septicaemia. It is important to gain the patient's confidence and to help with any emotional problems which may have precipitated the illness.

Corticotrophin.—(a) *The patient has not received corticotrophin or steroid drugs:* Give 120 units of corticotrophin daily for four days to test the response of the patient's illness to this drug, provided that delay in undertaking operation appears justifiable. (b) *Corticotrophin or steroid drugs have been given:* From a knowledge of the dose given a decision must be made whether these drugs received an adequate trial. If they did, corticotrophin should not be given; if not, a cautious trial of 120 units of corticotrophin daily for four days seems justifiable.

Indications for Surgical Treatment.—Unless operation is deliberately delayed for a trial of corticotrophin it should be performed as soon as the patient's obvious metabolic deficiencies have been met. Further delay is not permissible except when the disease appears to be going into remission after energetic general medical treatment. If a trial of corticotrophin is undertaken urgent operation is indicated if (a) there is no dramatic response to this drug and all other medical measures within four days; (b) the patient's condition deteriorates at any time during the treatment; or (c) after an initial successful response to corticotrophin a severe relapse occurs while he is still receiving the treatment.

Type of Operation.—We consider that the best procedure is immediate subtotal colectomy and ileostomy. If, however, the patient's general condition is desperate, or if inspection at laparotomy suggests that the colon is especially apt to perforate during mobilization, ileostomy alone may be preferable.

Summary

The results of treatment in 32 patients with very severe acute ulcerative colitis have been analysed.

The results of medical treatment were disappointing; one patient died without an attempt at surgical treatment, two patients responded to conservative measures, and two apparently responded to corticotrophin, 120 units daily (one of these patients did not respond to corticotrophin, 80 units daily).

Four patients were treated by ileostomy alone and all of them recovered. Reasons are given for supposing that these results were fortuitously favourable.

Twelve patients who had received no corticosteroid treatment were treated by immediate subtotal colectomy and ileostomy; three of them died and six made an uneventful recovery. It is suggested that this is the operation of choice in most cases.

Seven patients who had received corticosteroid therapy were treated by immediate subtotal colectomy and ileostomy; four of them died and two made an uneventful recovery. There was a dangerous deterioration in the condition of three of these patients during pre-operative medical treatment; two patients were not given extra cortisone at the time of operation. The colon was torn during colectomy rather more often among patients who had received corticosteroids than among those who had not received these drugs.

From our findings we suggest a possible regime for trial in the management of these very ill patients.

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LOCAL CORTICOSTEROID TREATMENT IN SEVERE ATTACKS OF ULCERATIVE COLITIS

BY

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Since 1955 considerable experience has been acquired in the use of corticosteroid solutions applied locally within the colon by means of a rectal drip for the treatment of ulcerative colitis. The initial studies showed that mild and moderate attacks were often checked abruptly, so that the patient became symptom-free in a few days, though a minority of attacks failed to respond (Truelove, 1956, 1957). A special feature of these early studies was that the water-soluble corticosteroid, hydrocortisone hemisuccinate sodium, was shown by serial biopsy of the mucosa to produce striking histological improvement in those patients showing a favourable symptomatic response. Consequently this agent, or another water-soluble corticosteroid, prednisolone 21-phosphate, has since been the agent of choice for this form of treatment.

Since these early studies, local corticosteroid treatment has been tested in two independent controlled therapeutic trials, carried out in Oxford and Leeds respectively, both of which were conducted on the so-called "double-blind" system with neither the physician nor the patient knowing whether a particular treatment was corticosteroid or "dummy." Both studies yielded convincing evidence that local corticosteroid treatment usually caused a rapid cessation of mild and moderate attacks of ulcerative colitis, whereas it was exceptional for a patient to undergo spontaneous loss of symptoms when given the dummy treatment (Truelove, 1958; Watkinson, 1958). Subsequently it has been found that local corticosteroid treatment is twice as likely to bring about a rapid clinical remission as a comparable dose of corticosteroid given by mouth, but that it is even more efficient to use combined systemic and local corticosteroid therapy consisting of prednisolone by mouth and hydrocortisone hemisuccinate sodium by rectal drip (Truelove, 1960).

All these published studies were concerned with the value of local corticosteroid therapy in mild or moderate attacks of ulcerative colitis, and it has sometimes been assumed that this form of treatment is useful only in such attacks and has little or no place in the management of a severe attack. In reality, local

corticosteroid treatment has been used in Oxford in the medical management of severe attacks of ulcerative colitis ever since the first study on the lesser attacks had suggested that this form of treatment was beneficial. Sufficient experience has now been obtained to warrant the conclusion that this form of therapy represents an advance in treatment for severe attacks as well as for mild or moderate ones.

The present article consists of three main sections. First, some illustrative case-histories are given to demonstrate some of the results obtained in individual cases and some of the practical problems entailed in this form of treatment. Secondly, based on experience of these and many other in-patients, a scheme for the medical management of severe attacks is formulated. Thirdly, some consideration is given to the evidence supporting the view that local corticosteroid therapy is beneficial in severe ulcerative colitis.

