Current Practice

Medical Management of Ulcerative Colitis

S. C. TRUELOVE,* M.D., F.R.C.P.

Brit. med. J., 1968, 2, 539-542

Ulcerative colitis is a chronic disease which characteristically presents as a series of attacks of bloody diarrhoea with complete freedom from symptoms between the attacks. This usual form is known as the *chronic intermittent* type of the disease. Some patients are never free from symptoms once the disease has developed, although the symptoms may vary in severity from time to time, and this represents the *chronic continuous* type. Some patients have one attack and never have another; but these are a small minority. The disease is associated with many complications, some of which occur during severe attacks while others appear during the course of chronic disease. Some of these complications are so dangerous that they influence our approach to management.

The ideal way to treat any disease is based on a thorough knowledge of the aetiology so that the root causes can be attacked directly. Unfortunately, our ignorance of the aetiology of ulcerative colitis is profound. This means that medical treatment has been forced to evolve by trial and error. A number of controlled therapeutic trials have been carried out in ulcerative colitis with the result that we understand fairly well the uses and limitations of the few methods of medical treatment which have been shown to influence the course of this disease.

At the present time medical management is based on two principles. Firstly, each attack should be treated without delay in the hope of bringing the patient rapidly into remission; this aim can usually be achieved except with severe attacks, in which it is not rare for medical treatment to fail. Secondly, steps should be taken to reduce the risk of subsequent relapse; some success is possible in this respect.

Attacks of ulcerative colitis vary greatly in severity. A mild attack usually takes the form of diarrhoea with only small amounts of blood present in the faeces and with little or no constitutional disturbance. At the other end of the scale a severe attack of ulcerative colitis may be a devastating illness in which there is profuse bloody diarrhoea accompanied by grave constitutional signs. The risk of death in a severe attack of ulcerative colitis is still substantial, so it is convenient to consider the medical management of such an attack as a separate item.

Management of a Severe Attack

Immediate admission to hospital is imperative. A presumptive diagnosis can be made by sigmoidoscopy, and treatment should be instituted without delay. Treatment consists of general medical measures to combat the effects of the bloody diarrhoea, specific therapeutic agents which help to shorten the attack, and some ancillary medical measures.

General Medical Measures

Correction of Dehydration and Electrolyte Depletion.—This usually requires the use of intravenous fluids. Particular attention should be paid to correcting potassium depletion, which is often pronounced when the diarrhoea is severe. The colon absorbs sodium but excretes an equivalent amount of potassium into its lumen. If the volume of fluid traversing the colon is large considerable quantities of potassium are carried away from the body by this mechanism. The standard glucose-saline fluid with potassium added at the rate of 1 or 2 g. per bottle is usually satisfactory, but repeated blood electrolyte estimations should be carried out so that electrolyte repletion can be tailored to the needs.

Correction of Anaemia.—Any appreciable degree of anaemia should be corrected by blood transfusion, which should be repeated as often as is necessary to keep the haemoglobin value close to normal. Patients with severe ulcerative colitis are losing large amounts of protein from the bowel. Blood transfusion helps to economize on the body stores of protein and thus diminishes the rate at which the patient wastes.

Maintenance of a Good State of Nutrition.—A high-calorie, high-protein diet should be given together with vitamin supplements. However, patients often suffer from anorexia and nausea during a severe attack, so that it may be impossible for them to eat adequately. Even if they eat well some wasting is likely to occur because of the heavy losses of protein from the bowel. The aim is to keep such wasting to a minimum while the attack is being checked. A period of parenteral feeding is sometimes advisable. Aminosol with fructose and alcohol is useful for this purpose. Each bottle represents 800 calories, so two bottles a day make a valuable contribution to nutritional needs.

Specific Agents Used to Check the Attack

Only two types of therapeutic agent have been shown to have a decisive influence in shortening an attack of ulcerative colitis. They are the corticosteroids and sulphasalazine (Salazopyrin). Neither of these is universally effective, but they increase the chance of the patient going into fairly rapid remission.

Corticosteroid Therapy.—Not long after the introduction of cortisone as a medical treatment this agent and also A.C.T.H. began to be used for the treatment of ulcerative colitis. A large-scale, multi-centre, controlled therapeutic trial was set up in six hospital regions of Britain. This showed that cortisone by mouth greatly increased the chance of a patient being in complete clinical remission within six weeks of starting medical treatment. Subsequently, another controlled therapeutic trial compared cortisone with A.C.T.H. in the treatment of a frank attack of ulcerative colitis. In first attacks of the disease there was little to choose between A.C.T.H. and cortisone. In relapses

* Nuffield Department of Clinical Medicine, the Radcliffe Infirmary, Oxford.

of established disease A.C.T.H. proved to be considerably more effective than cortisone in checking the attack, but at the price of more complications of treatment and of a higher relapse rate when treatment stopped.

