (4 months' follow-up)
17. Male aged 34	See Treatment No. 8	<i>Clinical:</i> For past 2 weeks had had 6 loose motions a day with gross blood present. Hb 81%, having previously been 102%. General malaise <i>Sigmoidoscopic:</i> Mild hyperaemia and granularity, with increased mucosal fragility stretching up as far as could be seen	<i>Remission:</i> Immediate response to treatment with 2 formed stools a day not containing blood. Feeling well <i>Sigmoidoscopic:</i> Very slight hyperaemia and fine granularity. Appearances near normal. Mucosal fragility not increased	Remaining symptom-free (4 months' follow-up)
18. Male aged 26	In 1955 began to pass blood with motions. Few small haemorrhoids injected but trouble continued. Seen by me in July, 1956, when sigmoidoscopy showed hyperaemia, oedema, and petechiae of rectum with the mucosa gradually becoming normal above 6 in. (15 cm.) from anal margin. Treated with "i-so-gel," symptoms became negligible. In Dec., 1956, symptoms recurred. Blood passed every day and much mucus, but motions firm	<i>Clinical:</i> 2 formed stools a day but with blood and much mucus <i>Sigmoidoscopic:</i> Marked inflammation up to 15 cm. from anal margin, thereafter becoming mild. Mucosal fragility much increased	<i>Little change</i> <i>Sigmoidoscopic:</i> Marked inflammation from anal margin up to 12 cm., thereafter fading off and becoming normal about 17 cm. from anus	Treated with salazopyrin, became symptom-free in 3 weeks (4 months' follow-up)

The close agreement between the clinical and sigmoidoscopic findings in the present study can be seen if the data are arranged in the form of a simple contingency table (Table II).

TABLE II.—Correlation Between the Clinical Response to Treatment and the Sigmoidoscopic Findings

Clinical Response to Treatment	Sigmoidoscopic Findings at End of Treatment		
	Normal or Very Mild	Improved, but Definite Inflammation	Unchanged
Remission	11	1	
Improved		2	4
No change or slight improvement only			

Histological Findings

Biopsy specimens were taken from all patients on the day on which treatment was begun, and all showed evidence of severe or moderate inflammation, using the criteria employed by my pathologist colleague, Dr. W. C. D. Richards, in a previous joint study (Truelove and Richards, 1956). On the day following the last night of treatment another specimen was taken from all patients except one. Thus there are 17 pairs of specimens for comparison.

The histological response showed a close agreement with the clinical response, as can be seen from Table III. In some of the specimens classed as showing improvement there was

TABLE III.—Correlation Between Clinical and Histological Response to Treatment

Clinical Response to Treatment	Histological Response to Treatment	
	Improved	No Change
Remission	9	1
Not in remission	1	6

little or no inflammation in the specimen taken at the end of treatment, although the glands might be stunted and reduced in number and large lymphoid follicles were often present in the lamina propria. In the other specimens classed as showing improvement there were still some inflammatory changes remaining at the end of treatment, but they were clearly less marked than at the beginning. An example of a good histological response is shown in Figs. 1 and 2.

Cytological Findings

In a previous study (Boddington and Truelove, 1956) it was found that the colonic epithelial cells are frequently abnormal in ulcerative colitis. Compared with normal colonic epithelial cells, many of those seen in active ulcerative colitis are much enlarged, with big nuclei having nucleoli and a disturbed chromatin pattern. Similar findings have been reported independently by Galambos *et al.* (1956). In view of the fact that a correlation was found to exist between the clinical and sigmoidoscopic evidence of active disease on the one hand and the degree of abnormality

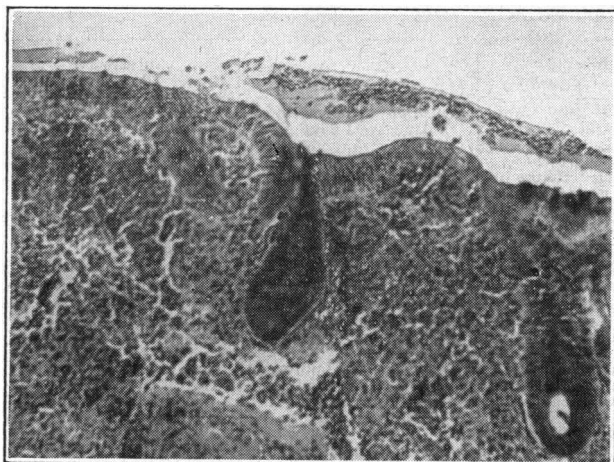


FIG. 1.—Histological appearances before treatment, showing heavy infiltration of the mucosa with inflammatory cells. (H. and E. $\times 150$.)