Case 1. Severe Attack Complicated by Massive Bleeding from Bowel

A married woman aged 33 was admitted to hospital on July 26, 1957, in a severe attack of ulcerative colitis. Two months before admission diarrhoea occurred, with up to 10 bowel actions daily and with bright blood in the faeces. There was lower abdominal pain and tenesmus. Four weeks before admission she developed anorexia, flatulence, and increasing weakness, while the diarrhoea became more severe and there was blood intimately mixed in the motions.

Past History.—Pulmonary tuberculosis had been discovered after her third pregnancy and had been treated with satisfactory results.

Family and Social History.—There was an extremely unstable background with an aggressive psychopathic husband. The family was in considerable financial difficulties, and one of the three children was being cared for in an institution because of lack of attention at home.

On admission she was a pale, emaciated, and anxious woman with fever and tachycardia, the temperature being 103° F. (39.4° C.) and the pulse rate 110 a minute. There were numerous aphthous ulcers in the mouth. The cardiovascular system showed a simple tachycardia with a blood-pressure of 95/65 but no other abnormalities. The abdomen showed tenderness in the left iliac fossa but no other abnormality.

Investigations on Admission.—Blood: haemoglobin, 60% (9.2 g./100 ml.); white cells, 8,100/c.mm.; film showed iron-deficiency changes; E.S.R., 86 mm. in one hour. Blood chemistry: some degree of hypokalaemia (serum potassium, 3.4 mEq/l.) and hypoalbuminaemia (albumin 3.1 g./100 ml.). Chest x-ray examination showed "minimal residual lesion in right second interspace." Stools: numerous red blood cells but no parasites, ova, or acid-fast bacilli; culture showed no pathogenic organisms. Barium enema: "Ulcerative colitis affecting the entire colon." Sigmoidoscopy showed "severe inflammation with a haemorrhagic mucosa which oozes blood freely."

Treatment and Progress

She was admitted to a large-scale trial of cortisone and corticotrophin therapy which was then in progress and was allotted to cortisone, which was given in a dose of 50 mg. four times a day. During the first three weeks of this treatment she had recurrent episodes of severe bleeding, each of them necessitating urgent blood transfusion. In the fourth week a severe abdominal episode occurred which was thought to be a small perforation of the colon with walling off of a localized abscess in the left iliac fossa. Cortisone was temporarily discontinued and terramycin and further blood transfusions were given. She resumed cortisone until the six-weeks trial period was completed; treatment was then changed to corticotrophin gel in a dose of 80 units daily. After treatment with corticotrophin for one week

she developed a severe urinary infection and diabetic precoma, with a blood-sugar of 550 mg./100 ml. and associated severe electrolyte disturbances of the blood. Corticosteroid therapy was stopped and general medical measures were taken, and insulin was given for the diabetic state. However, after another week further heavy bleeding from the bowel necessitated immediate transfusion of six bottles of blood.

At this point she was a severely ill woman with high fever and low weight (5 st.: 32 kg.). Emergency colectomy was contemplated, but was thought to be undesirable if it could possibly be avoided because of the unsatisfactory social background which would have fitted in badly with a permanent ileostomy life. It was therefore decided to try the effect of local hydrocortisone treatment, and a rectal drip of hydrocortisone hemisuccinate sodium was given three times a day together with 5 mg. of oral prednisolone four times a day. In a few days there was a marked improvement. Further blood transfusion was not needed, though she had previously received more than 60 bottles of blood (30 litres). The temperature, which was running at up to 105° F. (40.6° C.), settled to normal. Blood diminished in the stools and became absent, and she began to gain weight. Thereafter progress was uneventful, and when discharged from hospital she was having one or two normal motions a day and her weight had risen to 8½ st. (54 kg.).

Long-term Progress.—After discharge from hospital all treatment was discontinued, and she remained well until February 22, 1958. Then, while shopping in Oxford, she was suddenly seized with abdominal pain and went to a public lavatory, where she passed large amounts of blood per rectum. She came to the casualty department of the Radcliffe Infirmary, and I saw her sitting on a bedpan passing almost pure blood from the bowel. She was admitted, given a blood transfusion, and put on to a rectal drip of hydrocortisone hemisuccinate. This was well retained from the start. By the next morning there was no fresh blood in the faeces, and three days later blood was completely absent. She was discharged one week after admission with one normal motion a day, to continue on the daily rectal drip at home. Since that time she has been kept under regular observation. For one period she has needed treatment with the combination of oral prednisolone and the rectal drip of hydrocortisone, but otherwise has been well. Since December, 1958, she has received no treatment and has been symptom-free. At the time of writing the sigmoidoscopic and the barium-enema appearances were normal.

