Between 9 a.m. and 10 p.m. the pattern of change was different in each subject. The F.E.V. of the mildly disabled patients and the F.V.C. of some of the severely disabled patients varied in a regular manner. Other changes appeared random (Figs. 1 and 2). A number of patients showed a distinct fall in the F.V.C. after the midday meal.

These changes were recorded during a day spent in hospital. McKerrow *et al.* (1958) have shown that the F.E.V. of cotton-workers falls during their day in the dust of the mill. In contrast, coal-miners slightly increased their F.E.V. during the shift at the coal-face. These investigators also give experimental evidence for the relationship between the F.E.V. and airway resistance.

Patients shown by spirometry to have severe airway disease may be but moderately disabled by effort breathlessness. A comparatively small increase in the airway obstruction may then cause severe disability (Capel and Smart, 1959). Such an increase occurs during sleep. The severity of the morning breathlessness may therefore reflect the magnitude of the permanent airway obstruction rather than the magnitude of the morning deterioration alone.

Conclusion

Relatively large spontaneous variations in the F.E.V. and the F.V.C. of patients with obstructive airway disease may occur between 9 a.m. and 5 p.m. This might affect the interpretation of results when serial changes in these volumes are used to measure the action of drugs on the bronchial tree.

The early-morning decrease in the F.E.V. and the F.V.C. was found to be part of a cycle of changes occurring throughout the day both in health and in generalized obstructive airway disease. The decrease was greater in patients with airway disease. The severity of the resulting increase in breathlessness probably reflects the magnitude of permanent obstructive airway disease rather than the magnitude of the temporary decrease in the F.E.V. and the F.V.C.

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A scheme for the disposal of radioactive wastes used in Edinburgh for medical and research work has been agreed upon by the university, the Department of Health for Scotland, and the trade unions representing employees who will handle the waste. It covers disposal into sewers, municipal tips, and ocean dumping. Liquid wastes are kept in store until their radioactivity has exhausted itself, and then they are disposed of in the city sewers—with the safeguard that the maximum level of radioactivity is the same as that permitted in drinking-water. A further dilution takes place immediately the wastes enter the sewers, which discharge into the Forth estuary. Solid wastes of short-lived materials are wrapped securely in a strong paper bag and placed in a padlocked dustbin. This is taken to a corporation rubbish tip, where the dustbin is unlocked and the parcel dropped into a pit; this pit is then filled in. Materials much more "hot" in the radioactive sense are used in the university, chiefly for experiments. When these have to be disposed of the Department of Health will arrange for their dumping in the Atlantic. (*Glasgow Herald*, February 4.)

SYSTEMIC AND LOCAL CORTICOSTEROID THERAPY IN ULCERATIVE COLITIS

BY

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During the past decade it has been established that corticosteroids improve the chance of obtaining clinical remission when an attack of ulcerative colitis is being treated medically. However, there are two main ways of using corticosteroid therapy in this disease. On the one hand, cortisone and its analogues may be used systemically. On the other, they may be applied locally within the colon with the intention that their action shall be chiefly a direct one upon the inflamed mucosa.

Both these methods of employing corticosteroid therapy in ulcerative colitis have been shown to be beneficial. So far as oral cortisone is concerned, a large-scale "blind" controlled trial carried out with the co-operation of a number of physicians showed that patients receiving cortisone were nearly three times as likely to be in clinical remission within six weeks of starting medical treatment as were patients in the control group (Truelove and Witts, 1954, 1955). Local corticosteroid treatment has likewise been shown to be of value. Two independent controlled studies, using the water-soluble compound, hydrocortisone hemisuccinate sodium, as a nightly rectal drip, have provided convincing evidence that rapid remissions are often obtained in the less severe attacks of ulcerative colitis (Truelove, 1958; Watkinson, 1958).

There is plainly a need to know which of these two methods of using corticosteroids is to be preferred. Though neither has been shown to reduce the risk of subsequent attacks of ulcerative colitis, it is of consequence to know which is the more likely to bring an attack to an abrupt halt. If attacks of the disease can be checked promptly, many of its dangers disappear even though no permanent cure has yet been found.

