LOCAL CORTICOSTEROID TREATMENT OF ULCERATIVE COLITIS

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Ulcerative colitis is a diffuse inflammatory disease of a part or the whole of the colon, the aetiology of which is at present ill-understood. Medical treatment has, therefore, depended upon the application of general medical measures to combat the effects of the disease, together with the use of agents to diminish the inflammatory process. In the absence of precise aetiological knowledge, the search for agents useful in reducing or abolishing the inflammatory reaction has necessarily been on the basis of trial and error. It is, therefore, not surprising that a multitude of therapeutic agents has been employed. If we consider the natural history of the disease, it is again not altogether surprising that a large number of these miscellaneous agents have been claimed to be highly beneficial. The disease commonly presents as a series of attacks of bloody diarrhoea with periods of complete symptomatic freedom between them. Thus a treatment may be used on two or three patients who pass into a 'natural' remission and it is then tempting for the physician to claim that the treatment was specifically responsible. In the history of the disease, therapeutic agents of the most diverse variety have been credited with a valuable action because of their apparent usefulness in a handful of patients, only to be discredited in the light of subsequent experience. Fortunately, the controlled therapeutic trial has become an accepted clinical research method during the past one or two decades and there is nowadays no excuse for any useless treatment to remain in vogue for very long. Of course, clinical impressions are of the utmost value to the physician first trying out a new method of treatment. But if he thinks that the results are promising, it is essential that he (or other workers) should put the method to the test of formal trials. This is all the more true if the disease being treated is one which pursues a variable course so that prediction of the course of the individual case is impossible.

The Idea of Local Treatment in Ulcerative Colitis

The idea of using local applications within the bowel has been in existence for the past 40 years. Hurst (1921) made use of colonic irrigations with solutions of 'alargin' or of tannic acid, employing one and a half pints of fluid run into the rectum with the patient in the knee-elbow position to encourage the widespread distribution of the treatment throughout the colon. Since that time a multiplicity of agents has been used for intracolic treatment of the disease, such as acriflavine and other antiseptic agents, silver nitrate and other astringent solutions, vitamin A, cod-liver oil, adsorbent agents such as Kaolin and aluminium hydroxide,  Pectin, intrarectal oxygen, and antibiotics of various types (Durand, 1925; Rachet and Busson, 1935; Eyerley and Breuhaus, 1937; Best, 1938; Nasio, 1947). None of these measures seemed to make any substantial difference to the prognosis, and it is certainly true that no crucial tests of their efficiency have been reported. The probability is that they are all of negligible value.

Corticosteroids Used Locally in Ulcerative Colitis

My own interest in the local treatment of ulcerative colitis began in earnest in 1955, after a large-scale controlled therapeutic trial had shown that cortisone by mouth was a useful addition to general medical measures and greatly increased the chance of obtaining a remission within six weeks (Truelove and Witts, 1954, 1955). As cortisone, but more particularly hydrocortisone, had been found useful when applied topically in a number of skin diseases, eye-diseases and joint diseases, it seemed a logical step to try the effect of local application in ulcerative colitis. At that time, the available corticosteroids were limited and most of the preparations were almost insoluble in water. I chose to use hydrocortisone itself, which has a limited solubility in water but which is quite highly soluble in alcohol. An alcoholic solution of hydrocortisone was diluted down with normal
saline as the first preparation to be employed. It was also necessary to decide on the best method of applying the treatment, bearing in mind that the patients to be treated would be suffering from diarrhoea. I decided to use a drip into the rectum, employing a blood-transfusion-giving set slightly modified to carry a soft rubber catheter for actual insertion into the rectum (Fig. 1). Subsequent experience has shown that this is quite a satisfactory method of application and one which patients can readily be taught to use at home if they are not so severely ill that hospital treatment is essential.