Comment.—The severe first attack of the disease resisted treatment by general medical measures coupled with oral cortisone at first and later with intramuscular corticotrophin. Throughout she was liable to recurrent episodes of severe haemorrhage from the bowel. When systemic corticosteroids were stopped for a week, she continued to have severe ulcerative colitis and had a further severe haemorrhage. The institution of local hydrocortisone hemisuccinate therapy at this point, coupled with a comparatively small dose of oral prednisolone, was followed by rapid improvement and uneventful recovery. The long-term course has so far proved satisfactory and the bowel has reverted to normal as judged by sigmoidoscopy and barium-enema appearances.

Case 2. Severe Relapse Responding Rapidly to Local Hydrocortisone

A transport driver aged 31 was admitted to hospital in a severe relapse of ulcerative colitis on November 15, 1957. In 1946 he had an attack of diarrhoea with some blood in the motions while serving in the Army in India, this illness being labelled as "dysentery." Since that time he has been liable to attacks of diarrhoea with blood and mucus in the stools, and ulcerative colitis was diagnosed at the Radcliffe Infirmary in 1947. In August, 1956, he suffered from a

sharp relapse which was treated in hospital for two months with systemic prednisolone. Thereafter he was relatively well with about four motions a day until September, 1957, when there was a sharp relapse with 25-30 stools daily. He had severe abdominal pain during and after defaecation and tenesmus. He lost weight rapidly and was admitted to hospital.

On admission he was a thin, ill-looking man with fever, the temperature being 100° F. (37.8° C.). In the abdomen there was marked tenderness over the descending and iliac colon.

Investigations.—Blood: haemoglobin 94%; white cells, 27,000/c.mm.; E.S.R., 62 mm. in one hour. Blood chemistry was satisfactory. Barium enema: "severe ulceration affecting the whole of the colon." Sigmoidoscopy: appearances of severe ulcerative colitis.

Treatment and Progress

For the first week he was treated with general medical measures, but he continued to deteriorate rapidly with painful motions every half-hour and loss of nearly 1 st. (6.4 kg.) in weight. At this point he was treated with local hydrocortisone, which was used somewhat differently from the method employed in Case 1. A large quantity of hydrocortisone—namely, 400 mg. of the hemisuccinate—was dissolved in 1 pint (500 ml.) of normal saline and was run rapidly into the bowel each night after a preliminary intravenous injection of 30 mg. of propantheline bromide ("probanthine"). The intention was to ensure that the hydrocortisone travelled throughout the whole colon. In addition to this treatment he was given penicillin, 1 mega unit twice daily, and streptomycin, 1 g. twice daily, both by intramuscular injection. On this regime he rapidly went into remission. His bowel habit rapidly showed improvement, and both the white blood count and the E.S.R. fell swiftly to normal values. The one complicating feature was the development of anorexia and nausea, which were attributed to the effect of probanthine; these symptoms disappeared when the dose was reduced to 15 mg. He was discharged from hospital on January 6, 1958, treating himself with a nightly rectal drip of 100 mg. of hydrocortisone hemisuccinate in 150 ml. of saline.

Long-term Progress.—Since that time he has been kept under supervision as an out-patient. He has had one further relapse of ulcerative colitis, but this was rapidly checked by treating him as an out-patient with a combination of 5 mg. of prednisolone by mouth four times a day and a nightly rectal drip of 100 mg. of hydrocortisone hemisuccinate sodium. For the past year he has had no treatment and the sigmoidoscopic appearances were normal, while a recent barium-enema examination has been reported on as follows: "The examination shows a remarkable improvement in the colon, all parts of which show a smooth outline. The distal colon is devoid of haustrations, but after the enema there was a good evacuation and the colon contracted well" (Dr. K. Lumsden).

Comment.—A severe relapse of established ulcerative colitis responded to local hydrocortisone used in a particular way. A large quantity of hydrocortisone was employed in 1 pint (500 ml.) of saline after a preliminary intravenous injection of propantheline bromide to paralyse the gastro-intestinal tract and thus increase the chance of the hydrocortisone being retained in the colon. The response was good, but the method of administration is somewhat troublesome for the physicians concerned.

Case 3. Severe Relapse Treated with Systemic Triamcinolone and Local Hydrocortisone Hemisuccinate Sodium

A married woman aged 47 was admitted to hospital as an emergency case on August 18, 1958. There was a history

of ulcerative colitis extending over the past 22 years, the first attack occurring with her first pregnancy. Since that time she has been liable to attacks of the disease, but was completely well between attacks. The last previous attack was in 1956, when she spent 17 weeks in a London teaching hospital and was severely ill. On the present occasion bloody diarrhoea had begun two weeks before admission and had become severe.

On admission she was a flushed middle-aged woman with a fever, the temperature being 102.4° F. (39.1° C.), and with tachycardia, the pulse rate being 100. The abdomen was slightly distended and there was tenderness over the descending colon.

Investigations on Admission.—Blood: haemoglobin 105% (15.2 g./100 ml.); white cells, 9,000/c.mm.; E.S.R., 36 mm. in one hour. Faeces: culture showed no pathogenic organisms. Barium enema: "extensive changes of ulcerative colitis involving the rectum, sigmoid, and descending colon, and the distal half of the transverse colon."