Since that time the newer semisynthetic corticosteroids, such as prednisolone, have become the usual form in which corticosteroid therapy is applied. In the treatment of an acute attack of ulcerative colitis prednisolone by mouth in a dose of 40–60 mg. a day in divided doses is appropriate. If the patient suffers from nausea or vomiting corticosteroid therapy can be applied parenterally, using a water-soluble compound of hydrocortisone or of prednisolone. Other corticosteroids do not seem to have shown any decisive advantage over prednisolone. Triamcinolone seems to me to be conspicuously successful in checking an attack of ulcerative colitis, but it carries an appreciable risk of causing myopathy, and for this reason I usually hold it in reserve and employ it only if prednisolone is not effective.

Corticosteroid therapy carries the risk of some complications of treatment, which are too well known to require repetition. It is sufficient to say that the risks of side-effects of treatment are not great when the corticosteroids are being used for comparatively short periods under strict supervision in hospital. The main risk of corticosteroid therapy in the treatment of an acute attack of ulcerative colitis appears to me to be the danger that a physician may persist too long in the medical management of a patient who is failing to respond adequately, so that emergency colectomy is delayed to a time when it is a hazardous operation.

Local Corticosteroid Therapy.—Another way of applying corticosteroid therapy is locally within the colon. When treating an acute attack it is best to apply this in the form of a rectal drip making use of a blood transfusion giving set adapted to carry a soft rubber catheter at its end for actual insertion into the rectum. In making up the drip 100 mg. hydrocortisone hemisuccinate sodium is dissolved in about 120 ml. water or saline and is dripped into the rectum at the rate of about two drops a second. It is best to do this twice a day during the acute attack. At first there may be difficulty in the patient retaining the drip for any appreciable length of time. It is sometimes helpful to give 15–30 mg. of propantheline bromide intramuscularly shortly before the rectal drip in these circumstances; but, if so, no anticholinergic should be given in addition for fear of overdosage. In the treatment of an acute attack of ulcerative colitis it is best to combine systemic with local corticosteroid therapy and not to use either singly.

Instead of using a rectal drip of hydrocortisone, one can employ a commercial preparation of prednisolone 21-phosphate set up in solution in plastic bags fitted with a nozzle for insertion into the rectum; after the nozzle has been inserted the contents are transferred to the rectum by rolling up the bag like a tooth-paste tube. These plastic bags of corticosteroid solutions are sometimes known as Matts's bags, after the physician who devised this method of applying local corticosteroid treatment to the colon. They are specially convenient for outpatient use.

Sulphasalazine (Salazopyrin).—Salazopyrin is chemically salicylazosulphapyridine. Its mode of action is unknown. It is a yellow powder, formulated as large tablets, which is absorbed from the alimentary tract and is then deposited in connective tissue throughout the body, including that of the alimentary tract itself. In the tissues it slowly breaks down into free sulphapyridine and salicylate radicals.

A suitable dose for treating an acute attack is 1.0 g. four times a day. Some physicians have recommended larger doses such as 2.0–3.0 g. four times a day, but these larger doses give rise to a high incidence of side-effects and are usually inadvisable.

The commonest side-effects of sulphasalazine are nausea, vomiting, headache, and malaise. With doses of 2 g. four times a day about a quarter of the patients experience one or more of these side-effects. Even with a dose of 1.0 g. four times

a day these side-effects are not rare. Less common side-effects are arthritis, adenitis, and skin eruptions. Heinz-body anaemia may occur as a consequence of the sulphapyridine which is a component of the molecule. The most dangerous complication of treatment is agranulocytosis, but fortunately this is uncommon, though fatal cases have been recorded.

Some physicians like to treat an acute attack of ulcerative colitis initially with sulphasalazine, and then switch over to corticosteroid therapy if they do not get a good response. My personal approach is to use corticosteroid therapy and to employ sulphasalazine after the attack is over. I do this because a controlled therapeutic trial in which I took part showed that corticosteroid therapy was more effective than sulphasalazine in checking an attack. There is a distinct possibility that corticosteroids and sulphasalazine in combination may be better than either used alone, but there is no decisive evidence on this point.