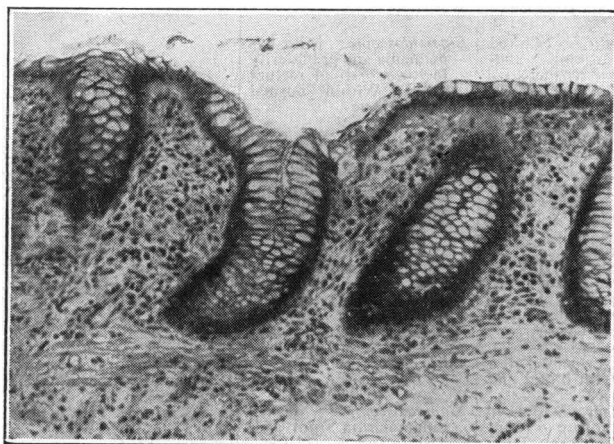


FIG. 2.—Histological appearances in the same patient after 10 days' treatment with local hydrocortisone hemisuccinate sodium. (H. and E. $\times 150$.)

shown by the epithelial cells on the other, it is probably valid to regard the state of the epithelial cells before and after treatment as an index of tissue response.

Making use of this index, it has been found that clinical remission with local hydrocortisone hemisuccinate sodium is accompanied by a change in the colonic epithelial cells towards normal appearances. The close correlation that exists is shown in Table IV, which has been constructed from data supplied by my cytologist colleague, Mr. M. M. Boddington, who has classified the cells as showing improvement, no change, or deterioration. Some patients are not included, for in them the specimens taken before or after treatment were not sufficiently rich in epithelial cells to permit him to form a satisfactory judgment of any changes that had occurred.

By contrast with this finding, the number of pus cells present in the colonic smears does not show any positive correlation with clinical response, as is shown in Table V. Although based on a somewhat rough-and-ready estimate, the complete discrepancy between clinical response and

TABLE IV.—Correlation Between Clinical Response and Changes in the Colonic Epithelial Cells

Clinical Response to Treatment	Appearance of Colonic Epithelial Cells after Treatment Compared with Appearance Before Treatment	
	Improved	No Change or Worse
Remission	5	1
Not in remission	1	4

diminution in pus cells should not be ignored, especially as we know that smears made from a healthy colon show either a complete absence of pus cells or only very occasional ones. This finding raises the possibility that infection is playing a part in many cases of ulcerative colitis and that such infection is not improved by local treatment with hydrocortisone. Nor would one expect it to be, for it is generally accepted that hydrocortisone encourages the spread of infections. It was indeed this possibility which caused me to exclude from this and the previous study those patients who were severely ill with ulcerative colitis, because of the risk that local hydrocortisone might cause extensive spread of a secondary, pyogenic infection.

TABLE V.—Lack of Correlation Between Clinical Response and Lessening of Pus Cells Seen in Colonic Smears

Clinical Response to Treatment	Change in Pus Cells in Colonic Smears	
	Pus Cells Clearly Less Frequent After Treatment	Pus Cells as Numerous After Treatment as Before
Remission	3	5
Not in remission	3	5

Discussion

The main interest of the present study has been the evidence of histological improvement in the colonic mucosa of those patients who pass into clinical remission with local treatment. In terms of clinical response, there is nothing to choose between the hemisuccinate sodium and ordinary hydrocortisone. We may therefore deduce with a reasonable degree of confidence that the improvement in histological response obtained by the use of hemisuccinate is to be attributed solely to its being freely soluble in water and thus able to be used without the disturbing presence of ethyl alcohol in the diluent. Nevertheless, on general principles it seems wise to prefer an agent with which the actual diseased tissue shows improvement, and therefore the hemisuccinate is recommended for future local use in the colon.

Taken in conjunction with the previous study (Truelove, 1956) the present findings constitute a *prima facie* case for regarding local hydrocortisone as a useful form of treatment in ulcerative colitis, at any rate in a proportion of the patients with the disease. This opinion is reinforced by the finding that a patient who has once responded to local hydrocortisone is likely to do so again if symptoms recur. There is now a small group of patients who have repeatedly responded swiftly to local treatment, one patient having been treated twice, one patient three times, and two patients four times. So far only a single patient has failed to respond to a second course of treatment after going into remission with the first. In view of the episodic nature of the disease in many patients, an occasional exception of this sort need not be taken as invalidating the general principle that one successful treatment means that future treatments will also be successful.

However, the view that local hydrocortisone is a useful treatment is based only on a personal judgment that rapid remission would not occur in as many as two out of every three instances unless the treatment was having some positive effect. In view of the variable course of ulcerative colitis, and especially in view of a widely held opinion that the disease is a psychosomatic disorder, it would be unwise to pay too much attention to clinical impressions. It is therefore essential that new forms of treatment should be the subject of comparative study. Perhaps the wisest view is to regard the present findings as encouraging enough to justify the initiation of controlled trials.

