Treatment of Ulcerative Colitis with Antimetabolites

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Ulcerative colitis is a disease of widely varying severity. The course in any patient is difficult to predict. In this community repeated episodes commonly lead to a chronic active stage, in which the sufferer becomes an invalid unless the process is relieved by colectomy. In this phase exacerbations and complications are common, and not infrequently lead to death. It is with patients in this group that the present trial has been concerned.

While ulcerative colitis as representative of an autoimmune disorder fails to fill all the criteria enumerated by McKay and Burnet (1963) for autoimmune disease, there remains strong evidence for immunological disturbance. This evidence has been reviewed by Kirsner (1961). I do not propose to discuss at length whether this disturbance represents a normal response to modified tissue or a defect of the immune mechanism. I consider the action of antimetabolites, together with observations made during this therapy, supports the view of primary tissue damage or modification.

With the exception of steroid hormones, the most powerful suppressants of the immune response, as measured by failure of graft rejection, are all agents developed for the treatment of cancer. These agents may be considered in their main groupings—nitrogen mustard and its derivatives, the sulphur mustards, the antimetabolites, and antibiotics. There is probably some selectivity of action of these agents, antagonism occurring between the antimetabolites, mercaptopurine, and the folic-acid antagonists. In our early trials we used the antimetabolites mercaptopurine and 6-thioguanine. More recently the sulphur mustard busulphan has been employed.

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At the time of writing seven patients are receiving treatment with antimetabolites. Brief case notes are appended.

Case 1

The patient was a 47-year-old man who at the beginning of treatment was a chronic bowel invalid. His early history has already been recorded (Bean, 1962). Not long after that report radiological examination revealed a persistent filling defect in his transverse colon. At laparotomy an obvious inflammatory polyp was removed, but because of sudden hypotension the planned colectomy was abandoned. After the operation antimetabolite therapy was suspended, but three months later he suffered a relapse and mercaptopurine therapy was recommenced. The disease rapidly remitted. More recently he received busulphan, the first dose of 100 mg. producing a remission lasting 10 months. Over the four-year period of treatment all parameters of the disease steadily improved, including the appearance of the barium enema, which has shown improvement from gross involvement to near normality (Figs. 1 and 2).

Case 2

A grazier aged 42 was a former prisoner-of-war of the Japanese. He had suffered from episodic diarrhoea since his internment. Specific antiamoebic therapy had been given on a number of occasions without benefit. He was admitted to the Repatriation General Hospital in November 1961 with acute ulcerative colitis. After four months' in-patient treatment, which included blood transfusions and steroid therapy, he gradually improved and was discharged with continuing but less active disease. During this admission he refused to have his colon removed, and was readmitted with a severe episode in October 1962. During an initial period of conservative therapy his condition rapidly deteriorated and treatment

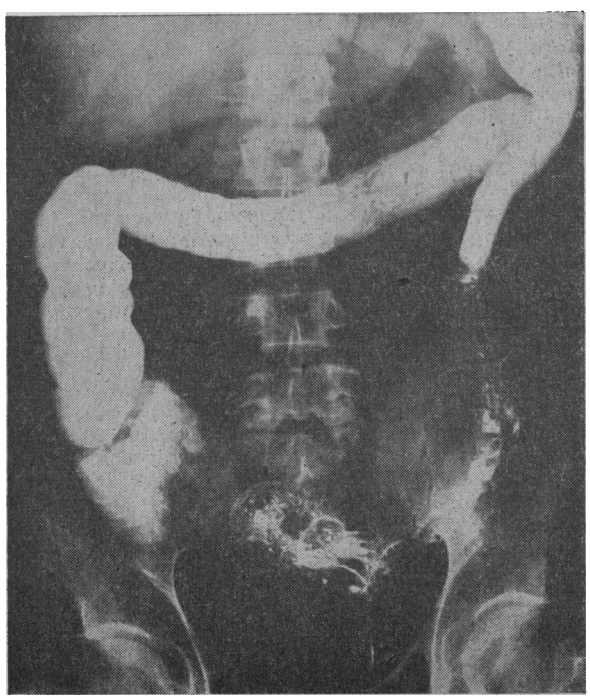

FIG. 1.—Case 1. Barium enema before therapy.

