Medical treatment of ulcerative colitis

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'The application of existing knowledge to the practical management of . . . ulcerative colitis is possible only if physicians and surgeons are willing to work together, preferably leaving the patient in one ward.'

F. Avery Jones (1952)

Medical treatment of ulcerative colitis in the period 1934-1949 sorely tested the patience and optimism of both patient and doctor. Some principles remain as important today as they were then, a diet generous in protein and calories, mineral and iron replacement, and blood transfusion. Other aspects sound unfamiliar such as prolonged bed rest and a strict low-residue diet. Two advances around 1950 promised new hope and Avery Jones, with his unerring instinct for progress, marked them both. In 1950, the first encouraging results were described of treatment with the newly available hormones, cortisone and corticotrophin. Around the same time, Bryan Brooke was perfecting his new technique for construction of an ileostomy by manually everting the mucosa to bring it into apposition with skin.

Physicians and surgeons long frustrated by their relative ineffectiveness in treatment sensed success and joined forces with enthusiasm. Avery Jones invited his surgical colleagues at the Central Middlesex Hospital to treat colitis in medical wards. Conversely, in 1950, the surgeons at St Mark's Hospital invited him to join them as Consulting Gastroenterologist and introduce new medical treatments there.

The advent of corticosteroids came at just the time when the concept of the controlled therapeutic trial was gaining force. By 1952, there were many anecdotal reports of improvement in colitis with cortisone and corticotrophin but, to quote Truelove and Witts (1954), 'in none . . . was there a formal trial in which some patients received therapy and some did not'. To remedy this uncertainty, these two had begun in 1952 a double-blind trial of cortisone against a dummy tablet 'to decide the issue'. They

invited Avery Jones and Richard Doll, among others, to collaborate and the result was a classic of medical literature (Truelove and Witts, 1955) which proved the efficacy of cortisone beyond all doubt. Stimulated by this success, the same team, slightly enlarged, went on to compare the effectiveness of cortisone and corticotrophin in acute disease and to test the possible use of cortisone in prolonging remission (Truelove and Witts, 1959).

Since many patients with colitis can be treated outside hospital, Avery Jones started a special clinic at St Mark's Hospital for their care from which the results of a series of controlled therapeutic trials in out-patients have been reported. The following account of current treatment in colitis is based on such trials performed at various centres and on knowledge gained by close collaboration with surgical colleagues. Avery Jones, by his initiative and leadership, has greatly affected the treatment of colitis. Many sufferers have cause individually to be grateful for his concern and care; as a group they can thank him for his contribution to knowledge about treatment of their disease.

The role of the doctor

A socially unacceptable illness is far more difficult to bear than one for which there is general sympathy. Because the symptoms are taboo and have to be hidden, colitis induces a sense of isolation. The doctor needs to understand the patient's nagging fear of incontinence in a public place, and the exasperating unpredictability of an illness which can apparently be cured at one time but then suddenly return to wreck the family holiday. The patient not only conceals or minimises the symptoms, but also hides fears which need sympathetic discussion; the ability to support a family, pregnancy, side effects of drugs, the 'need to wear a bag', cancer. It is a frustrating illness for patient and doctor alike because there is so much ignorance and uncertainty as to its cause and the best course of action. The care of patients with

colitis demands from the doctor, knowledge, availability, ingenuity, understanding and emotional resource.

The role of other patients

Patients with colitis can help one another not only because they have to deal with the same difficulties, but also because they can combine forces to educate themselves and inform doctors and the public about their disease and its problems. A Patients' Association therefore meets a real need. The Ileostomy Association fulfills a similar role and its members can greatly encourage those about to undergo the operation, or those who have recently needed a stoma, not so much by words, as by their appearance and manner which show that they are leading a full healthy life.

Adverse factors

Bowel infections often lead to a relapse of colitis and patients are well advised to avoid holidays in places where travellers' diarrhoea is common (Isgar, Harman and Whorwell, 1983). Prophylactic treatment with co-trimoxazole 2 tablets daily, seems well justified for a colitic who needs to travel in such areas (Dupont *et al.*, 1983). Similarly, antibiotics can cause diarrhoea, and even a form of mucosal inflammation, in normal subjects and their use needs especial care in a patient with colitis (Isgar *et al.*, 1983). There is also evidence that non-steroidal anti-inflammatory drugs may be associated with relapse (Rampton and Sladen, 1981; Rampton, McNeil and Sarnar, 1983) or that some drugs such as mefenamic acid, may cause colitis (Hall *et al.*, 1983; Phillips *et al.*, 1983). Even sulphasalazine seems to aggravate or cause colitis in a few patients (Schwartz *et al.*, 1982; Adler, 1982).