Ancillary Medical Measures

Anticholinergics may be of some value in reducing abdominal pain and lessening the severity of the diarrhoea. Propantheline bromide (Probanthine) appears to be a suitable agent for this purpose in a dose of 15 mg. three or four times a day. It should not be given by mouth if it is being given parenterally to aid in the retention of a rectal drip. There is the possibility that large doses of anticholinergics may predispose to the dangerous complication of acute dilatation of the colon.

Antibiotics have only a minor role to play in the treatment of ulcerative colitis. Broad spectrum antibiotics given by mouth are best avoided as they are themselves liable to cause a dangerous enterocolitis. At the height of a severe attack a broad spectrum antibiotic such as tetracycline 250 mg. four times a day can be given in the intravenous infusion for a maximum period of five days.

Sedatives are useful in relieving some of the patient's anxiety and in increasing the chance of his being able to get a good night's sleep.

Medical Measures which are Best Avoided

It is best not to give broad spectrum antibiotics by mouth. As mentioned above they are themselves apt to provoke a dangerous enterocolitis. I have seen a number of patients with ulcerative colitis in remission put into an acute attack by the administration of a broad spectrum antibiotic for some other trivial disease.

The use of opium and of codeine in large quantities in the hope of checking the diarrhoea is usually futile. These agents are not very effective in ulcerative colitis, and they are sometimes given in such large quantities that they are apt to befuddle the patient and make the clinical picture obscure.

Oral iron is best avoided during the attack. It may cause an exacerbation of the diarrhoea, and in any event there is evidence that iron is poorly utilized by the bone marrow during an acute attack of ulcerative colitis. If there is anaemia the correct treatment is blood transfusion. When the attack is over it is wise to replenish the body stores of iron either by a course of parenteral iron or by a small oral dose over a period.

Intensive Medical Management

When a patient is admitted severely ill with an uncomplicated attack of ulcerative colitis it has become our practice at Oxford to give immediately a five-day intensive course of medical treatment. Nothing is given by mouth other than sips of water. An intravenous drip is maintained throughout the five-day

period, with saline or glucose saline containing potassium supplements and with Aminosol plus fructose and alcohol. Corticosteroids are given in the intravenous saline drip, usually as hydrocortisone hemisuccinate sodium 200–300 mg. a day or as prednisolone 21-phosphate 40–60 mg. a day. Tetracycline in a dose of 250 mg. four times a day is also given in the intravenous drip. A rectal drip of hydrocortisone hemisuccinate sodium 100 mg. is given morning and evening.

Rapid improvement frequently occurs with this regimen. Assuming that this is so, treatment is switched to oral administration at the end of the five-day period. If improvement does not occur, the question of emergency colectomy must be considered.

It is also our practice to resort to a five-day intensive course if a patient admitted in a moderately ill state shows no favourable response to oral treatment after about a week.

No controlled therapeutic trials have been made on this approach to the treatment of severe attacks of ulcerative colitis, but our clinical impression is that it is a useful way of obtaining rapid improvement in a large proportion of the patients. It is, of course, essential to satisfy oneself that the patient is not suffering from a dangerous complication requiring emergency surgery—of which perforation of the colon is the prime example—before embarking on this intensive medical therapy.

Management of the Less Severe Attacks

Moderately severe attacks are managed along the same lines as a severe attack, but not all the general medical measures will be required. For example, blood transfusion is often unnecessary, and dehydration and electrolyte depletion may not be pronounced.

Mild attacks can almost all be checked by treatment on an outpatient basis. The sooner treatment begins the better the prospect of aborting the attack. My personal preference is to use immediately a combination of oral and topical corticosteroids. The usual outpatient treatment consists in prednisolone 5 mg. four times a day by mouth and hydrocortisone hemisuccinate sodium 100 mg. by rectal drip nightly. This regimen is continued for a month even if there is a rapid response. Assuming that the patient is then symptom-free, the oral prednisolone is tailed off over the course of the next few weeks, but the rectal drip is continued for about three months. If the patient is not already on sulphasalazine, he is put on this in a maintenance dose of 0.5 g. four times a day, unless there are specific contraindications; for example, it may be known that he has previously developed unpleasant side-effects or complications with this drug.

If the patient does not show prompt improvement with the combined oral and local corticosteroid treatment he should be admitted without delay as an inpatient, so that treatment can be given with bigger doses along the lines already covered. By strictly limiting the dosage of corticosteroids when dealing with outpatients, we have found that this form of treatment can be used extensively with negligible risks.