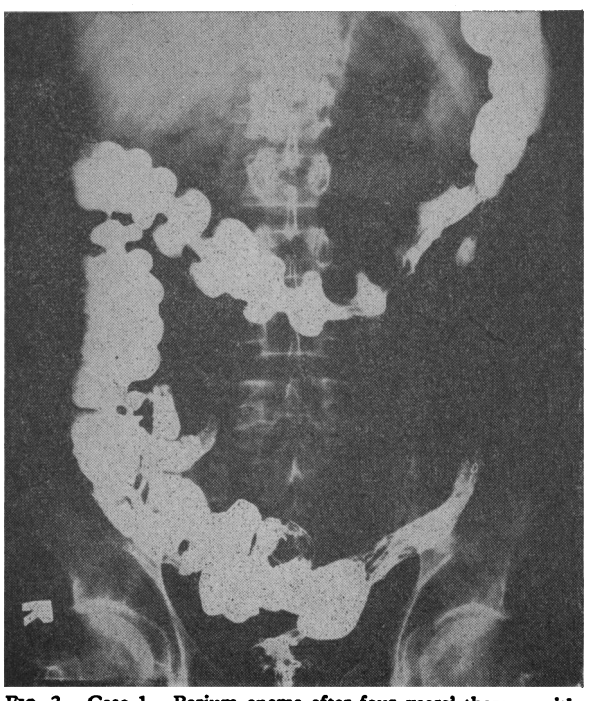

FIG. 2.—Case 1. Barium enema after four years' therapy with antimetabolites.

with mercaptopurine was started. Improvement was apparent within four days, and at 10 days his motions approached normal. At the time of writing he has received continuous treatment with mercaptopurine for nearly three years. Over this period his health and well-being have been excellent. At one period during treatment his liver became enlarged and biochemical tests showed a marked elevation of thymol turbidity. At this time he denied untoward symptoms. A liver biopsy showed mild fatty infiltration. After this episode 5 mg. of prednisolone was combined with each dose of mercaptopurine, and the thymol turbidity and liver size returned to normal limits. Over the total period of treatment both the rectal biopsy and the barium enema have shown a steady improvement (Figs. 3 and 4).

Case 3

A 40-year-old Serviceman had a resection of his transverse colon after several severe episodes of melaena. While the pre-operative diagnosis, largely based on radiological appearances, was regional colitis, later histological examination showed widespread changes, and not long after operation he suffered a further melaena. He strongly opposed further surgery, and mercaptopurine was given with dramatic improvement. Eleven weeks later he developed anaemia, and therapy was stopped, but 10 weeks after this he had another melaena. Treatment was recommenced, and has been continued virtually unaltered for the past three years. The patient has remained a full-time member of the Australian Military Forces.

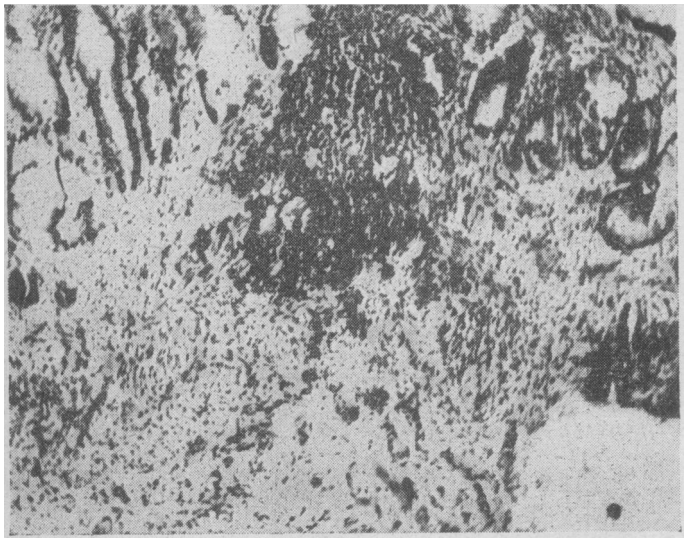

FIG. 3.—Case 2. Rectal biopsy before treatment.

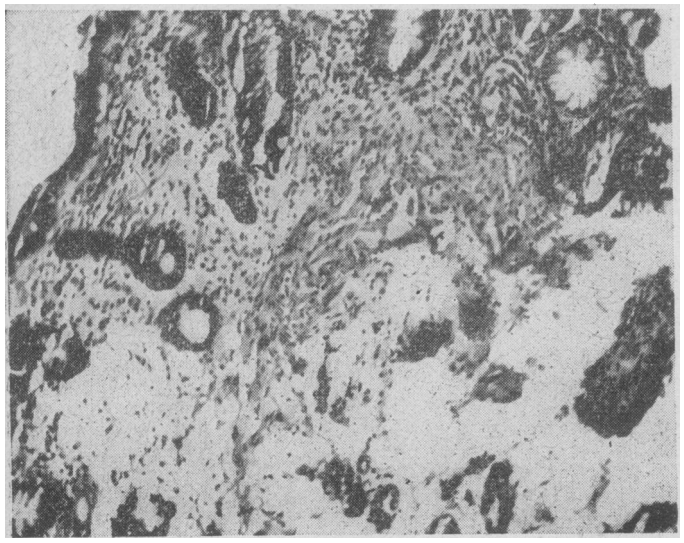

FIG. 4.—Case 2. Rectal biopsy after three years' therapy with mercaptopurine.