Although it is unlikely that colitis is due to psychological stress, clinical experience suggests that emotional factors can aggravate the disease.

Diet

There is no good evidence that the traditional low residue diet helps; conversely, there is little evidence that a high fibre intake is beneficial (Davies and Rhodes, 1978) except in patients with distal colitis and a tendency to constipation. Milk aggravates diarrhoea in a person unable to digest lactose but most patients in this country appear to take milk in normal quantities without ill-effect. Despite much popular writing, there is still no objective support for suggestions that sensitivity to particular food causes or aggravates ulcerative colitis. Even complete exclusion of food by mouth, using parenteral nutrition instead, does not appear to influence severe, acute colitis (Dickinson *et al.*, 1980).

Replacement of losses

All patients with colitis, even the mild distal forms, tend to lose iron so the haemoglobin level should be checked regularly. An oral iron supplement sometimes seems to make the symptoms of colitis worse, in which case parenteral administration is indicated.

Patients with severe diarrhoea, fever and anorexia rapidly become malnourished with obvious loss of muscle bulk and low serum albumin due to catabolism, exudation and poor intake. Faced with a severely ill patient, the clinician must recognise that only fluid, electrolytes, blood and serum protein can be replaced by infusion over hours or days. Tissue breakdown can be halted by an adequate calorie and protein intake, but replacement of lost tissue is a slow process limited by the synthetic rate of protein. Unless special care is taken, nutrition is almost always inadequate in an ill patient. The diet can be supplemented by drinks of a balanced liquid feed, of such a feed can be infused through a fine-bore nasogastric tube, or in the most severely ill patients, especially before and after operation, parenteral nutrition may be necessary (Hill *et al.*, 1977. See also Silk, 1984, this issue).

Drugs

Corticotrophin

Corticotrophin is undoubtedly effective in acute colitis but its use is controversial. A comparison of cortisone, 200 mg daily by mouth, with corticotrophin, 80 units of gel daily, showed that corticotrophin was the more effective but its superiority was observed mainly among patients treated for a relapse of disease (Truelove and Witts, 1959). It is possible that the blood cortisol levels achieved with these two regimes were different and three subsequent trials have measured cortisol levels. Two relatively small trials showed little difference in the therapeutic results with hydrocortisone infusion, 300 or 400 mg daily, and corticotrophin infusion (40 units daily) or injection (80 units daily) (Kaplan *et al.*, 1975; Powell-Tuck, Buckell and Lennard-Jones, 1977). In both trials, hydrocortisone tended to give better therapeutic results in patients who had previously received corticosteroid therapy. The most recent and larger comparison of the two drugs (Meyers *et al.*, 1983), both given by intravenous infusion over 24 hours, showed that corticotrophin 120 units was more effective than hydrocortisone 300 mg in patients previously untreated with corticosteroids, and less effective after prior steroid treatment. Serum steroid levels tended to be highest after ACTH in both groups of patients, and highest of all after ACTH in patients previously untreated with corticosteroids. Most physicians in this country use hydrocortisone or

prednisolone infusion rather than corticotrophin because a standard regime can be given which is independent of adrenal responsiveness.

Glucocorticoids

a) *Intravenous administration.* Prednisolone appears preferable to hydrocortisone because of the latter's greater tendency to sodium retention but the two drugs have not been directly compared. A dose of 60 mg daily (as the water soluble prednisolone 21-phosphate) is generally used as a reasonable compromise between therapeutic effectiveness and unwanted side effects. It has not been established that this is the optimum dose, nor whether the drug should be given as a single daily bolus to produce a transitory very high peak blood level, as a bolus two or three times daily, or as a continuous infusion to produce a lower steady blood level (Berghouse *et al.*, 1982).

Intravenous corticosteroid therapy is indicated in severe acute colitis (Truelove *et al.*, 1978) provided that an abdominal X-ray has excluded dilation of the colon and there is no other contra-indication to use of the drug. Response, if it is going to occur, is usually prompt. Some physicians (Truelove *et al.*, 1978) advise surgical treatment if there is no marked improvement within 5 days, others continue treatment for a longer period if the outcome is doubtful but, even so, failure to respond is usually obvious within 1–2 weeks.

b) *Oral administration.* The commonest indication for treatment with a glucocorticoid by mouth is an acute attack of moderate severity with some systemic effects such as anorexia, fever, erythema nodosum or arthritis. In the absence of systemic symptoms, an oral drug may be needed if diarrhoea or rectal urgency is so severe that topical preparations cannot be retained, or if distal colitis is very troublesome and unresponsive to local treatments.