If we assume for the moment that the hydrocortisone was indeed responsible for the rapid remissions experienced by the patients who did well with this form of treatment, there are various practical and theoretical issues which arise. One concerns the fact that patients either respond swiftly to the treatment or show little or no change: in this respect the

findings resemble what has been found for skin diseases (Sulzberger and Witten, 1954). However, it may have some bearing on the aetiology of ulcerative colitis. Numerous theories have been put forward to account for this condition, such as that it is an expression of allergy, dietary deficiency, damage from bacterial dysentery, overproduction of lysozyme, parasympathetic overactivity, or emotional stress.

Some workers regard "ulcerative colitis" as no more than a non-specific response of the colon to one or more of these factors (Brooke, 1954). Others seek, so far in vain, to explain the condition on the basis of a single causal mechanism and regard other apparently provoking factors as irrelevant. Yet others regard it as a specific response of the colon but conceive that any one of a number of factors may act as a "trigger" and fire off the disease in its overt form. Presumably a consistent difference of response to a local treatment such as hydrocortisone might indicate that different mechanisms are responsible for ulcerative colitis in different patients. In other words, such a variable response from one patient to the next might imply that in ulcerative colitis we are dealing not with a single disease but with a family of diseases.

However, there is another possible explanation of the failure of some patients to respond to treatment. Although students of the disease are now almost unanimous in regarding it as not being primarily an infective condition, secondary infection undoubtedly plays a dominant part in many of its complications. In view of the contents of the colon, it would be surprising if the mucosa, once being abnormal, were not liable to infection. The cytological findings of the present study lend some support to this idea. The situation may therefore be analogous to what occurs when an atopic dermatitis becomes secondarily infected. It is then commonly found that local treatment with hydrocortisone is useless, because hydrocortisone encourages the spread of most infective processes. It has been shown that in these circumstances a combination of hydrocortisone with an appropriate antibiotic will bring about healing, for there is no mutual interference, either chemical or biological, between hydrocortisone and antibiotics (Robinson *et al.*, 1956). It therefore seems important to test the effect of combining hydrocortisone with antibiotics for local use in ulcerative colitis. So far I have not used this combination, as it was considered essential to assess first the direct action of hydrocortisone alone.

Problems also arise in connexion with the exact details of treatment in those patients who show a beneficial response to local hydrocortisone. One way of using this agent is to give a short course of treatment whenever symptoms recur and hope that a reasonably long remission will follow each course; this is the approach which has been made so far. However, it is possible that patients should have a much longer course than has been used in the present study in the hope that a longer period of remission will follow. Another possibility is that treatment carried out once or twice a week might hold a patient in permanent remission. These are issues which will require further study under controlled conditions.

Summary

In a previous study it was found that about two out of every three patients with mild or moderate attacks of ulcerative colitis went into rapid remission when treated with a slow rectal drip of hydrocortisone dissolved in 5% ethyl alcohol. However, it was found that biopsy specimens of the colonic mucosa did not show a corresponding improvement.

A substance soluble in water—hydrocortisone hemisuccinate sodium—has now been used in place of hydrocortisone itself to determine whether the previous failure to obtain mucosal response was due to the weakly alcoholic solution which acted as a vehicle for the ordinary hydrocortisone.

Local treatment with hydrocortisone hemisuccinate sodium brought about rapid remission of symptoms in 11 out of 18 courses of treatment. The clinical response was therefore closely comparable to what was previously found for hydrocortisone itself.

The sigmoidoscopic appearances in those patients going into remission showed marked improvement and were only slightly abnormal at the end of 10–14 days.

The histological appearances of small biopsy specimens of the colonic mucosa in general showed improvement corresponding with the clinical and sigmoidoscopic appearances. It seems likely that the lack of histological improvement in the previous study was due to the presence of 5% ethyl alcohol in the rectal infusion.

Cytological study of colonic smears before and after treatment revealed a close correlation between clinical remission and a change of colonic epithelial cells towards a normal appearance. However, numerous pus cells were still present after treatment, even in those patients in remission, and suggest the possibility that an infective element is often present, which, as would be expected, is not improved by hydrocortisone.

The theoretical and practical implication of the findings are discussed with special reference to the issues which need to be settled by further studies. In particular, it is suggested that the present results are sufficiently encouraging to justify controlled trials.

I am grateful to Glaxo Laboratories for making a gift of the hydrocortisone hemisuccinate sodium; to Miss Shirley Thomas, who assisted at the sigmoidoscopic examinations and also prepared the histological sections; to my colleague, Mr. M. M. Boddington, for permitting me to use the cytological findings which are part of a study we are jointly making; to Mrs. B. Humphreys for keeping the records of the patients; and to Dr. Jean Grant for supplying me with blood transfusion sets already modified to carry a soft rubber catheter instead of an intravenous needle. I am indebted to the Medical Research Council for a personal grant in support of this and other studies into ulcerative colitis. It is fitting to pay a tribute to the patients themselves and especially to the way in which they have submitted to repeated sigmoidoscopic examinations even when symptom-free.

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