Case 4

A 40-year-old railway worker had suffered recurrent diarrhoea since 1944. His symptoms became more severe, and during an admission to hospital in 1962 his rectal mucosa showed the characteristics of ulcerative colitis. A barium-enema examination demonstrated characteristic and gross involvement of his colon. Treatment with 6-thioguanine was begun, with immediate improvement. After two months' therapy he complained of abdominal pain and nausea, and was found to be mildly anaemic. On admission his liver was enlarged and tender, and his serum alkaline phosphatase was elevated. Therapy with 6-thioguanine was stopped, and he rapidly improved. More recently he has been treated on two occasions with busulphan, 100 mg., remissions of six months being achieved after the first dose, and of 12 months after the second dose. He has continued at work.

Case 5

A 42-year-old ex-Service man developed frank ulcerative colitis in 1950 after a long history of recurrent diarrhoea. Between 1950 and 1963 he was unable to work, and was admitted to hospital on nine separate occasions with acute episodes of diarrhoea. While in hospital in 1963 his bowel motions consisted largely of blood and mucus, and a barium-enema examination revealed a pipe-stem colon. He had been declared a totally incapacitated ex-Service man. Surgery had been refused on a number of occasions, and therapy was begun with mercaptopurine. He did not tolerate the drug, developed nausea and headache, and his haemoglobin fell. Therapy was changed to 6-thioguanine, which was tolerated, and though his condition improved both subjectively and objectively he has not attained the same degree of well-being as the other members of the group. Though he has not suffered any acute episodes, at one stage he developed pain and limitation of movement in his right hip and left ankle. Treatment with 6-thioguanine was continued for 18 months. At the end of this period he complained of "light-headedness," and shortly after this developed a loss of vibration sense and unsteadiness of gait. Because a similar syndrome appeared in another patient receiving 6-thioguanine (Case 6) this drug was stopped, and he has had intermittent treatment with busulphan, 100 mg., long remissions resulting after each dose.

Case 6

A 44-year-old ex-Service man had suffered from pruritus ani since the second world war. In 1958 he developed frank ulcerative colitis, and in 1960 was admitted to hospital with an acute episode which required blood transfusions. Following this he received treatment with steroids. Over the next three years his disease remained in a chronic active phase, and in January 1963 he was admitted to this hospital with a fulminating episode. He was critically ill with a swinging fever, acidosis, proteinuria, profuse rectal bleeding, and an acute haemolytic anaemia. Although a wide donor panel was available it proved impossible to obtain compatible blood for transfusion, and therapy was begun with mercaptopurine, 400 mg./day. The aim of treatment was to control both the bowel symptoms and the vigorous haemolysis. The frequency and consistency of his motions rapidly improved, and the level of his haemoglobin was stabilized. After nine days' treatment he developed a sudden neutropenia, and the dose of mercaptopurine was reduced. Fortunately he did not suffer a further haemolytic episode. His blood was now readily cross-matched and transfusion was carried out without reaction.

Treatment was continued with a smaller dose of mercaptopurine, combined with intravenous hydrocortisone. Reduction of the dosage of mercaptopurine resulted in recurrent bowel symptoms, and reduction of intravenous hydrocortisone in further haemolysis. After a severe haemolytic episode in July 1963 a splenectomy was performed. Shortly after this he suffered from a single mild and self-limiting episode of haemolytic anaemia. Therapy with 6-thioguanine was begun; it was continued for 28 weeks, and ceased only after he developed unsteadiness of gait and a diminished appreciation of vibration sense similar to Case 5. This therapy was then stopped, and he has since received two doses of 100 mg. of busulphan, with remissions of 3 and 15 months respectively.

Case 7

A 57-year-old ex-Service man had suffered from post-encephalitic Parkinsonism for 15 years. A chemopallidectomy one year before admission had resulted in alleviation of the symptoms on the left side of his body. He gave a history of six months' increasingly severe diarrhoea, and for two months before his admission to this hospital had been receiving medical treatment as an in-patient at a provincial hospital. Over this period his condition had steadily deteriorated.

