THE MEDICAL TREATMENT OF ULCERATIVE COLITIS

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THE medical management of ulcerative colitis is a difficult and diffuse topic. The assessment of any measure is a complex task in a disease which varies greatly in severity and extent not only from patient to patient but in the same individual from attack to attack. The physician possesses a variety of drugs capable of inducing remission in perhaps half the cases treated but has no reliable way of predicting the therapeutic outcome in a particular instance.

In treating the colitic patient, the physician is faced with three duties, firstly in terminating the acute attack or exacerbation of colitis as quickly as possible, secondly in attempting to prevent recurrent attacks by some form of maintenance treatment, and thirdly, realizing that his therapeutic measures often fail, in knowing when to call in the surgeon. He should constantly be asking himself whether his efforts are prejudicing the outcome of surgery or the long-term well being of the patient.

Experience of treating over 300 colitic patients attending hospitals in Leeds and York over the last 13 years has given some insight into the common problems of the management of these patients.

Termination of an Acute Colitic Attack or Exacerbation

General Principles

In managing an acute attack of colitis the following general principles are adopted:

(1) *Rest of body, mind and gastrointestinal tract is attempted.*

(2) *Diet.* It is first necessary to maintain fluid and electrolyte balance, losses particularly of potassium being excessive. It follows, in acute disease, that frequent biochemical estimations of serum electrolyte levels are necessary and that intravenous replacement is frequently necessary.

A high calorie, high protein low residue diet of 2,000 to 3,000 calories is essential with vitamin supplements of folic acid, vitamin B and even vitamin B₁₂ given if necessary parenterally. I have had little experience of intravenous parenteral feeding (Wilkinson, 1961) but have found it a little disappointing in debilitated post-operative

patients, nor have I found anabolic agents helpful in wasted patients.

Interest in dietary treatment has been reawakened recently by Truelove's observations on the role of milk in causing and exacerbating colitic attacks. Truelove (1961) first reported five patients in whom the introduction of milk containing foods into their diets repeatedly induced relapses of their colitis whereas they remained well if maintained on a milk-free low residue diet. He supported his contention on the harmful effects of milk by showing, in conjunction with Dr. Keith Taylor, that the blood of a significantly greater proportion of colitic patients contained a high titre of antibodies to milk proteins than did the blood of matched control patients. Thus, 43% of 75 colitic patients showed titres of antibodies to milk proteins exceeding 1/20,000 as compared with 8% of controls (Taylor and Truelove, 1961). The presence of antibodies in colitic patients could not be related to age, sex, extent of disease, previous steroid therapy or activity of the disease but it appeared that high titres were only observed in patients with longstanding chronic disease. Colitic patients appeared to become sensitized to milk by bottle-feeding in the first month of life as a significantly greater proportion of colitic patients had been weaned early (Acheson and Truelove, 1961).

Milk allergy may then be an important factor in the causation of colitis and the exclusion of milk products from the diet of the colitic patient a valuable therapeutic measure. It might be possible, in the future, to screen colitic patients by examination of their blood for milk antibodies, enforcing a milk free diet in the proportion showing high titres of antibodies. The results of further work on this interesting new aspect of therapy in colitis will be eagerly awaited.

(3) *Symptomatic drugs.* It may be necessary, to control diarrhoea, to use a variety of gastrointestinal sedatives and astringents such as kaolin, codeine and morphia derivatives. Such drugs are not without risk when administered to patients

with acute colonic dilatation. Antispasmodics, such as belladonal retard and propantheline bromide, are useful in controlling the colicky pain which is such a disability to the patient. Sedatives such as phenobarbitone and amylobarbitone are used in the anxious subject while methods to combat anaemia are vigorously applied. Ferrous fumarate orally is best tolerated by the colitic patient but some patients are upset by any type of iron by mouth when parenteral therapy is advised.

(4) *Blood transfusion.* Transfusions of whole blood repeated as often as is necessary are of great importance and value, being a source both of haemoglobin and of nitrogen to help replete the falling protein stores of the body.

(5) *Sulphonamides.* Sulphonamides in the form of sulphaguanidine, sulphasuxidine and phthalylsulphathiazole, for so long the mainstay of treatment in colitis, have now largely been replaced by sulphasalazine but are sometimes used with oral steroids where they tend to reduce the occurrence of suppurative perianal complications.

