Current Practice

Medical Management of Ulcerative Colitis

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(Last week Dr. Truelove discussed the management of severe attacks and less severe episodes and reviewed the drugs used in the management of ulcerative colitis.)

Dietary Treatment

The theory that ulcerative colitis might be the result of food allergy was first put forward 40 years ago by an American physician, Andresen, who continued to study the disease in this connexion. In his last important article on the subject he described 50 patients with ulcerative colitis, in two-thirds of whom he judged food allergy to be the responsible mechanism. Cow's milk appeared to be the food most commonly at fault, being the sole allergen or one of several responsible allergens in 80% of the food allergy cases. Another American physician, Rowe, held similar views, basing his opinion on the results obtained by exclusion diets.

Although long neglected, there has recently been a revival of interest in the idea that food allergy may play a role in ulcerative colitis. A group of American physicians obtained many positive reactions in patients with ulcerative colitis when food extracts were injected into the rectal mucosa via a sigmoidoscope, whereas control subjects gave negative reactions. They claimed that exclusion of foods giving positive reactions was followed by excellent clinical responses. Unfortunately, no long-term clinical results have been published, so it is not generally known whether these initial benefits have been sustained.

A few years ago I reported a small group of patients who had failed to respond to standard medical therapy, but who rapidly became symptom-free when cow's milk and milk products were excluded from the diet. They remained well for months or years until challenged by milk deliberately reintroduced into the diet, when they all relapsed in the course of a few days or weeks. Subsequently it was found that patients with ulcerative colitis were more likely to have high titres of circulating antibodies to cow's milk proteins than were healthy control subjects. In addition, more patients with ulcerative colitis were found to have been weaned early from the breast than healthy control subjects; this finding is, of course, open to many different interpretations.

In any event, these findings encouraged us to carry out a controlled dietary trial in ulcerative colitis with simultaneous immunological observations. Patients on a milk-free diet were more likely to be free from relapses of ulcerative colitis during the trial period of one year than were those on a standard diet; and, conversely, patients on a milk-free diet were less likely to have repeated relapses than were those on a standard diet. The conclusion was that about one in every five patients with ulcerative colitis can be expected to derive substantial benefit from adhering to a strictly milk-free diet. Unfortunately, the

immunological studies performed in parallel with the clinical, sigmoidoscopic, and histological observations failed to show any close correlation between the immunological findings and the clinical responses. This was disappointing in several respects, perhaps most of all in failing to provide a guide as to which patients with ulcerative colitis could be expected to benefit from a milk-free diet.

There is the possibility that a milk-free diet is of benefit to some patients with ulcerative colitis for reasons which have nothing to do with immunological responses. During recent years deficiency of small-intestinal disaccharidases has been found to occur in a certain proportion of healthy subjects and also in a number of intestinal diseases, including ulcerative colitis. It has been suggested that a deficiency of lactase (the disaccharidase most commonly found to be deficient) might favour the growth of lactose-dependant bacteria in the colon, and that these, in turn, might have a harmful effect in ulcerative colitis.

A recent American study of this issue has yielded important results. Disaccharidase assays on biopsy specimens of the small intestine in 32 patients with ulcerative colitis revealed lactase deficiency in 46%, a significantly higher incidence than found in normal subjects. Serial biopsy specimens were obtained from some patients, and these showed that the lactase increased when clinical improvement occurred and diminished when there was a relapse of the ulcerative colitis. However, "double-blind" feeding trials with 50 or 100 g. of sugar daily showed that lactose was no more likely to increase the colitic symptoms than was glucose, and the occurrence of any such symptoms was not influenced by whether or not lactase deficiency was present. These findings strongly suggest that any benefits conferred by a milk-free diet in ulcerative colitis cannot be attributed to the existence of lactase deficiency.

At present, therefore, there is no way of telling in advance that a patient with ulcerative colitis will respond favourably to a milk-free diet. If a patient fails to respond to standard medical therapy, or if he repeatedly relapses when such therapy is withdrawn, it is well worth trying the effect of a milk-free diet. If the patient then becomes symptom-free he should continue on the diet indefinitely. The only way to determine whether the exclusion of milk has been responsible for the remission is to reintroduce it into the diet to see if clinical and sigmoidoscopic relapse occurs.