Treatment and Progress.—She was treated with systemic steroids, at first hydrocortisone intravenously and then triamcinolone orally in a dose of 8 mg. four times a day. Rectal drips of hydrocortisone hemisuccinate sodium, 100 mg. were given twice a day, together with propantheline bromide intravenously before the evening drip in order to keep the hydrocortisone in place. Improvement was rapid and normal stools were passed after one week. She was discharged on September 1, 1958, two weeks after admission, to continue treatment with rectal hydrocortisone at home. Treatment was continued on an out-patient basis until November, 1958, when it was stopped. Thereafter she remained well until February, 1959, when there was a recurrence. She was treated as an out-patient with triamcinolone, 4 mg. four times a day, by mouth, and a nightly rectal drip of hydrocortisone hemisuccinate, and showed a rapid response. Since that time she has remained well.

Comment.—This case-history illustrates the prompt response to combined local and systemic corticosteroid treatment which is shown by many patients.

Case 4. Sharp Relapse Complicated by Arthritis

A married woman aged 36 was admitted to hospital on July 31, 1958, because of ulcerative colitis. She developed the condition in 1939, when she was ill for 10 months; the diagnosis was confirmed by barium enema. There were recurrences in 1947, 1957, and 1958. In the 1958 attack she was treated with rectal hydrocortisone for three weeks and did well. Thereafter she remained well until six weeks before the present admission, when diarrhoea suddenly developed with 10 watery motions a day. She was treated as an out-patient with a rectal drip of hydrocortisone and improved, but then stopped it. The diarrhoea became worse, and severe pains developed in the left ankle, left calf, left shoulder, neck, and the right arm.

On admission she was moderately ill, with fever, the temperature being 101° F. (38.3° C.), and tachycardia, the pulse rate being 120. The neck was very painful on movement, and several other joints were also painful, though there was little to find on objective examination.

Investigations.—Blood: haemoglobin 82%; white cells, 14,200/c.mm. Blood chemistry: mild hypokalaemia (serum potassium, 3.7 mEq/l.).

Treatment and Progress.—After five days in hospital without benefit from general medical treatment she was given a combination of prednisolone by mouth in a dose of 10 mg. four times a day and a rectal drip of hydrocortisone twice daily. Because of severe aphthous ulceration prednisolone phosphate was prescribed as a mouth-wash. With this treatment she rapidly improved, becoming almost normal after three days. The temperature, which had continued to show an evening rise to 101-102° F. (38.3-38.9° C.) each day after admission, remained normal from

the start of this treatment. She was discharged after two weeks' treatment. Since that time she has remained well.

Comment.—Both arthritis and severe ulceration of the mouth are common complications of ulcerative colitis. When the colitis is treated successfully, whether by medical treatment or by colectomy, both these complications disappear. In this particular case treatment with corticosteroids was rapidly effective.

Case 5. A First Attack Presenting as a Sudden Haemorrhage from the Bowel

A married woman aged 58 was admitted to hospital on April 16, 1958, as a surgical emergency because of heavy bleeding from the bowel. Two days before admission she suffered from severe intermittent abdominal pain with vomiting, these symptoms persisting until admission. On the day before admission she developed diarrhoea and passed a small quantity of blood. On the day of admission large quantities of blood were passed per rectum. The provisional diagnosis on admission was acute diverticulitis with massive bleeding. However, the house-surgeon observed that faecal material was intimately mixed with the blood passed per rectum, and the possibility of ulcerative colitis occurred to him. It was arranged for me to carry out sigmoidoscopy without delay, and this showed that the entire mucosa of the rectum and lower sigmoid colon, as far as could be seen, was hyperaemic and oedematous, with marked contact-bleeding. The appearances were those of ulcerative colitis. A barium-enema examination one day later revealed multiple irregularities of the outline of the sigmoid and descending colon, suggesting ulcerative colitis.

Treatment and Progress.—Three pints (1.5 litres) of blood were transfused immediately. She continued to pass large amounts of blood per rectum until the day after her admission, when sigmoidoscopy showed the condition to be ulcerative colitis. She was then put on a rectal drip of hydrocortisone hemisuccinate, and thereafter had no further bleeding and the stools became normal. The bowels were not opened for three days after the first rectal drip. Seven days after starting the rectal drip repeat sigmoidoscopy showed only slight inflammation. She was kept under supervision as an out-patient. The nightly use of a rectal drip of hydrocortisone hemisuccinate was continued for some weeks after discharge from hospital; she was then entirely normal symptomatically and the sigmoidoscopic appearances were likewise normal. A repeat barium enema also showed normal appearances. She has remained entirely well since.

Comment.—My previous experience has been that patients who begin with heavy bleeding from the bowel usually suffer from a severe attack of ulcerative colitis. In this particular case the bleeding was immediately stopped by the use of local hydrocortisone hemisuccinate, with reversion of the bowel to entire normality so far as can be judged by our present methods of study.