(6) *Antibiotics.* Antibiotics should be used with caution in the colitic patient as they may both cause diarrhoea themselves and predispose to secondary infection with monilial organisms. However, used discriminately in the febrile toxic patient they can be of considerable value provided they are given in short courses and administered parenterally. I have found neomycin, streptomycin, tetracycline and chloramphenicol of most value. Absorption from the denuded ulcerated colon may be abnormally great and a few cases of renal tubular damage have followed treatment of colitis with the supposed non-absorbable drug neomycin. The value of antibiotics in colitis is therefore limited but they may be of value in the acute attack or as a pre-operative measure.

(7) *Psychotherapy.* There are many colitic patients who benefit from psychotherapy but others in whom even taking a detailed psychiatric history may prove harmful. The dangerous potentialities of the disease must never be forgotten and if psychotherapy is to be practised it should be used in conjunction with other methods of medical treatment by a physician capable of recognizing and treating any complications that may arise. It is best applied therefore by the physician or gastroenterologist personally treating the patient and there is little place for the specialized psychotherapist. Thus, Paulley (1950) was able to cure or control 31 of 42 patients treated; Grace, Pinsky and Wolff (1954) obtained good results in 11 of 19 patients treated, while Groen and Bastiaans improved or cured 18 of 33 patients treated. I can do no better than to quote from Dr. Groen's common-sense appraisal of the

role of psychotherapy in colitis who states (Groen, 1961):

'In general it is not the psychiatrist but the gastroenterologist, the physician or the family doctor who, according to our experience should treat his patient with a simple form of psychotherapy consisting of giving the patient time, kindness, tangible signs of understanding and support in his conflicts with his family, with his employers or even with other doctors and nurses. In short, it is the same approach of sympathetic listening and making things easier for the patient that is used by any good family doctor in his daily work'. Groen wonders 'How much of the beneficial effects obtained by drugs were actually achieved by the application of the drug which every doctor gives to a patient he is interested in, namely, himself'.

Drugs Capable of Terminating the Acute Colitic Episode

Two groups of drugs have been shown on critical appraisal to be capable of terminating the acute colitic attack in a significant proportion of patients treated, namely sulphasalazine, and the steroid group of drugs administered systemically or topically.

Sulphasalazine

Sulphasalazine or 'salazopyrin', or 'asulfidine', was introduced in the treatment of colitis by Professor Nanna Svartz in Sweden in 1940. As an azo-compound of salicylic acid and sulphapyridine, the drug has an affinity for connective tissue and has proved of value in both rheumatoid arthritis and ulcerative colitis. It is usually employed in a dosage of between 4 and 8 gm. daily, its use being limited by the development of side effects in about one in six patients treated. Side effects induced include nausea, indigestion, headache, drowsiness, drug fever, skin rashes and blood dyscrasias (Svartz, 1961).

The immediate results obtained by various workers by treating ulcerative colitis with sulphasalazine are detailed in Table 1.

It will be seen that in the 809 patients reviewed good results were obtained in between one-half and three-quarters of those treated, the incidence of side effects varying between 16% and 22%. Sulphasalazine, however, proved less effective than combined topical and systemic steroid therapy when critically assessed recently in a careful controlled trial in 116 patients (Draper, Truelove and Watkinson, 1962). Thus clinical remissions followed the administration of steroids in 65% as compared with 50% induced by sulphasalazine while 79% of steroid treated cases showed mucosal improvement as compared with 43% of those

TABLE I

IMMEDIATE RESULTS OF TREATMENT AND THE FREQUENCY OF DRUG INTOLERANCE IN ACUTE COLITIC EPISODES IN 809 PATIENTS TREATED IN SWEDEN, AMERICA AND ENGLAND. REMISSIONS WERE INDUCED IN FROM ONE-HALF TO THREE-QUARTERS OF PATIENTS RECEIVING THE DRUG

	Patients Treated	Percentage Recovered or Much Improved	Percentage Showing Drug Intolerance
Svartz (1956, 1961)	439	77%	'Few'
Morrison (1953) ..	60	70%	21%
Moertel and Bergen (1959) ..	183	64%	17%
Watkinson (1961b) ..	69	47%	16%
Draper, Truelove and Watkinson (1962)	58	50%	22%

treated with sulphasalazine. Lennard-Jones, Longmore, Newell, Wilson and Jones (1960) were always able to demonstrate an advantage for oral prednisone over sulphasalazine when they compared the two drugs in two groups of 20 patients. However, sulphasalazine emerges as a useful drug in the treatment of colitis with at least even chances of success in the immediate termination of the acute colitic attack. Salazodimidine is a similar compound of greater potency for which a reduced frequency of side effects is claimed. This drug is still under evaluation; in my limited experience nine of 20 treated patients showed remissions.