A comparative trial of three doses of prednisone suggested that 40 mg daily is the optimum starting dose (Baron *et al.*, 1962a). Prednisolone is equally efficacious whether this dose is all taken at breakfast or is divided into 4 doses spread through the day (Powell-Tuck, Bown and Lennard-Jones, 1978).

Provided there is a response to the drug, and this is usually evident within a few days, the dose can be reduced to 30 mg daily in the second week, and thereafter progressively reduced until the drug is stopped after a total course of 4–8 weeks. If there is no response within 2 weeks of starting oral prednisolone as an out-patient, then a change in treatment is

indicated, often admission to hospital for intravenous or intensive topical administration.

Recurrent symptoms develop in some patients when the dose of prednisolone is reduced below 10–15 mg daily, even though sulphasalazine is also being taken. In such patients, it is necessary to try and substitute topical corticosteroids and, if this fails, azathioprine may have to be considered.

There is no justification for giving a daily dose of a glucocorticoid to a patient who is well once corticosteroid treatment has been successfully withdrawn. Cortisone, 50 mg, and prednisone, 15 mg daily, have both been tested and found not to reduce the relapse rate (Truelove and Witts, 1959; Lennard-Jones *et al.*, 1965). There is suggestive evidence that prednisolone, 40 mg, in one dose on alternate days, may decrease the relapse rate over 3 months but such a regime is rarely appropriate and needs further study (Powell-Tuck *et al.*, 1981).

c) *Topical administration.* There is much evidence that glucocorticoids introduced into the rectum as a solution, suspension in a foam, or as a suppository, are an effective treatment. It is likely the drugs exert a topical rather than a systemic effect because poorly absorbed drugs are as effective as those which are well absorbed (Lee *et al.*, 1980; McIntyre *et al.*, 1984). The vehicle must therefore be retained for an adequate time and bring the steroid into contact with the whole area of inflamed mucosa. Suppositories are likely to be restricted in action to the rectum. A foam is easier to retain than an enema (Ruddell *et al.*, 1980) but the small volume (5 ml) generally used does not penetrate proximal to the sigmoid colon (Farthing, Rutland and Clark, 1979; Hay, Sharma and Irving, 1979). Enemas of 100 ml always reach the sigmoid colon but upward spread to the descending and transverse colon is unpredictable. When topical treatment of colitis involving these areas is desired, it is worth adding barium to a therapeutic enema to check the level of penetration (Swarbrick, Loose and Lennard-Jones, 1974) and to see if the level can be affected by alteration in posture.

The convenient water-soluble esters, prednisolone 21-phosphate and betamethasone phosphate are both absorbed from the rectum though side effects are rare with the former. Prednisolone metasulphobenzoate produces lower prednisolone levels in the blood than the phosphate ester but the two esters are equally efficacious (Lee *et al.*, 1980; McIntyre *et al.*, 1984). Similarly, beclomethasone dipropionate enemas are as effective as enemas containing 10 times the dose of betamethasone, yet without the evidence of corticosteroid side effects or adrenal suppression seen with the latter (Kumana *et al.*, 1982). The use of one of these poorly absorbed steroids may be advisable in patients

with impaired glucose tolerance or when prolonged treatment is needed over many months.

d) *Sulphasalazine, its analogues and 5-aminosalicylic acid (5ASA)*

Sulphasalazine was introduced by Nanna Swartz in 1941 and recommended by her during the 1940s and 1950s for the treatment of ulcerative colitis. The first controlled therapeutic trials of this drug were those of Avery Jones and his colleagues who showed that it not only brings about improvement in acute colitis (Baron *et al.*, 1962b), but also reduces the relapse rate when taken over a year by patients who are well (Misiewicz *et al.*, 1965). These results have been confirmed and extended by others (Dick *et al.*, 1964; Dissanayake and Truelove, 1973). The drug tends to act more slowly in acute disease than oral prednisone and with a higher incidence of side effects (Lennard-Jones *et al.*, 1960; Truelove, Watkinson and Draper, 1962). Sulphasalazine appears safe to use throughout pregnancy and breast feeding (Järnerot, 1981).