Scheme for the Medical Management of a Severe Attack of Ulcerative Colitis

A severe attack of ulcerative colitis demands urgent admission to hospital and the immediate institution of certain general medical measures which are applicable to the treatment of any case of severe bloody diarrhoea, no matter how caused. As soon as the diagnosis is made, which is usually not difficult in a severe attack of this disease, the other measures which are employed to shorten the attack should be brought into play.

General Medical Measures

1. *Correction of Dehydration and Electrolyte Depletion.*—Whenever there is profuse diarrhoea there is heavy loss of water and of electrolytes. In particular the loss of

potassium may be heavy, and the patient may be rendered gravely ill on this account alone. It is sometimes possible to correct electrolyte deficiencies by the oral administration of appropriate replacement fluids, but if there is vomiting or the electrolyte disturbance is severe it is best to employ intravenous infusion. Once corrected, regular biochemical observations should be made while the illness is in a severe stage, so that corrective measures can be reinstituted whenever necessary.

2. *Blood transfusion, to be repeated as often as necessary,* should be carried out to maintain the haemoglobin at a high level. In other words, the blood which is being lost per rectum is replaced without the body having to call upon its own stores of protein to make good the loss. In severe ulcerative colitis there is heavy loss of nitrogen from the bowel, so that any measure which spares the protein stores of the body is valuable in preventing rapid wasting.

3. *A high calorie intake,* preferably with a large amount of protein, should be instituted. This is sometimes impossible at first, because vomiting and anorexia are common features of an acute attack. In such circumstances glucose should be added to the intravenous infusions, and the measures designed to cut short the attack will usually restore the appetite in a few days.

4. *Vitamin supplements* should be administered, because deficiencies can occur in the course of the disease. Vitamin B complex should be given parenterally, especially if antibiotics are being used. Folic acid and vitamin B₁₂ are possibly worth giving if a severe attack lasts for more than a week or two. There is no convincing evidence that they do much good, but their use is harmless.

Specific Agents Used to Cut Short the Attack

Two main types of therapeutic agent have been extensively used in recent years because they appear to cut short the attack. They are salicylazosulphapyridine ("salazopyrin") and corticosteroid therapy. Salazopyrin is a Swedish preparation which was introduced in 1940 by Svartz and has since been much used in the treatment of ulcerative colitis. In Oxford we have not made extensive use of this agent in the treatment of severe attacks of the disease, such as are now being discussed, but those who are interested will find references to its use in a number of articles (Svartz, 1942, 1948, 1954, 1956; Lagercrantz, 1949, 1955; Bergen, 1955; Morrison, 1952, 1953; Spriggs *et al.*, 1958).

Corticosteroid therapy has been our mainstay in Oxford for cutting short attacks of ulcerative colitis. There are two distinct ways of using corticosteroid therapy—namely, systemically or by local application to the colon. Our general experience is that it is best to combine these two methods for the treatment of a severe attack. Certainly in the less severe attacks it has been shown that the combined use of systemic and local corticosteroid therapy is more efficient in producing rapid clinical remission than either method used alone (Truelove, 1960). It is reasonable to assume that the same general principle holds good in the treatment of a severe attack of the disease, though we employ higher dosage than in the lesser attacks. Nowadays we employ one of the newer analogues of cortisone for systemic therapy, and prednisolone by mouth in an initial dose of 1.5 mg. four times a day appears to be generally satisfactory, though triamcinolone and dexamethasone have also been used in some cases. When the attack is exceptionally severe, and especially if there is much nausea and vomiting, it is convenient to begin systemic corticosteroid therapy by giving intravenous injections.

We originally gave hydrocortisone hemisuccinate sodium in doses of 100 mg. twice a day, but more recently have used prednisolone 21-phosphate 25 mg. twice a day. Prednisolone phosphate enjoys an advantage over hydrocortisone hemisuccinate in having less effect on electrolytes, so that the control of electrolyte metabolism is easier. In addition, a comparative study of various forms of corticosteroid treatment in the less severe attacks of ulcerative

colitis has shown that the combination of systemic prednisolone and local hydrocortisone is a highly effective approach (Truelove, 1960).

At the same time that systemic corticosteroids are being used, local hydrocortisone hemisuccinate is administered by rectal drip twice a day. Before the evening rectal drip it is usual to give at the height of the attack an intravenous injection of propantheline bromide in a dose of 30 mg. for an adult in order to paralyse the gastro-intestinal tract and thus facilitate the retention of the local hydrocortisone within the colon. It is usual to employ 100 mg. of hydrocortisone dissolved in approximately 150 ml. of saline for each rectal drip, though on occasion we have used larger quantities of hydrocortisone dissolved in a much bigger volume of saline, as described in Case 2 above. It is not yet certain which is the better of these two methods of using hydrocortisone locally, but the large-volume method demands the presence of a physician and is therefore more troublesome. Radiological studies that have been made using barium suspensions on lesser attacks of the disease have shown that the bigger volumes travel further in the colon and can always be relied upon to reach the ascending colon, but similar studies have not yet been made in patients actually suffering from a severe attack.