I began by treating 21 patients with mild or moderate attacks of ulcerative colitis and obtained 14 complete remissions within two weeks of starting treatment (Truelove, 1956). The striking feature was the extreme speed with which the patients who responded to treatment did so. Although the method was not universally efficacious, it nevertheless seemed quite beyond the bounds of chance that as many as two-thirds of the patients would respond so rapidly if the treatment were inactive. There was, therefore, a prima facie case for concluding that this approach to treatment was worth further study.

All these patients were observed sigmoidoscopically immediately before and after two weeks' treatment and in every case a biopsy specimen of the colonic mucosa was taken by means of a special instrument developed for the purpose. It was observed that a striking sigmoidoscopic improvement occurred in all the patients who went into clinical remission (Fig. 2), but that the histological appearances of the biopsy specimens did not show a markedly favourable response. It appeared possible that the weakly alcoholic solution in which the hydrocortisone was applied might be impeding the healing of the actual mucosa. Fortunately, at this time Glaxo Laboratories were able to supply me with hydrocortisone hemisuccinate sodium, which is highly soluble in water. A second study was made employing this agent and it was found that, while the clinical and sigmoidoscopic responses were similar to those obtained in the earlier study, the histological responses were much more favourable (Truelove, 1957). Consequently, this agent, or another water-soluble corticosteroid, prednisolone 21-phosphate, has been the choice for local corticosteroid therapy.

It was then necessary to submit the method to the discipline of a formal therapeutic trial in order to confirm or refute the clinical impression that the treatment was valuable. Forty patients were allotted at random to local treatment either with real hydrocortisone hemisuccinate sodium or with a dummy preparation. Of the 20 patients receiving the dummy treatment only one had a spontaneous remission in the course of one week, whereas 11 of the 20 on real treatment were entirely symptom-free after one week. This difference is highly significant in a statistical sense. The sigmoidoscopic and histological responses also showed an unequivocal advantage on the side of the real treatment. The fact that a dummy drip was employed showed that the treatment was working by a pharmacological action and not by any psychological means (Truelove, 1958). Simultaneously, another 'blind' controlled trial was carried out independently by Watkinson (1958) in Leeds, with closely similar results. He employed the elegant and efficient method of sequential analysis for assessing the results and swiftly obtained an answer favouring the hydrocortisone group. As far as clinical responses were concerned, he found that one out of nine patients on 'dummy' treatment went into remission in two weeks, whereas nine out of ten patients on real treatment went into remission in the same time.

Optimum Length of Treatment with Local Corticosteroid Therapy

Most of my published work on local corticosteroid treatment has dealt with the clinical responses obtained with short courses of two or three weeks. This has been because a principal aim in the last few years has been to find forms of treatment which bring all attacks of ulcerative colitis swiftly to a halt. However, as soon as hydrocortisone hemisuccinate sodium became plentiful, I have made it a rule to continue treatment in responsive patients for several weeks at least after the cessation of symptoms. I believe
this to be beneficial in reducing the risk of early relapse although a close analysis of the results has not yet been completed.

**Long-term Treatment with Local Corticosteroid Treatment**

In general, I do not favour long-term treatment with any type of corticosteroid, but there are certain exceptions. For example, a group of pregnant women responding favourably to local corticosteroid therapy has been left on this form of treatment throughout the entire pregnancy. The results have been excellent, the patients being in good health throughout and deliveries being normal.

**Local Compared with Systemic and Combined Corticosteroid Treatment**

Both systemic and local corticosteroid treatment have been found useful in the medical management of attacks of ulcerative colitis. It is plainly of importance to know which of the two methods is the better or whether there is any advantage in combining these two methods of administration. Sufficient evidence comes from a comparative study of systemic, local and combined corticosteroid therapy in ulcerative colitis to suggest that in all but the mildest cases of the disease it is best to employ combined therapy to bring attacks to a rapid halt (Truelove, 1960a). Once the attack is checked, the oral corticosteroid can be tailed off but local treatment can be continued for some weeks longer with negligible risk of side-effects.