Systemic Steroid Treatment

A succession of careful controlled trials have established that systemic steroids are capable of terminating acute exacerbations of ulcerative colitis. Notable amongst these were the trials organized by the Medical Research Council between 1950 and 1958, in which I had the pleasure of participating, which I will now briefly detail. It was first established that the 41% remission rate induced in 109 patients treated with daily 100 mg. doses of cortisone was significantly better than the 16% remission rate observed in 101 patients receiving inert tablets. Patients with first attacks of colitis did better than relapsing cases both immediately and in long-term follow-up and at all grades of severity the cortisone-treated group recovered more completely and more frequently than the controls.

When the response of 85 colitic patients treated with a larger dose of cortisone of 200 mg. daily was compared with a similar number receiving 80 units of corticotrophin daily, corticotrophin was shown to possess a significant advantage, remission being induced in three in every five patients receiving it as compared with two in every five

patients receiving cortisone. In this instance the response of first attacks to both agents was comparable, 50% and 42% respectively, but chronic colitic patients treated with corticotrophin showed a significant advantage over those treated with cortisone, remissions occurring in 70% and 37% in each instance (Truelove and Witts, 1955, 1959).

It appeared that results marginally better might be obtained by employing larger doses of corticotrophin, Spencer, Kirsner, Mlynaryk, Reed and Palmer (1962) claiming a remission rate of 68% in 340 patients treated while Lennard-Jones and Vivian (1961) have suggested that in severe fulminating disease remissions may be induced by a dosage of 120 units of ACTH which will not respond to 80 units—however this has not been my experience and it appeared from the M.R.C. trials that dosage did not modify the therapeutic outcome.

The results obtained by more modern steroid compounds have been less well appraised, good results being claimed for prednisone and triamcinolone in comparable dosage (Lennard-Jones and others, 1960). My own experience of prednisone has been similar to that of Truelove (1960), remissions occurring in about a third of those patients treated.

Cortisone, I think, should be the drug of choice in the average acute colitic attack, corticotrophin being reserved for fulminating attacks and prednisone for milder attacks and for out-patient usage.

What are the costs of steroid therapy? In the M.R.C. trials the exhibition of cortisone halved the early mortality and recourse to surgery, the mortality in the cortisone treated group being 4.6% and for those in the control group 10.9%, 14.9% of the control group requiring early surgery as against 8.3% in those receiving steroids. Perforation must be accepted as a hazard in between 2% and 4% of acute fulminating colitic attacks and no evidence was accumulated to attribute this complication to steroid therapy (Truelove and Witts, 1955; Goldgraber, Kirsner and Palmer, 1957). It appeared that suppurative perianal complications were more common in both cortisone treated groups in each trial making it desirable to combine steroid therapy with a sulphonamide or with sulphasalazine. Complications of steroid therapy itself in the way of facial mooning, electrolyte disturbances and mental illness were more apparent with treatment with corticotrophin constituting some disadvantage to its use.

Topical Steroid Treatment

Prompted by favourable results obtained by the

TABLE 2

CLINICAL OUTCOME IN 114 PATIENTS WITH FULMINATING ACUTE ATTACKS OF COLITIS. THE HIGH MORTALITY AND FREQUENCY TO RECOURSE TO SURGERY WILL BE NOTED

CLINICAL OUTCOME IN ACUTE FULMINATING COLITIS

	No. of Patients	Clinical Remission	Total Deaths	Early Surgery	Operative Deaths
Demole (1961)	24	?	13 (54%)	?	?
Goulston, Rankin, Boden and Morrow (1960) ..	22	5 (24%)	11 (50%)	15 (68%)	9 (60%)
Watkinson (1961)	36	14 (40%)	6 (17%)	8 (23%)	3 (37%)
Lennard-Jones and Vivian (1960)	32	4 (13%)	9 (28%)	26 (81%)	8 (35%)

use of topical hydrocortisone in skin, eye and joint disease, Truelove in 1955 first advocated its topical use in ulcerative colitis. Subsequently a number of controlled trials have confirmed its value (Truelove, 1955, 1958; Watkinson, 1958, 1961; Matts, 1960; Matts and Gaskell, 1961) alone or in conjunction with oral prednisone (Truelove, 1960). Truelove (1961) and Matts (1962) have advocated topical steroids in acute fulminating disease but its main indication is in patients with colitis of mild to moderate severity with predominantly distal involvement.