Objects of the Present Study

The first object was to assess the relative efficacy of oral and local corticosteroid therapy in ulcerative colitis. The second object was to test a personal clinical impression that combined therapy with both systemic and local corticosteroid is better than either used alone. This impression was based on experience with a number of patients whose symptoms were unchanged by systemic and local corticosteroid treatment used singly but who went into clinical remission when the two methods were combined. The following may be taken as a typical example.

A medical student aged 22 was seen in August, 1957, because of bloody diarrhoea for the previous two months. There was a history of a bad attack of bloody diarrhoea 10 years previously which lasted for three months. In between he had been well. Sigmoidoscopy showed typical ulcerative colitis with hyperaemia, granularity, and contact bleeding. A barium enema showed contour irregularities of the rectum and sigmoid colon. Local hydrocortisone hemisuccinate sodium for two weeks gave no benefit, either

symptomatically or sigmoidoscopically. He was then given prednisolone by mouth, 5 mg. q.d.s. Once again his condition was unchanged. The two types of treatment were then combined, and he showed rapid improvement, was symptom-free in a fortnight, and had normal sigmoidoscopic appearances. Since 1957 he has had two further recurrences of the disease, but both were stopped in about 10 days by the use of combined corticosteroid treatment.

Selection of Patients

The patients chosen were all suffering from an attack of ulcerative colitis with sigmoidoscopic evidence of active disease. In the case of first attacks of the disease a barium enema also showed evidence of active disease. In the case of relapse of established disease a barium enema was not always carried out before treatment, but previous examinations had shown unequivocal evidence of ulcerative colitis.

Patients in whom the disease was confined to the rectum and recto-sigmoid junction (haemorrhagic proctitis) were not included. Those who had very severe attacks of ulcerative colitis were also excluded; such patients, who were defined as those in whom a profuse bloody diarrhoea was accompanied by serious constitutional symptoms or by major complications of the disease, were treated along more vigorous lines in hospital. Thus the patients considered here were examples of classical ulcerative colitis presenting as an attack of mild or moderate severity.

Treatment Groups

As the patients presented, they were allotted at random to one or other of three main types of treatment.

(*a*) *Oral Prednisolone,* in a dose of 5 mg. q.d.s., was given to one-third of the patients. This dose was chosen because from the outset the intention was to treat as many as possible on an out-patient basis, and this dose has appeared to be a safe one to use in such circumstances.

(*b*) *Local treatment,* administered as a nightly rectal drip, was given to another one-third of the patients. It was arranged in advance that in half of these patients the corticosteroid would be hydrocortisone hemisuccinate sodium, while the other half would have prednisolone 21-phosphate. This permitted an internal comparison, within this group, of two different corticosteroids used locally. The practical details for the use of a nightly rectal drip have been given in previous articles (Truelove, 1956, 1957). Hydrocortisone hemisuccinate sodium was given in a daily dose of 100 mg. of hydrocortisone. The prednisolone 21-phosphate drip was made by dissolving special tablets of this agent in tap-water, the daily dose being 40 mg. of prednisolone.

(*c*) *Combined treatment* was given to the remaining one-third of the patients. All these were given prednisolone by mouth in a dose of 5 mg. q.d.s. together with local treatment in the form of a nightly rectal drip. Half the patients used hydrocortisone hemisuccinate sodium as their local treatment, while the other half used prednisolone 21-phosphate.

Results

The results of 120 courses of treatment are now reported, there having been 40 of each of the three main types of treatment given. Since the trial took nearly two years to execute, some patients who were treated successfully in the early stages were later seen with a recurrent attack and were readmitted to the trial and assigned at random to one of the treatment groups. The actual number of patients concerned in the trial was 105.

