showed active inflammation, as indicated by the presence of polymorphs in the mucosa.

In patients who had been without symptoms for six or less months, the great majority, 14 out of 17, had an abnormal mucosa histologically, and in 13 of these it also appeared abnormal on sigmoidoscopy. However, the patients without symptoms for more than six months were different. About one-half showed a normal appearance by sigmoidoscopy and the other half abnormal, but of the 15 cases whose appearances were normal eight had an abnormal mucosa microscopically. This finding emphasizes the value of histological examination in ascertaining whether the mucosa has returned to normal, and indicates the value, on occasion, of mucosal biopsy in retrospective diagnosis.

Conversely, the finding of normal mucosal histology in patients who were judged to be sigmoidoscopically abnormal was surprising. The three possible explanations of this anomaly are erroneous interpretation of sigmoidoscopic appearances, unrepresentative biopsy specimens, and the possibility that some of the macroscopic changes regarded as being indicative of mild quiescent colitis might have been the result of disturbances which were not microscopically apparent. The reddening of the mucosa and the disappearance of the normally visible larger vessels are due to hyperaemia and oedema, both of which may be difficult to interpret on a small specimen, and neither change is considered in our criteria of histological abnormality. The cause of mucosal granularity, the most characteristic change of all, remains obscure.

In patients who have symptoms the mucosa is nearly always histologically abnormal, and during the six months after the cessation of symptoms a high proportion of cases still have an abnormal mucosa. After this period, about half the patients still show histological abnormality. There was no difference between the proportion of cases with an abnormal mucosa among those free of symptoms from six months to two years compared with those who had been free for over two years. With the passage of time after the first six months, we suspect that there is no increase in the proportion of cases in which the mucosa reverts to normal. Our figures suggest this, but the numbers are too small to draw any significant conclusion.

Summary

A series of 94 unselected cases of ulcerative colitis have been followed up after a period of 5 to 10 years.

Five patients had died either directly or indirectly from the disease, and five from other causes. Eight patients still under observation were alive and well but had been treated by ileostomy and colectomy.

Of the remaining patients, who had been treated medically, 55 were free of symptoms, 19 were having symptoms, and one could not be traced.

Sigmoidoscopy and colonic mucosal biopsy were carried out in 62 patients. In patients with symptoms, sigmoidoscopy was always abnormal and the histology almost always so. In those free of symptoms for six or less months, a high proportion had an abnormal mucosa, on both naked-eye and microscopical examination. Less than half the patients who had been symptom-free for over six months showed an abnormal sigmoidoscopic appearance, but a greater proportion had histological abnormality. Of 19 symptom-free

patients in whom sigmoidoscopy was normal nine had an abnormal mucosa microscopically.

Apart from the grossly disorganized glandular pattern found in the regenerated mucosa of severe cases, an abnormal glandular pattern is frequently seen in milder cases of ulcerative colitis and may be the only abnormality which persists.

Histological abnormality may persist, with or without an abnormal sigmoidoscopic appearance, for many years, perhaps indefinitely, in patients who have apparently recovered from ulcerative colitis.

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INTRARECTAL TREATMENT OF 100 CASES OF ULCERATIVE COLITIS WITH PREDNISOLONE-21-PHOSPHATE ENEMATA

BY

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Ulcerative colitis is a disease for which many and varied treatments have been tried. Intrarectal injections as an aid to therapy were first suggested by Hurst (1921), but met with little success at that time. A slow-drip method of giving these solutions was first mentioned by Martin (1925), but his variation of intrarectal treatment was equally unsuccessful. It was not until the work of Truelove (1956, 1957) and Watkinson (1958) that the slow-drip method of intrarectal therapy was really shown to be effective. The active agent that Truelove infused was a solution of freshly prepared hydrocortisone hemisuccinate, and this method was found to be valuable. However, its rather complicated nature appeared to delay its general adoption into the treatment of the disease, especially in out-patients (Lennard-Jones *et al.*, 1960).

Recently a more simple method of giving intrarectal therapy has been described (Matts, 1960a, 1960b). The active agent here infused was a solution of prednisolone-21-phosphate. As the results of using this appeared encouraging, further work on the subject was justified.