Steroids can be administered topically as a rectal drip or by a plastic enema bag containing 100 mg. of hydrocortisone hemisuccinate sodium, 20 mg. of prednisolone-21-phosphate or, most recently, 2.5 to 10 mg. of betamethasone. The retention of the rectal infusion can be facilitated by the preliminary administration of an antispasmodic such as propantheline bromide. Truelove in the course of various trials conducted between 1958 and 1960 has reported remission in between 69% and 75% of colitic patients treated with hydrocortisone, while Matts (1961) achieved a remission rate of 88% in 100 patients treated with prednisolone. The methods have fared less well in my hands, remissions occurring in 52% of those treated by topical methods. Suppositories containing 5 mg. of prednisolone proved helpful in patients with hæmorrhagic proctocolitis.

One of the advantages of topical steroid therapy has been the fact that the compound is not absorbed and side effects were not observed. When betamethasone, a steroid 50 times more potent than hydrocortisone, was used for topical treatment an excellent remission rate was obtained when doses of between 5 and 10 mg. were employed but side effects in the way of face mooning and skin acne developed in all patients. Reduction of dosage to 4 mg. halved the frequency of side effects but proved only half as effective in producing clinical remissions (Matts, 1962). It appears therefore that these more potent steroids will therefore have to be used with greater caution topically than heretofore.

Combined Topical and Systemic Steroid Treatment

Truelove in 1960 felt he had achieved the best results to date in treating colitic patients by combining topical treatment, by a rectal drip containing 100 mg. of hydrocortisone, with 20 mg. of prednisone by mouth. Recently, Draper, Truelove and Watkinson compared this combined treatment with salazopyrin by a controlled trial employing sequential analysis. Sixty-five per cent. of 58 patients treated with steroids developed clinical remissions and 79% showed a significant lessening of mucosal inflammation, results which were significantly better than those achieved with sulphasalazine (Draper, Truelove and Watkinson, 1962).

Topical treatment therefore, alone or with oral prednisone, emerges as a valuable measure in colitis of any type or severity but is particularly of value in colitis of moderate severity and predominantly distal involvement.

The Management of the Acute Fulminating Attack

Acute fulminating colitis is a serious disease, carrying a high mortality, to which the gloomy experiences of many authors attest (Table 2). Here it emerges that mortalities varying between 17% and 54% are reported, that emergency surgery is frequently required and that operation in a debilitated patient of this type carries an alarming mortality varying between 35% and 60%. The poor results of medical treatment made Goulston and others (1960) advocate the routine use of surgery in this type of patient (Table 2).

I would agree with them that cases of this type should be managed jointly from the outset by physician and surgeon. All available methods of medical treatment should be given to the patient. Vigorous attempts should be made to keep pace with losses of hæmoglobin, fluid, electrolytes and protein. A blood culture should be performed as an *E.coli* septicæmia is not uncommon in this type of case. Occasionally resolution of emotional

factors precipitating the attack may be attempted. Corticotrophin, in a dosage of 80 to 120 units daily, is given together with 200 mg. of cortisone by mouth for four to seven days, while the effects of the corticotrophin become apparent. Salazopyrin is given by mouth in full dosage and if rectal hydrocortisone can be retained, this is also given nightly.

This treatment should be continued for up to two weeks, the possibility of operation being constantly reviewed. Surgery is indicated if no dramatic improvement follows medical treatment for seven to ten days, if the patient's condition deteriorates at any time under treatment and if a relapse follows an initial improvement induced by corticotrophin.

Colectomy is the treatment of choice though there may be a place for ileostomy alone when at laparotomy the patient's general condition appears desperate or inspection suggests that the colon might perforate when mobilized.

Maintenance Treatment

Having controlled the acute colitic attack, the physician now attempts to prevent relapse by maintenance treatment, about which little controlled information is available. Many patients stay well if treated with sulphasalazine for long periods, Svartz (1956) claiming that three-quarters of 119 patients followed for five years were still in remission, while Moertal and Bergen (1959) reported that 57% of 123 patients receiving sulphasalazine were well a year later. In my hands maintenance treatment with sulphasalazine prevented relapse in 31 of 57 patients treated for periods varying between six months and ten years.

In attempting to prevent relapse by steroid therapy one may follow two courses: either to give doses of steroids sufficiently large to suppress the disease, accepting a formidable array of side effects, a procedure followed by Kirsner and Palmer in Chicago, or, as most British gastroenterologists have done, attempt control on a small maintenance dose of steroids accepting an appreciable relapse rate and recourse to surgery but avoiding steroid complications.