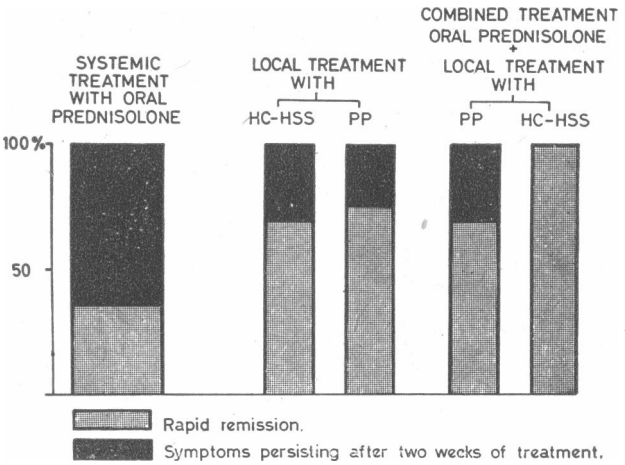
The effects of treatment have been assessed by determining how many patients went into rapid clinical remission with the various treatments used. A rapid clinical remission was defined as complete loss of any symptoms within two weeks of starting treatment and with the sigmoidoscopic appearances showing a decisive improvement.

The Table and Chart show the results obtained. With oral prednisolone, about one-third of the patients were in clinical remission at the end of the two-week trial period. With local treatment used alone, approximately three-quarters of the patients had a rapid remission. There is little to choose between hydrocortisone hemisuccinate sodium and prednisolone 21-phosphate when used alone as local therapy. The difference between local therapy and systemic therapy is highly significant in a statistical sense; if the results for the two types of local treatment are considered as a single unit, which

Results of Treatment, Showing the Number of Patients Going into Rapid Remission with the Various Treatments

Type of Treatment	No. of Patients	No. Symptom-free at End of 2-Weeks Treatment
Systemic Treatment:		
Prednisolone by mouth	40	14 (35%)
Local Treatment:		
Nightly rectal drip:		
(*a*) With hydrocortisone hemisuccinate sodium	20	14 (70%)
(*b*) With prednisolone 21-phosphate	20	15 (75%)
Combined Treatment:		
Prednisolone by mouth combined with a nightly rectal drip:		
(*a*) With prednisolone 21-phosphate	20	14 (70%)
(*b*) With hydrocortisone hemisuccinate sodium	20	20 (100%)

Statistical Significance of the Differences.—Both types of local treatment give significantly more rapid remissions than oral prednisolone ($P = 0.01$). Combined treatment with oral prednisolone and local prednisolone 21-phosphate is similar to local treatment used alone. Combined treatment with oral prednisolone and local hydrocortisone hemisuccinate sodium is significantly better than local treatment used alone. (An exact test of significance gives a value of $P = 0.024$ when this treatment is compared with the best other treatment.)



The different proportions of patients with rapid remission of symptoms according to the type of corticosteroid therapy. (HC-HSS = Hydrocortisone hemisuccinate sodium. PP = Prednisolone 21-phosphate.)

gives 29 rapid remissions out of 40 treatments, this difference from the results obtained by oral prednisolone would occur by chance less often than once in a thousand times. It can therefore be taken as adequately proved that local corticosteroid therapy is much more efficient in producing rapid clinical remission of an attack of ulcerative colitis than is systemic corticosteroid therapy, at any rate in the doses used in this study.

With combined systemic and local treatment, a somewhat surprising result emerges. When oral prednisolone is given in conjunction with local treatment with prednisone 21-phosphate the proportion of rapid clinical remissions is similar to that obtained with local treatment used alone. On the other hand, when oral prednisolone is combined with local treatment with hydrocortisone hemisuccinate sodium every patient so treated in the present study had a rapid clinical remission. This difference is statistically significant. There is therefore a prima facie case for regarding the combination of oral prednisolone with local hydrocortisone hemisuccinate sodium as demonstrably more efficient in an attack of ulcerative colitis than any other treatment tested in the present study.

Discussion

The results presented have both practical and theoretical implications.

On the practical side, topical use of corticosteroids within the colon has proved decisively more effective in aborting attacks of ulcerative colitis than oral prednisolone in the dose used. The local method of application enjoys the additional advantage that side-effects of corticosteroid therapy do not appear to arise. It is therefore recommended that, for the truly mild attack of ulcerative colitis, initial treatment should consist of local corticosteroid therapy, and either hydrocortisone hemisuccinate sodium or prednisolone 21-phosphate can be used in the equal expectation that most of the attacks will be checked. For the minority of mild attacks which fail to show a rapid response to local treatment used alone, combined treatment with oral prednisolone and local hydrocortisone hemisuccinate sodium should be employed. The same combination should be used from the outset in those attacks which are bad enough to be classed as of moderate severity, by which is implied an attack with profuse bloody diarrhoea but without serious constitutional disturbances. In such attacks the necessity for halting the symptoms as quickly as possible outweighs the minor risks involved in the use of oral prednisolone in the dose used in this study. Once the patient has been rendered symptom-free the oral prednisolone can be tailed off and discontinued after two or three weeks, and the risk of immediate relapse is negligible.