Present Investigation

This investigation was undertaken to gain experience of the method of treatment and to apply it to a wide range of cases of ulcerative colitis. The patients were completely unselected, the only criterion being that their condition was deteriorating owing to a flare-up of acute or subacute ulcerative colitis. They had all been diagnosed as suffering from ulcerative colitis on the history, sigmoidoscopic findings, and barium-enema examination (which also determined the extent of the disease in the bowel). If they were already on treatment, this was continued unchanged, in addition to the enemata. The patients were assessed immediately before beginning the prednisolone enemata and immediately after stopping them. They were later reviewed at three, six, and nine months to check on their progress after cessation of prednisolone enemata therapy.

The method of assessment was mainly clinical, the following factors being carefully considered: the general feeling of the patient; appetite; sense of well-being; condition of the psyche so far as depression, elation, or mental activity was concerned; energy; presence or absence of abdominal pain; number of bowel actions daily; condition of stools; presence or absence of blood and excess mucus. In addition, sigmoidoscopic examination was undertaken and the haemoglobin level and erythrocyte sedimentation rate were determined.

The method of treatment was initially that described in the previous trial (Matts, 1960a). This consisted of the same technique as before, using the filled enema bag and the solution tablet. Later on, when a stable solution of prednisolone-21-phosphate became available, this was used in the redesigned bag, each bag still containing the equivalent of 20 mg. of prednisolone. The patients were then given a sheet of instructions as follows:

COLITIS CLINIC

PREDNISOLONE-21-PHOSPHATE ENEMATA

METHOD OF APPLYING TREATMENT

Every night, when preparing for bed, take out one filled enema bag.

When ready, go to bed and lie on the left side with knees drawn up; then remove the stopper of the bag and lubricate the nozzle with petroleum jelly.

Gently insert the nozzle into the rectum (about half the nozzle should be inserted). Slowly roll up the bag like a tube of toothpaste and the solution will be gradually introduced into the rectum (one to two minutes).

When all the solution has been introduced, remove and discard the bag (being careful that the fluid does not siphon back into the bag before removal).

Roll over on to the abdomen for three to five minutes and then go to sleep in any comfortable position.

The treatment is to be carried out nightly or as directed.

The normal course of treatment is four weeks.

When necessary, any questions were answered, and if the method was not quite clear it was demonstrated to the patient. It was found, however, that with a very brief explanation plus the written sheet of instructions nearly all the patients were able to grasp the simplified method in less than five minutes and carry it out correctly at home. This constituted a considerable step forward in time-saving and ease of starting the patients on the local prednisolone-21-phosphate therapy.

The duration of treatment was variable. It was found that in most cases an initial course of 28 days gave the best results; therefore this was the minimum course advised. In a few cases treatment was continued for

up to four months with interesting results (see case histories).

On completion of therapy patients were given a reserve supply of 14 filled enema bags and advised to start using these immediately a relapse occurred and to come up to the clinic as soon as possible afterwards. Very few needed to use these, as will be seen from the results, but when they did the response was dramatic. This meant that by the time they came up to the clinic they were already greatly improved. This seemed to result in the relapses being of a minor nature and easily checked. I believe this to be an extremely important point, and suggest that, if local therapy is begun immediately a relapse occurs, then it will be checked and progression of the disease may be arrested. It may be found that, by having a portable method of local therapy immediately available, the patients can, by early self-treatment, prevent severe relapses. Further, one could conceive that in some cases this early treatment by suppressing the inflammation may prevent irreversible colonic changes occurring and may in time reduce the number of patients ultimately requiring surgery. This is already supported by the decreasing number of patients having severe symptoms among those attending the colitis clinic during the period it has been functioning.

Another important feature of the early therapy is that by arresting the relapse it reduces the patient's incapacity, increases his yearly working-time, and reduces hospital admissions. All three factors have important financial implications irrespective of the saving of suffering on the part of the patient.

Results

Improvement was obtained in 88 of the 100 cases treated. Among these 88, no relapse occurred for three months in 78, for six months in 70, and for nine months in 66. Further details are as follows.

Breakdown of Therapy in Cases Treated

On prednisolone-21-phosphate enemata only	56
" enemata plus prednisolone disodium phosphate suppositories	8
" " " sulphasalazine	16
" " " systemic corticoids	20

Extent of Disease in All Cases (Judged Radiologically)

Generalized throughout large bowel	20
Left side of colon only	44
Sigmoid colon and rectum only	36

Cases Improved in Each Group of Extent of Disease

Generalized throughout large bowel	13 improved out of 20
Left side of colon only	43 " " 44
Sigmoid colon and rectum only	32 " " 36

Possible Reasons for Failure to Improve

Generalized disease involving small bowel also	2
throughout large bowel	4
Stricture present	1
Mechanical difficulty in administering therapy	2
Failure to retain solution	2
Unknown	1