By employing daily maintenance doses of ACTH of the order of 20 to 80 units or of prednisone in a dose of 15 to 30 mg., the workers at the Chicago clinic were able to maintain 38% of their 340 patients in remission for long periods while a further 28% remained improved. Surgery was infrequently required and a low medical mortality of around 7% achieved. However, side effects of varying severity developed in 85% of those treated. These included psychological upsets in 16%, diabetes or glycosuria in 12%, serious

electrolyte upsets in 12% and osteoporosis in 4%. Four patients developed peptic ulcer and seven melæna while nine deaths could be attributed to steroid therapy. The authors feel that control of this dreaded disease is a reasonable reward for the side effects induced (Spencer and others, 1962).

When the effect of a 50 mg. maintenance dose of steroids was assessed by a controlled trial (Truelove and Witts, 1959) no difference in relapse rates could be shown in two groups of patients receiving potent and inert tablets for one year, remissions being maintained in about half the patients in each group. Those who had received corticotrophin initially seemed to relapse earlier and more frequently than those treated initially with cortisone. My own experience has been similar, for of 65 patients maintained on small doses of steroids over ten years there have been 30 medical failures while 20 had required surgery. In the remainder gratifying remissions are maintained.

Indications for Operation

Colitic patients are best followed up at a combined medical and surgical clinic where in discussion with the surgeon the possibility of operation can be constantly reviewed.

Operation may be required in acute fulminating colitis if perforation, severe hæmorrhage or progressive toxic dilatation occurs. If under intensive medical treatment the patient's condition continues to deteriorate or a relapse occurs after an initial improvement surgery should be undertaken.

In chronic ulcerative colitis operation is advised when the condition fails to respond to medical treatment and is inducing invalidism, repeated hospitalization and loss of work, or if irreversible structural damage to the colon has developed by stricture formation, pseudopolyposis, or if carcinoma is suspected. The presence of recurrent or intractable para-rectal disease with fistulæ and rectovaginal abscess is a frequent indication. Occasionally uncontrollable systemic complications, such as recurrent iritis or arthritis, may occasion operation. Children with the disease present particular problems as often their growth and endocrine maturation are retarded while their age does not protect them from malignant change in the colon (Rosenqvist, Ohrling, Lagercrantz and Edling, 1959). For these reasons despite their tender years operation may have to be enforced.

Some surgeons have argued that previous steroid therapy adversely affects the outcome of surgery in the colitic patients by predisposing to hypotensive vascular collapse and rendering the bowel more friable and difficult to handle at operation (Brooke, 1952). Our experience in Leeds has not supported this contention though

the data is difficult to appraise. In 100 patients Professor J. C. Goligher performed colectomy as an elective procedure during a phase of quiescence of the disease. The operative mortality was greater in the 63 patients who had not been given steroids than in the 37 who had, namely three deaths as compared with no deaths, nor was there any difference in their post-operative course. In 41 patients operation was undertaken as an emergency or life-saving procedure for a fulminating exacerbation of the colitis. There were eight deaths in 28 patients who had been given steroids and the incidence of pre-operative perforation and post-operative complications was appreciably greater than in 13 patients who had not been given the drug. However, the data could not be easily compared in that the steroid treated group contained most of the severely ill patients. Ewart and Lennard-Jones (1960) encountered similar difficulties when they analysed the effect of corticosteroids on the outcome of surgery in 131 patients undergoing colectomy at St. Mark's Hospital, London, between 1951 and 1959. While the mortality and post-operative morbidity were greater in urgent operations for fulminating disease, again far more of these patients were severely ill than among those who had not received cortisone. They felt that cortisone had probably no effect on the outcome of operation. In any

patient who has ever received steroids cortisone should be given throughout the operative and post-operative period and used liberally intravenously if post-operative hypotensive collapse occurs.

Summary

The medical treatment of ulcerative colitis has been detailed based on the experience of treating 300 patients over the last 13 years.

Rest, appropriate diet, symptomatic drugs and blood transfusion are frequently required in acute exacerbations of the disease. Antibiotics used parenterally for short periods are useful in the febrile toxic case while common sense psychotherapy by the attending physician is frequently helpful.

Two drugs are capable of terminating acute colitic attacks, namely sulphasalazine and steroids given systemically or topically. The results of the short and long-term usage are detailed.

The indications for colectomy are detailed and the effect of previous corticosteroid therapy on the outcome of surgery discussed.

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