There is also the strong suggestion that local hydrocortisone hemisuccinate with oral prednisolone is a better combination than prednisolone phosphate locally and prednisolone by mouth. The explanation for this difference is uncertain but one possibility is that different corticosteroids may have a synergistic action, a possibility which, if proved, would accord with some interesting theoretical explanations of synergism advanced by Veldstra (1956). It certainly appears true that the metabolic pathways of hydrocortisone and prednisolone are not identical (Nugent, Eik-Nes and Tyler, 1959).

**Local Treatment in Severe Attacks of the Disease**

It is sometimes supposed that local corticosteroid treatment is of value only in comparatively mild attacks of ulcerative colitis and especially when only the distal part of the colon is affected. In reality, there is strong presumptive evidence that this form of treatment can be a valuable part of the medical management of severe attacks. This is not surprising since it is appreciated that liquids introduced into the rectum spread extensively through the colon so that there is no prima facie case for avoiding local treatment merely because the disease is widespread.

Certain practical points are of great importance when using local corticosteroids in severe attacks of the disease. Firstly, it appears best to use local treatment at least twice a day in such severe attacks and to employ systemic corticosteroids in addition. Secondly, if the diarrhea is very severe, it may be necessary, at first, to employ intravenous probanthine to paralyse the colon temporarily to allow the evening treatment to act for at least some hours; overdosage with the probanthine must be avoided. Thirdly, the use of corticosteroid treatment does not absolve the physician from the duty of applying certain general medical measures—blood transfusion, control of water and electrolyte balance, and adequate dietary intake—without which a severe attack rapidly brings the patient into a state of jeopardy or even to his death.

All these issues have been dealt with in some detail in a previous article (Truelove, 1960b) and will not be enlarged upon here.
Site of Action of Corticosteroids Used Locally in the Colon

It is of some consequence to know whether local corticosteroid treatment acts directly upon the inflamed colonic mucosa or whether it acts by being absorbed and then exerting a systemic action. It would be manifestly absurd to administer an agent by rectal drip if the results were identical with those obtained by giving the agent more simply as a tablet to be swallowed.

Clinically, there is some evidence that local corticosteroid treatment is not the same as systemic treatment. The clinical response to local corticosteroid treatment is much more frequently dramatic than that obtained by systemic corticosteroids. Moreover, as far as hydrocortisone hemisuccinate is concerned, it is possible to have patients on daily rectal drips containing 100 mg. of hydrocortisone for several months with no clinical evidence of hypercortisonism. This clinical finding is in line with the laboratory evidence brought forward by Schwartz, Cohn, Bondy, Brodoff, Upton and Spiro (1958) who labelled hydrocortisone with $^{14}$C and found that topical application of the hemisuccinate to the colon in quite large quantities produced no appreciable change in the level of circulating hydrocortisone in the blood. In other words, it is probable that the main action of topical hydrocortisone in ulcerative colitis is directly upon the inflamed mucosa. The exact chemical composition of the particular corticosteroid preparation used may be of crucial importance. Thus Nabarro, Moxham, Walker and Slater (1957) found that hydrocortisone itself was readily absorbed from the rectum but that hydrocortisone acetate was not appreciably absorbed (which might be due to its negligible solubility in water) while only small amounts of hydrocortisone hemisuccinate sodium were absorbed in spite of the high water-solubility of this compound. This is an aspect of local corticosteroid treatment which deserves further study.

Favourable Experiences of Other Physicians

Among the first to use local corticosteroid treatment in ulcerative colitis were the Italian workers, Allodi and Muratori (1956). They introduced hydrocortisone into the bowel through a sigmoidoscope, daily or every other day, during attacks of ulcerative colitis and claimed excellent responses in seven of the nine patients treated. However, this is a method of application which can hardly be regarded as ideal. In the United States, Patterson and McGivney (1959) have used local hydrocortisone with a considerable measure of success and so also have Schwartz, Bardoff, Cohn and Spiro (1959). Among English physicians, reference has already been made to the work of Watkinson (1958).