Though the present trial period lasted for only two weeks, it should not be supposed that treatment ceased as soon as this time elapsed. It has appeared to be beneficial to continue with nightly local treatment for at least several weeks once a clinical remission has been obtained, because there is a strong suggestion that such a procedure diminishes the chance of a recurrent attack in the succeeding months. At present the data are inadequate for a definite statement, but in due course it will be possible to settle the point with some precision, and the relevant facts will then be reported.

So far as the results obtained with oral prednisolone are concerned, it may be contended that the results would have been better if a larger dose had been used. This is probably true, but doses appreciably larger than the one used are apt to cause a greater number of complications of treatment and should therefore be avoided if possible. The aim in the present study was to compare corticosteroids in doses that previous experience had shown to be safe in routine use, even with out-patients. It can also be mentioned that in the large-scale controlled trial of oral cortisone a dose of 25 mg. q.d.s. (which corresponds roughly to the dose of prednisolone used in the present study) was given in the first half of the trial period, while physicians could use up to 75 mg. q.d.s. in the second half. There was little additional benefit from giving the higher doses, though this point was not dealt with in the published report by Truelove and Witts (1954, 1955).

Severe attacks of ulcerative colitis were not included in the present study. Such attacks demand much more intensive treatment, including blood transfusion and control of electrolyte balance, than the present patients received. Nevertheless, it can be said that, *mutatis mutandis*, the principles of treatment which emerge from studying the less severe attacks apply also to the more severe. Combined systemic and local treatment has been used in a considerable number of severe attacks in Oxford and the results appear to represent an advance on previous medical therapy. However, there are various technical points requiring attention when severe attacks are treated with local corticosteroids, and these will be dealt with in a separate communication.

The fact that the great majority of the less severe attacks of ulcerative colitis can now be aborted by medical treatment has important practical implications in the management of the disease. In the case of first attacks the aim should be to diagnose the disease at the earliest possible moment so that treatment can be started with minimal delay. Most of the first attacks begin gradually, with symptoms worsening over the course of weeks or even months. Until the advent of modern medical measures, such patients had almost as bad a prognosis as those in whom the first attack began abruptly with the rapid development of a severe illness, and the fatality rate in the first attack was high (19% reported by Rice-Oxley and Truelove (1950); 46% reported from Switzerland by Demole (1956); 18% reported by Kellock and White (1957): all these figures referring to patients treated in hospitals). The need is to exclude infective dysentery and focal lesions, such as carcinoma coli and diverticulitis, and to obtain the sigmoidoscopic and radiological evidence of ulcerative colitis as quickly as possible so that appropriate treatment can be given before the patient becomes seriously ill. With established disease it is probably best if the patient remains in touch with a physician who has a special interest in the disease, so that any relapse can be treated promptly, while those who fail to do well can be selected for surgery.

From a theoretical standpoint it is of interest that combining systemic prednisolone with local prednisolone 21-phosphate gave results no better than using local corticosteroids alone, whereas combining systemic prednisolone with local hydrocortisone hemisuccinate sodium gave the best results in the trial, being effective in all the 20 patients so treated. There seem to be two main possibilities to account for this finding. The first is that prednisolone 21-phosphate differs from hydro-

cortisone hemisuccinate in physical or simple chemical properties in such a way that its local action in the colon is different. So far as hydrocortisone is concerned there is evidence that the amount of absorption which occurs when it is introduced into the colon is largely dependent upon the chemical nature of the particular hydrocortisone preparation used.