Complications

The complications of ulcerative colitis are so numerous and diverse that they cannot be covered adequately in a brief article. Only some important points will be mentioned here; for further information reference should be made to the article by Edwards and Truelove,¹ which deals with all but the very unusual complication.

The complications of ulcerative colitis fall into two main groups. The first consists of the local complications which arise

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in and around the inflamed colon and rectum. The second consists of the remote or systemic complications which occur in extra-colonic sites.

Some local complications occur only during acute attacks of the disease. The chief examples are perforation of the colon, acute dilatation of the colon, and massive haemorrhage from the bowel.

Perforation of the colon is a complication liable to occur in a severe attack of colitis, and is specially liable to occur during a first attack of the disease if this happens to be severe; it is the only major complication showing this selective preference for the first attack. Sometimes the symptoms and signs of perforation are obvious and dramatic. Confirmation that perforation has occurred is readily obtained by emergency x-ray examination carried out on the ward. As well as a supine film with overcouch tube to show the distribution of gastrointestinal gas shadows, views taken with a horizontal beam with the patient lying first on his left side and then on his right side should be taken. These horizontal beam views will show free gas in the peritoneal cavity if perforation has occurred. Sometimes a patient suffers from perforation of the colon without obvious symptoms and signs, although there is almost invariably a deterioration in his general condition. It has sometimes been supposed that the use of corticosteroids has increased the liability of perforation to occur "silently," but examination of case records shows that this was frequent before the introduction of corticosteroids and that the diagnosis was often made only when the patient came to necropsy. In fact, the introduction of corticosteroid treatment has been followed by a lower incidence of perforation, while the diagnosis is made more readily than formerly provided plain radiographs are taken. The rule should be to suspect the possibility of perforation if any sudden deterioration of the patient's condition occurs, and to carry out an immediate emergency x-ray examination. When perforation is diagnosed emergency surgery is indicated. Colectomy with ileostomy is the accepted choice. The experienced colonic surgeon usually performs a panproctocolectomy, thus avoiding the need for a subsequent operation to remove the rectal stump.

Acute *dilatation* of the colon also occurs, for all practical purposes, only during the course of an acute attack. There is abdominal distension and pain associated with a continuation of the diarrhoea. Plain x-rays show the distended, gas-filled colon, the distension being maximal in the caecum, ascending colon, and transverse colon, while the descending colon is usually much less distended. The mucosal surface of the colon characteristically displays a coarsely polypoid condition which is due to swollen areas of inflamed mucosa; these can usually be seen both in profile and *en face*. An associated perforation of the colon may co-exist; the plain x-ray films will show free gas if this is so. It is generally held that acute dilatation of the colon is an indication for emergency colectomy. I am personally unorthodox, and if the patient's general condition is reasonably good and there is no radiological evidence of perforation, prefer to begin with a trial of intensive intravenous therapy along the lines set out earlier in this article, and with the addition of gastric suction to minimize the chance of further dilatation. If there is no improvement in 24–48 hours emergency surgery is then employed.

Massive haemorrhage from the bowel is not a frequent complication. When it does occur, it usually responds to blood transfusion, but it is occasionally a reason for emergency colectomy.

Ischio-rectal abscess, fistula-in-ano, and recto-vaginal fistula may occur either during an acute attack or during the course of chronic disease, even when the colitis is apparently quiescent. An ischio-rectal abscess needs surgical drainage. Fistula-in-ano is usually curable by local surgery, but, if severe and multiple, may be an indication for colectomy. Recto-vaginal fistulas are difficult to treat unless the faecal stream is diverted; colectomy is therefore often necessary, but we have treated

some by temporary "double-barrelled" ileostomy to allow conservative vaginal surgery when there were no other good indications for colectomy.

The remote or systemic complications of ulcerative colitis are diverse. Skin eruptions are frequent. The first possibility to consider is that they may be complications of medical treatment, such as reactions to barbiturates or sulphasalazine. One characteristic type of skin lesion is pyoderma gangrenosum, which is virtually confined to ulcerative colitis and Crohn's disease. It is a serious complication, but it usually responds to corticosteroids, although in the past it was an indication for colectomy.

