Treatment of Ulcerative Colitis with Local Hydrocortisone

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A CONTROLLED therapeutic trial of patients with ulcerative colitis carried out by the co-operation of a number of physicians showed that cortisone *by mouth* increased the chances of a patient going into clinical remission within six weeks of starting medical treatment. (Truelove and Witts, 1954, 1955).

The finding that cortisone by mouth is beneficial in cutting short an attack of ulcerative colitis immediately suggested the possibility of using hydrocortisone locally in the colon. It was first necessary to find the best way to introduce hydrocortisone into the colon without it immediately being thrown out by the inflamed organ. I decided to use a drip into the rectum, making use of a blood transfusion giving-set slightly modified to carry a rubber catheter at the end for actual insertion into the rectum. Subsequent experience has shown that this is effective in all but a very few patients. Patients who are not severely ill can carry out this treatment at home without difficulty.

Since 1955 I have given 107 courses of treatment with local hydrocortisone to 80 separate patients, a number of the patients having been treated more than once. These treatments can be divided into four main groups (Table I). The first three groups represent formal

TABLE I.—TREATMENT OF U.C. WITH LOCAL HYDROCORTISONE UP TO JANUARY, 1958

	Treatment	No. of courses of treatment	Rapid remissions	
I	Hydrocortisone (free alcohol) in dilute alcoholic solution. 60–120 mg. HC nightly	21	14	Truelove (1956)
II	Hydrocortisone hemisuccinate sodium in saline. 100 mg. HC nightly	18	11	Truelove (1957)
III	Controlled trial of HC-HSS for 1 week followed by known HC-HSS + antibiotics for 2 weeks	40	29	To be published
IV	Miscellaneous treatments not included in I–III	28	Severe cases U.C. in pregnancy Juvenile cases Long-continued treatment	

studies, the first two of which have been reported (Truelove, 1956, 1957) while the third will be reported in detail shortly (Truelove, 1958). The fourth group consists of a miscellaneous collection of patients.

The first study (Row I in Table I) involved 21 courses of treatment using hydrocortisone itself. Because hydrocortisone has a low solubility in water (though much greater than that of cortisone) the manufacturers supplied it dissolved in 50% ethyl alcohol, in which it is quite soluble. This was diluted with ten times its volume of saline for actual use in the colon and was dripped into the rectum from the modified blood transfusion set (Fig. 1). The result of

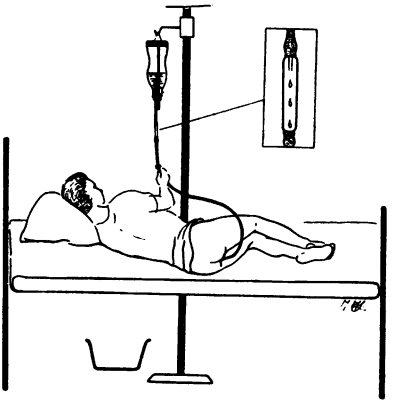

FIG. 1.—Method of self-administration of rectal drip.

this form of treatment was apparently good, because in 14 instances there was rapid clinical remission, i.e. within a few days.

The number of patients who responded to the treatment in this first study seemed to me quite encouraging. The sigmoidoscopic appearances also improved in parallel with the clinical responses. However, there was an odd discrepancy in that the histological responses, as judged by small biopsy specimens taken from the lower colon by means of an instrument devised for this purpose, did not show a corresponding improvement. This raised the possibility that the alcohol which formed part of the diluent for the hydrocortisone might itself be having a bad effect upon the inflamed colonic mucosa and preventing it from healing.

Fortunately, at about this time, Glaxo Laboratories were able to give me hydrocortisone hemisuccinate sodium, which is highly soluble in water. From Row II of Table I, it will be seen that the second study involved 18 courses of treatment given with this agent. The clinical response to hemisuccinate was closely similar to that obtained with hydrocortisone itself for there were 11 rapid remissions. The sigmoidoscopic appearances improved in parallel with the clinical response. Moreover, a favourable clinical response was accompanied by a definite improvement in the colonic mucosa, as judged from biopsy specimens. It therefore appears that a water-soluble compound such as the hemisuccinate is better than hydrocortisone itself, because, on first principles, it seems wise to choose an agent with which the actual diseased tissue shows evidence of reverting toward normality.

At this stage it seemed imperative to put this form of treatment to a formal test to make quite sure that the favourable judgment which I had formed on clinical impressions alone was indeed true. I therefore carried out last year a planned therapeutic trial involving 40 courses of treatment. The first part of the trial involved the use of either real hydrocortisone hemisuccinate or a similar-looking inert preparation. These were prepared by the manufacturers and nobody at Oxford knew which was which until the study was finished. The patients were allotted at random to one or other and this "blind" part of the trial lasted for one week. In every case, this was followed by two weeks of treatment with known hydrocortisone hemisuccinate sodium, together with penicillin and streptomycin added to the rectal drip, because I also wished to find out whether the addition of antibiotics would improve the action of the hydrocortisone and bring into remission cases that did not respond to hydrocortisone alone. At the end of the first week, out of 20 courses of treatment given with the inert preparation, only one resulted in clinical remission; whereas out of 20 courses of treatment with real hydrocortisone hemisuccinate, 11 patients were in remission. The difference is considerable and is statistically highly significant ($P < \cdot 01$). A fortnight later, after known treatment with hydrocortisone and antibiotics, the two groups were closely similar. We may therefore take it as reasonably certain that hydrocortisone hemisuccinate dripped into the rectum has a real effect in bringing about clinical remission in quite a large proportion of the patients. In other words, its action is pharmacological and not due to any placebo or psychological effect.