More recently, Mats (1960) has employed prednisolone phosphate already prepared in solution in disposable plastic enema bags. This appears to be a convenient method of administering local treatment to the colon, although my own experience of the method is small. Mats' initial results were most encouraging and in his latest study, which deals with 100 patients treated by this method, he reports improvement in 88 (Mats, 1961). Of course, relapse is liable to occur in patients who have responded well to treatment but comparatively few break down quickly and 75% of the patients who showed improvement with their first course of treatment were still free from relapse nine months later. Furthermore, most patients who relapsed responded well to a further course of treatment.

A Discordant Note

By contrast with the favourable experiences just mentioned, one group of physicians has found local corticosteroid treatment to be disappointing. Lennard-Jones, Longmore, Newell, Wilson and Jones (1960) report their experiences of a trial of different forms of therapy in the management of outpatients with ulcerative colitis, one type of therapy being a daily rectal drip of hydrocortisone hemisuccinate sodium. Their results with this form of treatment were so poor that one is immediately forced to wonder why they should be so different from those obtained by other workers. Perhaps a clue is provided in the authors' own remark that 'The technique used was cumbersome and complicated, suitable more for hospital than outpatient use'. This does not accord with my own experience in treating more than 200 outpatients by the method. My own clinic is organized so that the giving apparatus is ready at hand to present to the patient who is also given a short talk on exactly what to do. Originally this talk was always given by me but, more recently, owing to the pressure of numbers, by an experienced technician who assists in the clinic. The number of patients who have had the slightest difficulty in carrying out the treatment has been trivial. There are only two dons (one from Cambridge) among my patients, so there is no reason to suspect an unduly high level of intelligence among the Oxford patients. Nevertheless, the need for some organization and instruction is apparent and it is possible that the disposable enema bag pioneered by Mats will supplant the use of a rectal drip for outpatient use.
Possible Dangers of Local Corticosteroid Treatment

The rate of absorption from the colon is so low, at any rate as far as hydrocortisone hemisuccinate is concerned, that systemic side-effects of therapy do not arise. On theoretical grounds one might fear that local corticosteroid treatment would lead to an increase of pyogenic complications around the rectum, such as ischio-rectal abscess, fistula-in-ano and recto-vaginal fistula. Practical experience has shown that this fear is groundless. Brooke (1956) has described thinning and excessive friability of the colon as a complication of corticosteroid treatment, including its local use, but such changes in the colon were encountered before the introduction of corticosteroid treatment. The main risk of corticosteroid therapy, including its use as a local application, is that an unwary physician may persist blindly with medical treatment in the minority of patients who show no favourable response. If the patient is very ill, such persistence may result in some dangerous complication of the disease, such as perforation of the colon, or may so delay recourse to surgery that the risks of emergency operation are greatly increased. In brief, corticosteroid treatment needs to be handled with skill when one is dealing with the more savage attacks of the disease. However, it is no new situation in medicine to find that potent remedies can be dangerous unless employed with skill. William Withering (1785) himself remarked in connection with the unguarded way in which most other physicians of his day employed digitalis, 'shall we wonder then that patients refuse to repeat such a medicine, and that practitioners tremble to prescribe it?' Yet digitalis was one of the few therapeutic agents of any value to be discovered before the 20th century and is one of the even smaller number which survive as essential drugs today.

Local Corticosteroid Treatment Used in Combination with Other Forms of Medical Treatment

The combined use of local and systemic corticosteroid treatment has already been mentioned. Apart from corticosteroid therapy, there is only one pharmacological agent which appears to be of major benefit in ulcerative colitis, if we exclude those general medical measures which are essential to preserve life and strength during an acute attack of the disease. This is salicylsulphapyridine, which is more commonly known as 'salazopyrine' or 'asulfdine'. This compound was introduced in 1940 by the Swedish physician, Dr. Nanna Svartz, who has used it extensively (Svartz, 1954, 1956). Although it has not been put to such crucial tests of efficiency as has cortico-

steroid treatment, there is ample evidence that it is beneficial in a considerable proportion of patients. The salient facts of its pharmacology and use have been given in a previous article in this journal (Truelove, 1959) and will not be reiterated. At present it is a moot point whether salazopyrine is as good as combined corticosteroid treatment in checking an attack of ulcerative colitis but a formal trial to settle this point is in full progress. However, in the present context, it is sufficient to remark that, in patients who resist either salazopyrine or corticosteroid treatment used separately, it is possible to combine these treatments and the combination often appears to be successful.