Five remote complications form a group in that they tend to clump up together in the same patients, so that one is tempted to think that some aetiological mechanism must be common to them all. They are aphthous ulceration of the mouth, uveitis, arthritis of the big joints, ankylosing spondylitis, and erythema nodosum. They all respond favourably to successful treatment of the colitis with corticosteroids, with the exception of ankylosing spondylitis, which is usually progressive; likewise, if colectomy is performed, these complications cease to occur, but existing ankylosing spondylitis continues to progress.

The *liver* is sometimes affected in ulcerative colitis. Mild and transient hepatitis is fairly frequent, and chronic hepatitis progressing to cirrhosis of the liver is a good deal more common in patients with ulcerative colitis than in the general population. The mechanism of liver involvement is unknown, though a popular view is that portal bacteraemia is responsible. It is still uncertain whether colectomy will arrest the progress of a chronic hepatitis in this disease. The combination of chronic liver disease and ulcerative colitis carries a bad prognosis.

Deep venous thrombosis of the legs is common during attacks of ulcerative colitis. Pulmonary embolism is also likely to occur, and is one of the more common immediate causes of death. Sometimes pulmonary embolism occurs when there is no clinical evidence of leg vein thrombosis; it is tempting to suppose that, in such cases, thrombosis may have occurred in the pelvic veins; but, in any event, no prophylactic measures are possible in such circumstances. However, as some examples of pulmonary embolism occur when leg vein thrombosis is known to be present, the question arises whether anticoagulant therapy should be used when a deep venous thrombosis occurs in the legs. There is strong presumptive evidence that anticoagulant therapy greatly reduces the risk of a dangerous pulmonary embolism when used in these circumstances, and it is interesting that this form of therapy usually does not cause any great increase in the loss of blood from the bowel. In effect, therefore, the occurrence of leg vein thrombosis is a strong indication for anticoagulant therapy, as the benefits far outweigh the risks.

Carcinoma of the colon is a complication of chronic disease. For the first few years after the onset of ulcerative colitis the risk of carcinoma is negligible and need not enter into considerations of management. Thereafter the risk increases steadily with increasing length of time, and it becomes an important element in management. Carcinoma of the colon is not distributed at random among the patients with ulcerative colitis, but certain factors greatly influence the risk. The main factors associated with a high risk of carcinoma of the colon are as follows:

- (1) A severe first attack of ulcerative colitis.
- (2) Radiological evidence of involvement of the entire colon.
- (3) Chronic continuous symptoms of the colitis.
- (4) Onset of the ulcerative colitis in childhood.

When two or more of these factors coexist in the same patient the risk of carcinoma of the colon becomes considerable, and there is a good case for preventive colectomy, even if this is not indicated on other grounds. When none of these factors are present the risk of carcinoma is low, probably being less than the risk of colectomy, so there is no reason to embark on major surgery unless this is indicated on other grounds.

Resorting to Surgery

At the present time the only certain method of achieving the permanent cure of ulcerative colitis is by radical surgery, which usually implies panproctocolectomy with permanent ileostomy, although some surgeons perform colectomy with ileo-rectal anastomosis when the rectum is free from local complications. Panproctocolectomy is a large operation, but it carries only a low risk in expert hands when performed as an elective procedure; its risk is still considerable when performed as an emergency operation on an ill patient. The physician treating ulcerative colitis should have a shrewd idea of when to abandon medical treatment.

Emergency radical surgery is indicated during an acute attack if perforation of the colon occurs, is frequently necessary if acute dilatation sets in, and is occasionally required for massive haemorrhage from the bowel. If a patient fails to respond to medical treatment during a severe attack, emergency surgery is indicated. At present there is a move towards early surgery in acute attacks of ulcerative colitis not showing a favourable response to standard medical therapy after about a week. Surgeons at Leeds have followed this policy with a low operative fatality rate. However, this implies that some patients are treated by colectomy who might otherwise have recovered from the attack with intact colons.

When the disease becomes chronic some patients are sufficiently disabled to make radical surgery the treatment of choice. When symptoms are continuous, or when relapses are frequent and severe, colectomy is advisable. Whenever possible this operation should be performed as an elective procedure.