Case 1

Woman aged 36. Long history of ulcerative colitis; subject to frequent relapses necessitating hospital admission. Had been treated in hospital with hydrocortisone rectal drips but was unable to carry out this treatment herself at home. Sent into hospital again with relapse: bowels open 15 times daily; much blood in loose watery motions. Haemoglobin, 74%. E.S.R., 50 mm./hour. Sigmoidoscopy: Ulcerated bleeding rectal mucosa. Barium-enema examination: Narrowing of left side of colon with ulcerative mucosal changes. Put on prednisolone enemata and sent home after two days (usual length of hospital stay, two weeks minimum) to continue therapy for one month.

Review after one month's therapy showed the following results. Bowel action down to twice daily, formed motion, no blood. Haemoglobin, 88%; E.S.R., 12 mm./hour. Sigmoidoscopy: Slight granular rectal mucosa, no ulceration or bleeding.

Case 2

Man aged 40. Six-year history of ulcerative colitis. Subject to severe relapses. Had been on systemic prednisone for past 12 months. Recent relapse, bowels open 20 times (or more) daily, with much blood. Haemoglobin, 52%. E.S.R., 60 mm./hour. Sigmoidoscopy: Grossly ulcerated bleeding mucosa in rectum and lower sigmoid. Barium-enema examination: Generalized mucosal changes with narrowing and loss of haustration throughout colon; ? filling defect in caecum.

In view of this, operative intervention was advised, but the patient declined and asked to be referred to the Central Middlesex Hospital for further opinion. This was done, and similar advice was given there. Patient again refused operation, and, in an endeavour to help him, long-term prednisolone enemata therapy was added to his previous treatment (systemic prednisone). Improvement was gradual, but four months later had become dramatic. Bowels open once or twice daily; no blood. Haemoglobin, 89%. E.S.R., 14 mm./hour. Sigmoidoscopy: Granular mucosa; no bleeding or ulceration. Barium-enema examination: Haustrations returned to right half of colon; left side still shows slight narrowing and reduced haustrations; no sign of filling defect previously noted.

This case is of particular interest because of the reversal of radiological changes. It is reasonably certain that the best course would have been operative intervention; but, failing this, local treatment produced a great improvement, which more than justified its use.

Case 3

Woman aged 44. Ulcerative colitis for four and a half years. Gradual recent deterioration; treated with systemic corticoids with little improvement. Admitted to hospital. Bowels open nine times daily; bloody diarrhoea. Haemoglobin, 55%. E.S.R., 44 mm./hour. Sigmoidoscopy: Ulcerated bleeding mucosa in rectum. Barium-enema examination: Loss of haustration in transverse and descending colon; gross mucosal ulceration in whole colon with much undermining of mucous membrane (see Fig. 1).

Operation was advised in view of the severity of symptoms and signs. This was declined by the patient, and, in view

of the previous experience with Case 2, long-term prednisolone enemata were started.

Improvement was slow at first, but by three months it had become striking. Bowels open once daily; no blood. Haemoglobin, 94%. E.S.R., 7 mm./hour. Sigmoidoscopy: Normal appearances. Barium-enema examination: Normal haustrations of ascending and transverse colon; loss of haustration in descending colon, most marked at lower end; minimal mucosal changes of ulcerative colitis present in sigmoid colon (see Fig. 2).

This case again shows slow but marked reversal of changes of ulcerative colitis with local therapy. Again surgery would probably have been best; but, failing this, local therapy has produced a good response.

Discussion

Local treatment of ulcerative colitis with prednisolone-21-phosphate enemata had been shown to be of value in the earlier trial. This more extensive trial has confirmed its value. Of greater importance, its wide application to the field of therapeutics in ulcerative colitis has been demonstrated. The method has been further simplified and made more portable. The amount of time needed for explanation of its use has been cut down and the time taken by the patient to administer therapy has also been shortened.

The safety of the method in general has been proved by the lack of complications of therapy in use. It can be easily combined with other methods of treatment, as has been done in this trial. Fairly long courses of treatment are recommended, but the expense of these is more than justified by the saving of hospital admissions and the shortening of the period in which the patient is incapacitated from work, and by the saving of pain and discomfort.

The prednisolone enemata are easy to dispense and use, and the fact that the patient can have a reserve supply for immediate early treatment of relapse is important. The full value of early treatment cannot be finally proved for several years, but already there are indications of its value in reducing permanent damage to the bowel in relapses of ulcerative colitis. In some cases radiological changes of ulcerative colitis in the bowel may be reversed by local treatment.