A word of caution must be interpolated about the use of intravenous propantheline. When it is used nightly, as described above, it is essential that neither propantheline nor any other anticholinergic agent be given by mouth in addition, if overdosage is to be avoided. Even when using a nightly dose of 30 mg. intravenously on its own we have in a few patients encountered evidence of overdosage, which has shown itself as abdominal distension, anorexia, nausea, and tachycardia, with a general picture resembling that of a paralytic ileus. It is important to keep this cause of abdominal distension in mind, because abdominal distension can occur in ulcerative colitis from other causes, notably from potassium depletion or from a perforation of the colon, which, if small, may not be clinically obvious, especially if corticosteroids are being used in treatment. If signs of overdosage of propantheline appear, the dose should be reduced or this treatment stopped for a day or two.

Accessory Measures

Antibiotics and sulphonamides have a secondary but important role in the treatment of acute attacks. They minimize the chance of developing a pyogenic complication of the disease, and this is particularly important when corticosteroid therapy is being employed at full dosage. Penicillin has the virtue of negligible toxicity, but is effective against a limited range of organisms. The combined use of penicillin and streptomycin by intramuscular injection appears to be a good method of combating the risk of pyogenic complications in severe cases, but streptomycin should not be continued for more than about a week. The broad-spectrum antibiotics should not, in my opinion, be given by mouth in this disease, because they are themselves liable to create a dangerous enterocolitis. When broad-spectrum antibiotics are used it is best to choose one which can be given parenterally and to keep to a short course of treatment. It has now become usual for us to employ intravenous achromycin or terramycin for a few days at the beginning of a treatment of a severe attack when there is much fever present.

It will be appreciated that the foregoing scheme is a provisional one which may have to be altered as new developments in corticosteroid therapy occur. In addition, it is designed for the treatment of an uncomplicated attack of ulcerative colitis. Certain complications demand emergency surgery, perforation of the colon being the outstanding example. Other complications of the acute attack are often improved by treating the colitis along the lines covered, but there are exceptions. A notable one is when moniliasis of the mouth develops, because there is evidence that both

broad-spectrum antibiotics and systemic corticosteroid therapy are apt to cause a spread of moniliasis which may affect the entire gastrointestinal system or the respiratory system. When moniliasis develops, it is usually best to stop temporarily the use of broad-spectrum antibiotics and systemic corticosteroids and to employ nystatin tablets for local and systemic treatment until the fungous infection has come under control.

Evidence that Local Corticosteroid Treatment is Beneficial

The presentation of a group of favourable case reports, such as those given above, cannot be regarded as entirely adequate evidence that local hydrocortisone has been a beneficial addition to the medical management of a severe attack of ulcerative colitis. Any physician with an extensive experience of this disease can assemble a group of patients who made a dramatic response to medical treatment before corticosteroid therapy was introduced. It is therefore necessary to take a much more general view of the results than can be obtained from isolated case histories.

Number of Deaths from Ulcerative Colitis in Radcliffe Infirmary and Churchill Hospital During the Period 1938-59 Inclusive (multiple admissions of the same patient in any one year are counted as a single patient being admitted)

	No. of Admissions	Deaths in Hospital	
		No.	%
1938-43 ..	78	12	15.4
1944-49 ..	151	13	8.6
1950-51 ..	59	5	8.5
1952-53 ..	78	7	9.0
1954-55 ..	82	6	7.3
1956-57 ..	105	1	0.95
1958-59 ..	103	2	1.9

The Table and Chart show the case-fatality rate of in-patients with ulcerative colitis treated in the Radcliffe Infirmary and Churchill Hospital since 1938, when the medical records were put on to a modern system. Patients who were admitted more than once in the same year are counted as a single case for that year, but a similar picture would be obtained if the Table and Chart were presented in the form of fatality rate per 100 admissions, though the rate would be somewhat lower throughout. It will be seen that during the first six years of the period under review, 1938-43 inclusive, no less than 15% of the patients admitted to hospital died in hospital. Then, at the end of the war, the rate fell to approximately 8%. It is probable that this drop

Mean annual case-fatality rate among in-patients with ulcerative colitis treated in the Radcliffe Infirmary and Churchill Hospital, Oxford.

represented an improvement in general medical care and in particular the full realization of the importance of electrolyte control in the severe attacks.

From 1944 onwards the fatality rate did not differ much from 8% until 1956, though the use of systemic corticosteroids began in 1952 and were widely used by 1954, when the results of a controlled trial showing that they were beneficial were available (Truelove and Witts, 1954). The six-year period 1950-5 has been broken down into three two-year periods to show that the rate remained remarkably steady throughout. Local hydrocortisone treatment began to be used in Oxford in 1955 and was applied to the treatment of severe attacks from 1956 onwards. It can be seen that since that time there has been a sharp fall in the case-fatality rate from ulcerative colitis among in-patients, the rate now being approximately 1.5%. This level represents the death of three patients during the four-year period 1956-9 inclusive.