As already mentioned, fistulae around the rectum, if severe, may be an indication for colectomy. Carcinoma of the colon is an absolute indication for surgery, and there are circumstances, already described, in which colectomy should be performed as a preventive procedure to eliminate the risk of carcinoma.

Conclusions

Ulcerative colitis usually presents as a series of attacks of bloody diarrhoea with complete freedom from symptoms between the attacks. The periods of freedom may vary from a few weeks to many years. A minority of patients have chronic continuous symptoms.

TODAY'S DRUGS

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

Chloramphenicol and Tetracyclines

These are the original "broad spectrum" antibiotics. Discovered almost simultaneously about 20 years ago, they proved to be effective against a wider range of bacteria than either penicillin or streptomycin, the only other antibiotics then in use, and even against rickettsias and the large viruses. Moreover, they could be administered by the mouth, whereas their predecessors had to be injected. It is small wonder that they made enormous fortunes for their manufacturers within a few years. Much has happened since then to restrict their use—the observation of toxic or other side-effects, the development of bacterial resistance, and the discovery of many further antibiotics applicable to most of the same purposes. A reassessment of their therapeutic position is due, but some of the conclusions to be drawn are matters of opinion.

Chloramphenicol

Originally derived from *Streptomyces venezuelae* and known as Chloromycetin, chloramphenicol is now produced

The essence of medical management is to stop each attack as quickly as possible and to apply such limited means as are available to reduce the chance of recurrence. A severe attack demands rapid admission to hospital and vigorous treatment.

Mild and moderate attacks can usually be checked by the use of corticosteroids by mouth, corticosteroids used locally, and sulphasalazine, either alone or in combination. Such general medical measures are employed as are appropriate. The prompt treatment of relapses before they become severe is of cardinal importance in long-term medical management.

Among measures designed to prevent relapse small doses of corticosteroids are useless, and larger doses carry the risks of the therapy. Sulphasalazine has been shown to reduce the relapse rate greatly when used in a maintenance dose of 0.5 g. q.d.s. over the period of one year.

Immunosuppressive drugs have been used in several small series of patients with favourable results, but marrow depression has been a frequent side-effect. At present it cannot be said categorically that the benefits outweigh the risks.

Dietary treatment has a certain limited use. There is evidence that a milk-free diet is highly beneficial to about one in five patients, but it is at present impossible to predict which patients will respond favourably.

The local complications of ulcerative colitis may occur either in the acute attack or during the chronic course of the disease. Dangerous complications which are apt to occur during a sharp attack are perforation of the colon, acute dilatation of the colon, and massive haemorrhage from the bowel.

Permanent cure can be achieved by panproctocolectomy with permanent ileostomy. An alternative method of radical surgery is colectomy with ileo-rectal anastomosis, but most surgeons employ this in only a minority of patients. Radical surgery is indicated in severe attacks not responding to medical treatment, and for certain dangerous complications of an acute attack. Elective radical surgery is necessary for patients in whom the attacks are frequent and troublesome. Preventive surgery to eliminate the risk of carcinoma of the colon is indicated in patients with factors associated with a high risk of this complication.

REFERENCE

- ¹ Edwards, F. C., and Truelove, S. C., *Gut*, 1964, 5, 1.

synthetically. It is usually given in capsules, but children can neither swallow these nor tolerate the intensely bitter taste, and a suspension of chloramphenicol palmitate is available. This substance is broken down in the bowel and absorbed as chloramphenicol. The parenteral form of the drug is the succinate. Chloramphenicol is well absorbed from the bowel, and satisfactory blood levels can be maintained by administration at 6-hour intervals, the usual total daily dose for treating a serious infection being 2 g. Chloramphenicol diffuses well into the cerebrospinal fluid—better, in fact, than any other antibiotic. Excretion is almost entirely renal (levels in the bile are low), but about 90% of the excreted drug is conjugated and inactive.

Antibacterial Activity

The action of chloramphenicol on some common bacteria is compared with that of tetracycline in the Table. Against streptococci, pneumococci, and staphylococci chloramphenicol possesses a decidedly lower degree of activity than the tetracyclines—and in fact lower than some penicillins or erythromycin. Though it has been used for some of these infections, particularly staphylococcal, it is hard to see how