Local Corticosteroid Treatment Combined with Conservative Surgery

The accepted surgical approach today is colectomy either with permanent ileostomy or with ileo-rectal anastomosis. However, there are some circumstances when a physician can only regard this major procedure as unfortunate. With the active collaboration of a surgical colleague, Mr. Harold Ellis, a group of patients has been treated with temporary double-barrelled ileostomy to facilitate local treatment of the colon. In a sense, this is attempting to put the clock back, because by 1921 Hurst was advocating appendicostomy to permit irrigation of the colon with fluid agents, although it is unlikely that the agents at his disposal were of any benefit. Ellis (1961) has given the indications for the combined surgical and medical treatment which we have been employing. In essence, we have used it on the one hand when a savage attack has appeared to be resisting medical treatment and, on the other, when pararectal complications, such as rectovaginal fistula, have required diversion of the faecal stream to permit of their satisfactory surgical repair after treatment of the colitis. It is too early to state dogmatically that this approach to treatment is a good one, but the results so far are not discouraging.

Assessment of the Present Situation

Local corticosteroid treatment is not a cure for ulcerative colitis. The liability to relapse persists, although it is unusual for immediate relapse to occur after a course of treatment which has been successful in checking an attack. All that we can say is that local corticosteroid treatment is one of the ways in which attacks of ulcerative colitis can be checked or aborted and that, when it is successful, it commonly works with great speed. There is a distinct possibility that, if first attacks of the disease are promptly diagnosed and treated by
some method such as local corticosteroids which reduces the inflammatory reaction and thus minimizes the damage to the colon, the long-term course of the disease is improved. In any event, if patients with ulcerative colitis are kept under medical supervision and attacks of the disease are treated without delay as soon as they arise, there is every indication that the prognosis of the disease is greatly improved.

In principle, it is easy to see how we should treat ulcerative colitis if we had the necessary knowledge. With the first attack, the essential aim would be to stop the attack promptly to remove immediate danger and discomfort. This done, we should then identify and remove or correct whatever factor was found to be responsible for the chronic liability to develop attacks of this illness. The first of these two steps can nowadays be accomplished successfully in the great majority of instances by medical management and I believe that local corticosteroid treatment is a useful part of this management. The second step—that of identifying and eliminating the responsible chronic factor—is usually impossible for us. Some workers, among whom Andresen (1942) was the pioneer, have regarded allergy to certain foods as an important cause of ulcerative colitis, and I have personally made some observations which suggest that specific foods may be of great importance in some of the subjects (Truelove, 1961). There are also some patients in whom psychological difficulties are apparent and improvement in the clinical course may result from successful handling of these difficulties. Indeed, there are some physicians who regard the illness as psychosomatic and consequently regard psychotherapy as the mainstay of long-term treatment (Paulley, 1956; Groen and Bastiaans, 1951; Grace, Pinsky and Wolff, 1954). But most of us find ourselves unable to give any satisfactory explanation in the majority of our patients to account for the liability to relapse. It is evident that further work on etiology is urgently needed. Observations by Broberger and Perlman (1959) suggest that auto-immune reactions commonly occur in the disease but the importance of these in causation or in perpetuation of the disorder remains uncertain.

In brief, the cardinal problem in the medical management of ulcerative colitis today is how to prevent relapses occurring after a patient has once been rendered symptom-free. To this we have no satisfactory answer at present. However, it may be remarked that this problem has been thrown up into sharp relief chiefly because the dangers of the individual attacks have been substantially reduced in recent years. Among the measures which have been responsible for this improvement, local corticosteroid therapy has played a useful part.

Acknowledgments

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