FIG. 1

FIG. 2

FIG. 1.—Case 3. Radiological appearance of colon before treatment with prednisolone enemata. FIG. 2.—Case 3. Radiological appearance after prednisolone treatment.

This method of therapy is particularly valuable for out-patients, and most of the patients in this series were treated as such.

The results obtained in this series (88% initial improvement) were maintained by most of the patients over a nine-months period. In those cases in which relapses did occur they were slight and easily controlled by further local treatment. No deaths occurred in this series. These results compare favourably with the experience of others with local therapy (Truelove, 1956, 1957, 1958; Watkinson, 1958).

Corticosteroid therapy has many disadvantages when given systemically. Among these are the insidious onset of infection (*British Medical Journal*, 1954; Stevens, 1960), acute adrenal insufficiency in response to sudden stress (*Lancet*, 1957), and other multiple possible dangers (corticoid psychosis, osteoporosis, perforation of peptic ulcer, etc.). Local corticosteroid therapy, however, carries none of these risks and, so far, no complications have been reported following its use.

If systemic corticoid therapy is to be used in ulcerative colitis, then the co-employment of local steroids enables a smaller dosage to be given and thus reduces the dangers.

Summary

One hundred cases of ulcerative colitis were treated with prednisolone-21-phosphate enemata. The results on the whole are good, an 88% improvement rate being obtained initially. A follow-up for nine months after therapy is reported.

The patient should have a reserve supply of treatment for immediate use in a relapse.

Very long courses of treatment have been found of value in certain cases.

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"The National Spastics Society's projects for 1961 include the construction of the first purpose-built secondary school in Britain for spastic children and a centre for spastics who require special education. Work will be started on building our sheltered workshop in Birmingham for 120 spastics regarded as unemployable in open industry, and we hope to finalize the site for a similar project in the south of England. In addition, major extensions and alterations to improve facilities at nine of our schools and centres will be carried out. Early in the New Year we shall be taking the first steps in providing a staff training centre, where expert advice will be given to those who look after and teach spastics. Altogether £800,000 will be spent on building programmes during the coming year." (Dr. C. P. Stevens, director, National Spastics Society.)

DEPRESSION TREATED WITH IMIPRAMINE: A FOLLOW-UP STUDY

BY

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A controlled trial of imipramine ("tofranil") in the treatment of out-patients suffering from depressive states was reported by Ball and Kiloh (1959). It was found, when assessed after a period of four weeks, that 74% of the cases of endogenous depression showed a good response to imipramine as compared with 22% of the cases receiving placebo. In reactive depression a similar degree of improvement was obtained in 59% of the patients on imipramine as compared with 20% given placebo.

It was stated that many of the patients who failed to respond to their initial treatment were given the alternative tablets. This constituted a cross-over experiment within the main trial. Furthermore, the view was expressed that a follow-up study of the trial cases to provide a longer-term assessment of the effects of treatment might be of value.

An extensive literature now exists concerning imipramine, but controlled studies of its effects are still scanty. Up to May, 1960, only three papers have been traced describing investigations in which some attempt has been made at control. One of these (Sloane *et al.*, 1959) involved only 12 patients and was abandoned after two weeks. A partially controlled trial was reported by Lehmann *et al.* (1958). Eighty-four patients were treated, 51 of whom suffered from endogenous depression. After the first 42 patients had been collected and treatment was in progress, it was decided to subject these to a double-blind procedure. One-half continued to take imipramine and the other half were given placebo tablets. Assessments were made after two weeks. Of the 21 patients on placebo, 10 became worse, whilst of the 21 patients remaining on imipramine 3 relapsed. The difference was accepted as significant statistically. All 10 patients who relapsed on placebo improved within two weeks when imipramine was substituted.

Leyberg and Denmark (1959), as a prelude to a full-scale trial of imipramine, conducted a controlled cross-over study of its effects on 20 long-term hospitalized cases of endogenous depression. For two weeks half the patients were given imipramine and half placebo. In the second two weeks the procedure was reversed. The results were regarded as encouraging.

None of these studies can be accepted as adequately controlled.

Cross-over Study

Endogenous Depression.—Of the original placebo group, 17 cases were subsequently given imipramine, and eight of these showed a satisfactory response within four weeks. 27 cases were treated initially with imipramine, and five of the seven which failed to respond