Studies on the metabolism of sulphasalazine have shown that it is split by bacteria active in the colon to its two constituents, sulphapyridine and 5-aminosalicylic acid (5ASA). Therapeutic experiments have shown that 5ASA is poorly absorbed from the colon and appears to be the active moiety by direct action on the mucosa (Azad Khan, Piris and Truelove, 1977). The untoward effects of sulphasalazine, such as reversible infertility in men (Toovey *et al.*, 1981), dyspepsia, malaise, skin rash and occasional blood dyscrasias are all probably due to the sulphapyridine. New analogues which do not include a sulphonamide (Willoughby *et al.*, 1982; Chan *et al.*, 1983) and preparations of 5ASA itself designed to liberate the compound in the distal intestine or colon (Rasmussen *et al.*, 1982; Dew *et al.*, 1983) are therefore being tested.

Sulphasalazine may be used in active disease of moderate severity; it should not be relied upon as the only treatment in severe disease. It is wise to start with a dose of 0.5 g three times daily and increase to 3 g daily after a week if the drug is well tolerated. Some side effects, such as malaise and dyspepsia, are dose dependent, other such as skin rash and fever are idiosyncratic and successful desensitisation to these reactions has been reported (Holdsworth, 1981).

For distal acute disease, retention enemas (Palmer, Goepel and Holdsworth, 1981) or suppositories containing sulphasalazine have been tested and shown to be beneficial. A comparison of freshly prepared enemas (5ASA solution darkens with time) containing either a suspension of 4 g 5ASA or 100 mg of hydrocortisone showed that the 5ASA gave better

results, (Campieri *et al.*, 1981). A commercially available topical preparation of 5ASA is awaited.

Sulphasalazine in a dose of 2 g daily by mouth taken over one year or longer reduces the relapse rate when taken by patients whose disease is in remission. The effect is quantitative and a comparative trial showed that 4 g daily is more effective than 2 g daily but side effects usually preclude the higher dose. Similarly, 2 g is superior to 1 g daily but the latter is worthwhile if any more causes side effects (Azad Khan *et al.*, 1980). A delayed release preparation containing 5ASA appears to maintain remission as effectively as sulphasalazine; no advantage was gained by increasing the dose of 5ASA above that present in the usual effective dose of sulphasalazine (Dew *et al.*, 1982, 1983).

Any patient who has recovered from an attack of colitis should take sulphasalazine or a 5ASA preparation for at least a year. If a relapse occurs soon after stopping the drug, it seems reasonable to advise, and a patient will usually accept, the need to take prophylactic dose for longer, even for many years.

Azathioprine

Azathioprine exerts a steroid-sparing effect in colitis (Rosenberg *et al.*, 1975; Kirk and Lennard-Jones, 1982) and probably has an intrinsic anti-inflammatory action though this is hard to demonstrate (Jewell and Truelove, 1974). The indication for a trial of azathioprine appears to be chronic, active, troublesome, steroid-dependent disease for which surgical treatment is inappropriate. The dose used is 2–2.5 mg/kg body weight. About 10% of patients are unable to take the drug because of severe nausea, febrile reaction, or occasionally acute pancreatitis which develops during the first 4 weeks of treatment. Marrow depression is rare with this dose but a monthly full blood count is advisable. Azathioprine appears to act slowly over weeks or months and, after it is started, an effective steroid dose should be maintained for at least a month before attempts are made at reduction. If well tolerated, azathioprine should be continued for several months and perhaps longer; no controlled data are available to show the optimal duration of treatment.

Other drugs

Suppositories each containing acetarsol, 0.25 g, and a traditional remedy for proctitis and a controlled trial has shown that they can be as effective as steroid suppository (Connell *et al.*, 1965). Unfortunately, these suppositories are no longer available commercially and a vaginal pessary has to be used. Other suppositories have to be specially made. The initial promise of disodium cromoglycate in colitis

FIG. 1. Survival curves from published actuarial tables for patients with ulcerative colitis in different time periods. (Reproduced from Ritchie, Powell-Tuck and Lennard-Jones, 1978 with permission of the publisher).

does not seem to have been fulfilled (Binder *et al.*, 1981).

To date, there is no evidence that antibiotics benefit colitis (Davies *et al.*, 1977). Anti-diarrhoeal drugs are not usually helpful (Engbaek *et al.*, 1975) and may even cause trouble by leading to retention of hard stools in the normal colon proximal to the inflamed mucosa.

Conclusion

Over one professional lifetime, honoured in this volume, the survival rate of patients with colitis appears to have improved as Fig. 1 illustrates. Nutritional and drug therapy have become more effective; surgical treatment has become safer, and the indications for the various measures available are now better defined.

Progress has been made, but there is still much to

do. We need more active, non-toxic and reliable drugs for use in the acute attack and, just as important, for the prevention of relapse. Surgery needs to move closer to its goal of a safe operation which removes all the diseased mucosa and yet gives a good predictable result without troublesome symptoms or a stoma.

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