The first of these deaths occurred in an elderly man with long-established ulcerative colitis who died a few days after admission to hospital from a large pulmonary embolism secondary to a silent leg-vein thrombosis which he had presumably developed at home before admission. The second death was in an elderly woman who first came to the Radcliffe Infirmary in 1957 with a history of ulcerative colitis since 1942, untreated except in the first attack; a carcinoma of the sigmoid colon was present, and she was treated by colectomy and ileostomy. Thereafter she had episodes of obstructive symptoms, causing her to be readmitted for exploration in 1958, when intra-abdominal metastases were found. She subsequently died from ileal perforation and peritonitis. The third death was in a severe first attack of the disease occurring in a man who suffered also from the haemorrhagic condition Christmas disease; in him it was impossible to stop massive haemorrhage from the bowel, so that, after 80 bottles of blood had been transfused in the course of a few weeks, surgery became imperative as a final attempt to save his life, but without avail. There have been no deaths from uncomplicated ulcerative colitis during the period—a considerable change from earlier years.

In assessing the value to be attached to these figures, certain other facts must also be taken into account. It will be observed that the number of patients admitted to the hospital has grown steadily, and it might therefore be supposed that part of the improvement in the case-fatality rate is due to the admission of less severe cases of the disease. This does not appear to be the case, and the main reason for the increase in admissions is that a larger proportion of patients are coming to the hospital from outside the Oxford region than ever before. Even so, in the most recent years the number of admissions has not increased. Secondly, it is essential to be certain that the improved results are indeed due to an advance in medical treatment and not to the use of emergency surgery.

It has now become exceptional for us to employ emergency colectomy in the treatment of an acute attack of ulcerative colitis. A few patients fail to respond to vigorous medical treatment or develop a complication, such as perforation of the colon, calling for surgical treatment, but they are a small proportion of the total. It is our experience that emergency colectomy should be avoided whenever possible in the treatment of an acute attack of ulcerative colitis and that the major use

of surgery lies in elective operation for the patient who has troublesome chronic disease or who develops some complication which cannot be managed by medical means alone.

There are therefore excellent reasons for the conclusion that the improved results obtained in recent years represent an improvement in medical management. It would be wrong, of course, to attribute the improvement entirely to the use of local corticosteroid therapy, especially as this form of treatment is usually combined with systemic corticosteroid therapy. However, the principles of general medical care now employed have been in force in Oxford for at least a decade, while systemic corticosteroid therapy was introduced for this disease four years before the recent improvement in results. The exact coincidence of the improvement with the introduction of local corticosteroid therapy must be taken as strong presumptive evidence that this form of treatment has been a valuable addition to medical management.

Summary

Local corticosteroid treatment to the colon by means of a rectal drip of hydrocortisone hemisuccinate solution has been used in most in-patients with severe attacks of ulcerative colitis treated in Oxford since 1956. It appears to be best to combine it with systemic corticosteroid therapy. The simultaneous application of certain general medical measures is of profound importance.

Representative case-histories are given to illustrate some of the responses obtained and some of the problems entailed in the use of this form of treatment.

A provisional scheme for the medical treatment of a severe uncomplicated attack of ulcerative colitis, incorporating local corticosteroid therapy as one of its main features, has been drawn up. The essential features are as follows:

General medical measures should be instituted without delay and consist in (a) correction of dehydration and electrolyte depletion, special attention being paid to potassium depletion; (b) blood transfusion, to be repeated as often as necessary; (c) maintenance of nutritional state by high-calorie high-protein diet; and (d) vitamin supplements.

Systemic corticosteroid therapy should normally be applied by oral administration—for example, prednisolone in an initial dose of 15 mg. q.d.s. four times a day—but, if there is vomiting, treatment should begin with intravenous prednisolone phosphate, 25 mg. twice daily.

Local corticosteroid therapy consists in a rectal drip of 100 mg. of hydrocortisone hemisuccinate sodium in saline, morning and evening. Retention of the evening drip is facilitated by preliminary intravenous injection of propantheline bromide, but overdosage with this agent must be avoided.

Sulphonamides and antibiotics occupy a secondary role. Broad-spectrum antibiotics should not normally be given by mouth in ulcerative colitis, but they can be used parenterally for a few days at the start of treatment if there is high fever.

Since the addition of local corticosteroid therapy to the medical treatment of ulcerative colitis the case-fatality rate for in-patients admitted to two Oxford hospitals has shown a sharp decrease, and is now about

1.5%, after having been steadily around 8% during the previous 12 years. The evidence that at least a part of this recent improvement in results is directly due to local corticosteroid treatment is discussed.

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THE RESEMBLANCE BETWEEN SARCROIDOSIS WITH HYPERCALCAEMIA AND HYPERPARATHYROIDISM

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Hypercalcaemia was first observed in sarcoidosis by Harrell and Fisher (1939); since then it has been recognized with increasing frequency, and probably occurs in at least 5% of cases (Longcope and Freiman, 1952). If left untreated it may lead to nephrocalcinosis, which is the commonest cause of renal failure in sarcoidosis (Citron, 1955). The metabolic abnormality in this condition closely resembles vitamin-D intoxication, with an increased absorption of calcium from the gut which is reversible by cortisone (Anderson *et al.*, 1954; Henneman *et al.*, 1956).