One practical point is worth emphasis. Some physicians take up a "wait-and-see" attitude when a patient with ulcerative colitis develops a minor relapse. I regard this as mistaken, for some of these minor relapses will evolve into severe attacks unless active measures are taken to abort them. The risks of short-term corticosteroid therapy are trivial in relation to the risk of doing nothing and taking the chance of a severe attack developing. Consequently, every patient with ulcerative colitis should be encouraged to report without delay at the first signs of colitic symptoms. If sigmoidoscopy shows active inflammation a course of treatment should be given no matter how slight the symptoms. The vigorous application of this simple rule is one of the most important ways of making the best use of our present medical methods.

Long-term Treatment with Corticosteroids

As long-term treatment for ulcerative colitis corticosteroids are disappointing. A controlled therapeutic trial of cortisone in a dose of 50 mg. a day showed no influence whatsoever on the relapse rate. Similarly, a controlled therapeutic trial of prednisolone 5 mg. t.d.s. showed this to be totally ineffective in checking relapses. In other words, when corticosteroids are being reduced after the successful treatment of an attack there is no point in continuing with small doses in the hope of preventing relapse.

In larger doses corticosteroids will almost certainly hold in remission some patients who relapse soon after they are discontinued. Unfortunately, long-term treatment with corticosteroids carries pronounced risks of this form of therapy, such as hypertension, diabetes mellitus, and osteoporosis, which cannot be viewed lightly. In addition, if it is later decided to treat the patient by radical surgery the morbidity of the operation is increased.

Inevitably, a few patients get treated with prolonged corticosteroid therapy in full pharmacological doses. These are chiefly those patients who respond well to corticosteroid therapy but who relapse as soon as the dose is tailed off, and in whom the disease does not appear to be severe or extensive, so that one wishes to defer the question of radical surgery. In such cases the rule should be to tail off the corticosteroids from time to time to see if a natural remission has occurred.

Long-term Treatment with Sulphasalazine

One of the important findings in the treatment of ulcerative colitis has been the demonstration by a team in London of the value of sulphasalazine as long-term treatment for ulcerative colitis. They showed by a controlled trial that a maintenance dose of 0.5 g. four times a day sharply reduced the relapse rate during the trial period of one year. In this dosage sulphasalazine can be tolerated by most patients, and the risk of dangerous complications of therapy is small. It is now our usual practice to put patients on this treatment for at least a year after an attack has been checked by corticosteroids. Some patients who do not tolerate this dose manage well with a smaller one—for example, 0.5 g. twice a day—but a small number are intolerant even of this dose.

Psychotherapy

Some physicians regard ulcerative colitis as a psychosomatic disease in the most strict sense of the term—namely, as an illness in which an emotional disturbance is the primary event and the diseased organ is the somatic consequence. Other physicians regard psychological factors as important in the aetiology of the disease without going as far as regarding them as the sole cause. Others are sceptical of the role of psychological factors in causation and regard any emotional disturbances as by-products of a serious organic disease.

The view that psychological factors are of importance in causation rests upon two separate types of observation. On the one hand, a close temporal relationship can often be established between an emotional event and the onset of ulcerative colitis. The loss, real or imagined, of the patient's mother, or of some other person acting as a substitute mother, has sometimes been regarded as the most frequent precipitant of ulcerative colitis. On the other hand, personality profiles of patients with ulcerative colitis have been claimed to show that the patients do not represent a random sample of the general population, but are often excessively neat and tidy, shy, unaggressive, and inclined to bottle up their feelings rather than express them overtly.

It is natural that some of the physicians who regard psychological factors as of cardinal importance in the genesis of ulcerative colitis should also regard psychotherapy as equally

important in its treatment. Strong claims for the beneficial effects of this approach to management have been made by a few enthusiasts, but, in general, the physicians and surgeons with extensive experience of ulcerative colitis regard psychotherapy as a secondary approach to treatment.

This is not to underestimate the necessity of taking psychological factors into account when dealing with patients with ulcerative colitis. However sceptical one may be about the role of psychological factors in the initiation of the disease, there can be little doubt that once the disease is established an emotional disturbance may trigger off a relapse. In addition, the disease is one which, when it takes a severe form, is debilitating and disagreeable; patients so afflicted require much care as human beings. As this is an illness which is likely to react on other members of the family, attention to human and social factors should ideally extend outside the patient himself. The services of a psychiatrist and of a medical social worker are often highly advantageous, but it seems best to regard them as complementary to, and not a substitute for, ordinary medical and surgical care.