Nabarro *et al.* (1957) based their estimate of absorption on the amount of metabolites of hydrocortisone excreted in the urine. They found evidence that hydrocortisone in the form of the free alcohol was absorbed in considerable amounts. Hydrocortisone acetate was but little absorbed, a finding which might be related to its very low solubility in water. Hydrocortisone hemisuccinate sodium was likewise poorly absorbed, a finding not to be explained on the basis of low aqueous solubility, because this compound is highly soluble in water. Schwartz *et al.* (1958), using hydrocortisone labelled with ^{14}C, have shown that when the hemisuccinate is applied topically within the colon there is no appreciable change in the level of circulating hydrocortisone in the blood; in other words, the presumptive conclusion is that the beneficial action of topical hydrocortisone hemisuccinate in ulcerative colitis is a local one upon the mucosa. Comparable information is not available for prednisolone 21-phosphate.

The other possibility is that prednisolone and hydrocortisone have a truly synergistic action at tissue level, but this must be regarded as highly speculative, as there do not appear to have been any systematic studies of the use of combinations of different corticosteroids as therapeutic agents. There is work in existence which demonstrates the possibility of such a synergistic action. A lengthy review by Veldstra (1956) on synergism and potentiation, with special reference to the combination of structural analogues, takes into account a number of ways in which a truly synergistic action could occur between two closely related substances such as prednisolone and hydrocortisone. In particular, Veldstra brings forward much evidence to support his view that synergism may occur when the components of a mixture are acting "in series" towards the same end-effect—for example, when antimetabolites are competing with different intermediates in a biosynthetic chain.

In this connexion it is of great interest that Nugent *et al.* (1959) have brought forward evidence that different metabolic pathways are involved in the breakdown of hydrocortisone and prednisolone in the body. It therefore appears that the possibility of obtaining synergistic action by using mixtures of different corticosteroids is a topic which deserves systematic study quite outside any applications there may be in the particular disease, ulcerative colitis, now being discussed.

Summary

A comparative study of different types of corticosteroid therapy has been made to determine their relative efficacy in bringing about a rapid clinical remission in ulcerative colitis of mild or moderate severity. A rapid clinical remission is defined as complete loss of symptoms within two weeks of starting treatment and with decisive improvement in the sigmoidoscopic appearances.

Patients were allotted at random to one or other of three treatments: (1) Prednisolone by mouth in a dose of 5 mg. q.d.s. (2) Local treatment with a water-soluble corticosteroid applied by means of a nightly rectal drip. Two different corticosteroids were used—namely, hydrocortisone hemisuccinate sodium and prednisolone 21-phosphate. (3) Combined systemic and local treatment, in which the patients received oral prednisolone in a dose of 5 mg. q.d.s. and a nightly rectal drip of either hydrocortisone hemisuccinate sodium or prednisolone 21-phosphate.

The results obtained in 120 courses of treatment are presented, there being 40 patients in each of the three main treatment groups.

About one-third of the patients treated with oral prednisolone went into rapid clinical remission. With local corticosteroid treatment nearly three-quarters of the patients had a rapid clinical remission. There is little to choose between the two corticosteroids used for local treatment, each of them being much more effective than oral prednisolone in the dose used.

With combined systemic and local treatment the results depended upon the particular combination used. When oral prednisolone was combined with local prednisolone 21-phosphate the results were similar to those of local treatment used alone. When oral prednisolone was combined with local hydrocortisone hemisuccinate sodium all the patients so treated showed rapid remission. This second combination therefore emerges as the best of the various treatments studied.

Some practical and theoretical implications of the present results are discussed.

I am grateful to the Medical Research Council for a grant for technical and secretarial expenses in this and other studies on ulcerative colitis. I am also indebted to Glaxo Laboratories, who made a gift of the prednisolone 21-phosphate solution tablets and of much of the hydrocortisone hemisuccinate sodium. I thank the many physicians and surgeons who have referred patients.

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The Catarrhal Child contains the papers read at a symposium held in Glasgow under the chairmanship of Professor Stanley Graham. The symposium, arranged by the Chest and Heart Association in conjunction with the Glasgow Chest Clinic Services, covers, among other aspects of the subject, incidence, bacteriology, and treatment, as well as giving incidental advice on such practical topics as nose-blowing and school attendance. Indeed, its down-to-earth approach to the problem will be of particular value to the general practitioner, who, at least during the winter months, can rarely get through the day without seeing a catarrhal child. (Chest and Heart Association, Tavistock House North, Tavistock Square, London, W.C.1; pp. 44, 6s., illustrated.)