In this paper we report a case of sarcoidosis with hypercalcaemia in which there was an unusually close biochemical resemblance to hyperparathyroidism and discuss the differential diagnosis between the two conditions. This differentiation is important because excellent treatment is available for both; that it may also be difficult is shown by reports of at least 10 patients with sarcoidosis who have been subjected to operation because they were suspected of having a parathyroid adenoma (Albright and Reifstein, 1948; Westra and Visser, 1949; Howard *et al.*, 1949; Klatskin and Gordon, 1953; Anderson *et al.*, 1954; Davidson *et al.*, 1954; Scholz and Keating, 1956; Hauch and Fisher, 1957).

Case Report

A married man aged 48 was referred to one of us (P.E.) for investigation of splenomegaly and admitted to St. Stephen's Hospital on September 3, 1956. He complained

of tiredness and shortness of breath on exertion for one year and loss of appetite, loss of weight, constipation, lower abdominal pain, and increasing thirst and nocturnal frequency and polyuria for two months. At the age of 2 he had tuberculous cervical glands removed. In 1939 he first noticed pain and swelling in the ankles, and over a period of many years he developed slight outward bowing of the tibiae. He was given calciferol for three months for these symptoms in 1946, but he had not received vitamin D in any form after that time.

His wife had quiescent pulmonary tuberculosis. He had been an engineer for most of his life, but recently he had worked in the open air as a builder's labourer. His diet was adequate and had not recently altered, and he had never taken excessive amounts of milk or alkali.

On examination he had a ruddy complexion and did not look ill. There were numerous firm, moderately enlarged axillary, inguinal, and femoral lymph nodes, and the firm edges of both liver and spleen were palpable 2 in. (5 cm.) below the costal margins. The blood-pressure was 160/100, and the fundi were normal. There were bands of calcification in both corneae. The tibiae were bowed outwards and the knees separated by 1½ in. (3.8 cm.). The patient's weight was 130 lb. (59 kg.), height 63 in. (160 cm.) (crown to pubis 31½ in. (80 cm.), pubis to heels 31½ in.), and span 67 in. (170 cm.).

The urine contained a trace of protein and a few pus cells and granular casts; it was sterile, and culture for tubercle bacilli was negative. No Bence Jones protein was detected. The specific gravity range was 1006–1010. An intravenous pyelogram showed impaired concentration only. The haemoglobin was 10.5 g./100 ml. and E.S.R. 68 mm. in one hour (Westergren). Results of biochemical determinations on blood were: urea, 55 mg./100 ml.; calcium, 12.9 mg./100 ml.; inorganic phosphorus, 2.6 mg./100 ml.; alkaline phosphatase, 3.9 units (King-Armstrong); bilirubin, 0.5 mg./100 ml.; zinc sulphate turbidity, 16 units; albumin, 3.5 g./100 ml.; globulin 4.4 g./100 ml. Electrophoresis showed a slight increase in gamma-globulin. The Mantoux test was positive to 1/100. A skeletal survey was normal. X-ray examination of the chest showed increased striations in both lower zones. Biopsy of a right axillary gland showed histological appearances typical of sarcoidosis.

After four weeks in hospital with no treatment except bed rest the patient felt much better and had gained 4½ lb. (2 kg.) in weight; the serum calcium had fallen to 10.9 mg./100 ml. and the serum inorganic phosphorus to 2.2 mg./100 ml. However, the E.S.R. was still raised (67 mm. in one hour), the blood urea was 56 mg./100 ml., and maximum urine specific gravity 1012; a 24-hour specimen of urine contained 465 mg. of calcium in 960 ml. Because of the hypercalciuria and renal insufficiency he was started on cortisone 100 mg. daily despite the absence of symptoms and the normal serum calcium. The E.S.R. fell progressively, the haemoglobin increased to 13.5 g./100 ml., and he continued to gain weight. The serum calcium remained at the upper limit of normal (see Fig. 1).

After two weeks the 24-hour urine calcium was still 420 mg., and after one week on a low-calcium diet (less than 200 mg. daily) it was 326 mg. Despite the persistence of hypercalciuria there was a gradual improvement in renal function; after a month's treatment the maximum urine specific gravity had risen to 1018, the urine no longer contained any protein casts or pus cells, and there had been a gradual fall in blood urea. After three months' treatment the corneal calcification had almost disappeared. The dose of cortisone was reduced progressively to 37.5 mg. daily, but later had to be increased to 50 mg. daily. One year after treatment was started the 24-hour urine calcium excretion was 294 mg. and the patient was symptom-free; however, the serum calcium remained between 10.5 and 11.5 mg./100 ml. The affected lymph nodes gradually became smaller, but there was no significant change in the spleen or liver for two years. However, when the patient was last seen (October, 1959) his spleen was only just palpable.

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