Immunosuppressive Drugs

During the past few years the occurrence of autoimmune reactions has been demonstrated in ulcerative colitis by a variety of techniques. These reactions are shown more readily in children with the disease than in adults. This discovery has caused some physicians to regard ulcerative colitis as one of the fashionable "autoimmune diseases" and has encouraged the trial of immunosuppressive drugs in its treatment.

Experience with this approach to treatment is still limited. An Australian physician appears to have been the first to employ it, and there are now two small Australian series in which the results obtained with either 6-mercaptopurine or azathioprine have been encouraging. Marrow depression was common, making close supervision essential, but no fatalities occurred. Small series have been reported from U.S.A., also with marrow depression as a common side-effect. A fatal case of marrow depression has been reported from Britain. My own experience with this form of treatment is small but encouraging.

At present immunosuppressive drugs cannot be recommended as suitable for general use in ulcerative colitis. There is a need for their precise evaluation in specialist medical centres.

(This article will be concluded next week with an account of dietary treatment, complications, and indications for surgery.)

B.M.J. Publications

The following are available from the Publishing Manager, B.M.A. House, Tavistock Square, London W.C.1. The prices include postage.

<i>Porphyria—a Royal Malady</i> ...	Price 13s. 6d.
<i>Is There an Alternative?</i> ...	Price 7s. 6d.
<i>Treatment of Common Skin Diseases</i> ...	Price 10s.
<i>Obstetrics in General Practice</i> ...	Price 32s. 6d.
<i>Child Care</i> ...	Price 32s. 6d.
<i>Charles Hastings and Worcester</i> ...	Price 3s. 6d.

TODAY'S DRUGS

With the help of expert contributors we print in this section notes on drugs in current use.

Penicillins and Cephalosporins

Benzyl penicillin (penicillin G), though the first of the major therapeutic antibiotics to be discovered, still retains a pre-eminent position. It is very highly active and rapidly so, because it kills bacteria instead of merely preventing their growth. Furthermore it is non-toxic even in enormous doses and it is cheap. Nevertheless it has limitations, many of which have been overcome in the modified forms of the antibiotic which have been introduced in the past eight years. All the newer penicillins are bactericidal, though they vary widely in other features of their behaviour. A description of these must be preceded by a short account of penicillin itself.

Benzyl Penicillin

Range of Activity

This can only be described in bacterial terms, with some remarks on what these mean clinically, since therapeutic success depends on the sensitivity of the causative organism rather than on the site or nature of the disease.

Streptococci.—Haemolytic streptococci of group A are always highly sensitive to penicillin, so septic infection of all kinds caused by these organisms can be treated successfully (infections of wounds and burns, septicaemia, puerperal fever, erysipelas, and scarlet fever). Another use in this connexion is the prophylaxis of rheumatic fever. *Streptococcus viridans*, chiefly of interest as a cause of endocarditis, varies in sensitivity: infection by one of a minority of more resistant strains

may not respond to penicillin alone. *Str. faecalis* is always more but by no means entirely resistant.

Pneumococci are also always fully sensitive. Penicillin should always succeed in pneumococcal pneumonia, and affords the best treatment for pneumococcal meningitis. Other antibiotics should not be given with the penicillin, since they may interfere with its action.

Staphylococci were once almost all sensitive, but resistant strains have become increasingly common. They owe this resistance to their action of forming penicillinase, an enzyme which destroys penicillin. Some of the newer penicillins are resistant to the enzyme and therefore effective even against such organisms. They are therefore preferable for the initial treatment of severe staphylococcal infections (extensive carbuncles, wound infections, osteomyelitis, etc.); if the infecting strain is later found to be sensitive to benzyl penicillin this should be substituted.

Gonococci and Meningococci.—All gonococci used to be highly sensitive to penicillin, but moderately resistant strains are now becoming fairly common. So far no resistance has been seen in meningococci, and, since these organisms are now sometimes sulphonamide-resistant, penicillin is now to be preferred for treating cerebrospinal fever.

Treponema pallidum.—The spirochaete of syphilis is highly penicillin-sensitive, and penicillin has replaced organic arsenicals in the treatment of this disease.

Among other sensitive species are *Clostridia* (but fairly large doses are advisable for the prevention of gas gangrene), the anthrax bacillus, *Actinomyces israeli*, *Erysipelothrix rhusiopathiae*, and Vincent's organisms. Most Gram-negative bacilli are resistant, but *Haemophilus influenzae*, *Proteus mirabilis*, and even some strains of *Escherichia coli* are sensitive to attainable concentrations.