Antibiotics do not make much overall difference, sometimes being helpful and sometimes being deleterious, but this point will not be discussed further here except to say that they should not be used routinely.

Group IV of the treatments shown in Table I is a miscellaneous collection of patients who have not been included in any of the previous three studies for a variety of reasons. Only one or two points will be mentioned:

Severe cases.—In general, the local treatment has been used for patients suffering only from mild or moderate attacks of ulcerative colitis. This has been done for two reasons:

(1) A severe attack of ulcerative colitis is a dangerous illness and it seems right to gain a good deal of experience with any new form of treatment in the less severe cases before applying it to those patients who are gravely ill.

(2) An additional reason has been that a second large-scale trial is taking place in 12 hospital centres in this country of the systemic use of cortisone and of ACTH and the more severe cases that I have seen have been admitted to this national trial.

However, a few patients with severe attacks have been given the local treatment, particularly when they have failed to respond to the corticoids used systemically. In general, the results have been highly favourable. However, various technical problems arise when treating severe cases by this method: these are being studied at present.

Ulcerative Colitis in Pregnancy

It is known that ulcerative colitis in pregnancy can be severe and is at the least a great inconvenience and trouble to the patient if the symptoms persist throughout the pregnancy. Two patients having symptoms during pregnancy have been treated with a nightly rectal drip of hydrocortisone which has been continued until after the baby has been born. The results have been excellent in both patients.

Juvenile Cases

I do not see many children with this disease but three that I have seen in the last year and have treated by this method have all done well. These have been treated in the same way as the pregnant patients, in that treatment has been continued for months rather than for two or three weeks. I mention this point because I think it possible that this will be the future method of choice when a favourable response is obtained to local treatment.

Long-term Results

The use of hydrocortisone locally, even when it brings about remission, does not mean that these patients are going to be free from further attacks of the disease. Indeed, there is no known medical treatment which will guarantee freedom from recurrent attacks once a person has suffered from this illness. However, it should not be thought that rapid relapse is particularly likely to occur when the treatment is stopped. Indeed, immediate relapse is unusual although relapse over the course of the next few months is fairly frequent. Some patients have remained in perfect remission after a single course. For example, the first patient who was treated two and a half years ago has been symptom-free ever since.

Some idea of the early long-term results can be gained from considering what has happened to 15 patients who responded well to treatment in 1955 and 1956. 6 of them have remained in perfect remission; 7 have had one or more recurrences but have responded swiftly to further courses of local treatment; and 2 have had recurrences which did not respond to a further course so that alternative treatment was necessary.

REFERENCES

Truelove, S. C. (1956) *Brit. med. J.*, ii, 1267.
—— (1957) *Brit. med. J.*, i, 1437.
—— (1958) In preparation.
——, and Witts, L. J. (1954) *Brit. med. J.*, ii, 375.
——, —— (1955) *Brit. med. J.*, ii, 1041.

Observations on the Management of Idiopathic Proctitis [*Abridged*]

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These observations are part of a larger study of the natural history of idiopathic proctitis, and are based on the study of 150 patients attending the out-patients at St. Mark's Hospital in the six and a half year period from January 1951 to June 1957. They were patients with typical sigmoidoscopic appearance but with minimal X-ray evidence of disease of the colon itself although undoubtedly a proportion of patients had the same inflammatory process extending upwards into the sigmoid. In the series of 150 there were 94 females and 56 males. Of the 150 cases follow-up information had been obtained from all but 6 of them; 50 at the time of last examination had continuing symptoms and of these 12 had had extension of the disease process often involving the entire bowel and necessitating surgical treatment.

The view was firmly established from this survey that idiopathic proctitis was one and the same disease as ulcerative colitis but in a localized and milder form.

Observations were made on the effect of treatment with prednisone and, initially, a comparison was made between three weeks' treatment with calcium lactate and the same period with prednisone taking alternate cases. Of the 13 patients treated with calcium lactate 9 were not improved or worse at the end of three weeks compared with only 1 out of 10 treated with prednisone who had not improved or got worse. Altogether 44 patients were treated with prednisone and at the end of treatment 16 had no symptoms with normal sigmoidoscopic appearance, 12 had no symptoms with low-grade proctitis present, 11 had persistent symptoms and signs but improvement in both, only 5 showed no improvement. Within three months, however, another 11 had relapsed and needed further treatment. The patients were all treated in the out-patients' department starting with 20 mg. three times a day for one week reducing the dose to 15 mg. three times a day for the second week and then 10 mg. three times a day for another two or three weeks subsequently tailing the dose off. There were side-effects in half the patients but these proved temporary only. One patient developed diabetes, 5 had indigestion and 6 a moderate degree of acne. Symptoms all responded to dose reduction and cessation of treatment.