On admission he was a disturbed and miserable man with a haemoglobin of 10.8 g./100 ml., profuse bloody diarrhoea, and gross limitation of movement. This combination of disabilities resulted in an almost intolerable situation. In view of the failure of conservative therapy, treatment was commenced with mercaptopurine, 300 mg./day, combined with 10 mg. of prednisolone daily. The effect was dramatic, and he was discharged to his home town after 14 days. Over the last seven months he has been under review at regular intervals. At the time of writing he is receiving 50 mg. of mercaptopurine and 5 mg. of prednisolone on alternate days, and his bowels are normal in every way. His haemoglobin level is 15.1 g./100 ml., and the appearance of his rectal mucosa at sigmoidoscopy is completely normal. There has been an accompanying improvement in general health and well-being, and further surgery for his Parkinson's disease is under consideration.

Discussion

Acceptable statistical evaluation of a new procedure in a small group of patients such as this presents major difficulties, and has not been attempted. However, as well as frequent clinical observations, changes in peripheral blood and serum proteins were carefully followed, and periodical rectal biopsies and barium-enema examinations performed. So long as treatment was continued there was consistent improvement in all these parameters. This situation was in marked contrast with both the clinical condition of the patients for the year previous to treatment and the behaviour of a number of patients with less incapacitating disease who had not received antimetabolite therapy. In this latter group, while symptoms have waxed and waned, there has been little objective change, as shown by either the rectal biopsy or the barium enema.

The changes in the peripheral blood in treated patients consisted in a rise in haemoglobin, and during the early stages of therapy when the full dosage régime was employed there was often some depression of the white-cell count. This did not seem to affect one cell type more than another. In Case 6, when a high-dosage régime had to be continued to control the haemolysis, this depression was severe. Successful maintenance therapy has not been accompanied by consistent depression of any member of the white-cell series. The most remarkable and consistent changes were seen in the blood platelets. High total levels were found in most patients when the disease was in relapse, and these fell to a normal figure during successful therapy. The high levels appeared to be due to excessive platelet production, and in the early stages of treatment a number of different patterns of response had been observed. These have been reported elsewhere (Bean, 1966).

A striking facet of successful treatment of these disorders was the rapidity of improvement. The return to normality of bowel habits was rapid, and the patients quickly regained their health and well-being. The rectal mucosa returned to a normal appearance, and a parallel improvement occurred in the biopsy. Nevertheless, the improvement continued for only as long as therapy continued. If treatment with drugs such as mercaptopurine or 6-thioguanine was stopped after complete control had been established, within two weeks the inflammatory infiltrate in the rectal mucosa became heavier, within two months there were macroscopic changes in the rectal mucosa, and within three months frank relapse usually occurred. Though under these circumstances control was readily re-established, I have been disturbed by the inevitability and severity of these episodes, and the greatest success was achieved in those patients whose treatment had not been stopped.

Several agents were used in this trial. Although the number of patients treated was small, therapy was continued in some patients for long periods, and the number of treatment-years was approximately 25. Mercaptopurine was given to every patient in the group, and in my experience has proved the safest and most predictable agent to use. In relapse the average adult received 300 mg. of the drug a day in divided doses, and as improvement occurred the dose was reduced stepwise to a maintenance dose of 25–75 mg. a day. Some degree of marrow suppression was common in the early stages of treatment, and in Case 6, whose condition was critical when therapy was started, this gave rise to anxiety. Two patients showed abnormal liver-function tests while receiving the drugs. Over the last two years a small dose of prednisolone had been given concurrently with mercaptopurine, and no further reactions have been seen. Because of the development of neurological manifestations in the two patients who received long-term therapy with 6-thioguanine, the use of this drug has been abandoned. Busulphan, given in doses of 100 mg. at long intervals, was used in three patients. Remissions were induced lasting from three to more than 12 months. Because of the delay of three to four weeks between administration and effect, this drug was not suitable for treatment in a relapse.

There are evident disadvantages to treatment with antimetabolites which make them unsuitable for general use. Until a survey has been carried out on a wider group of patients I feel that it would be wise to restrict the use of these drugs to patients in the older age group in whom surgery is contraindicated or refused. There may be a place for the drugs in the patient with a fulminating episode uncontrollable by other means.

Side-effects have occurred under conditions in which patients were subject to careful and regular supervision, including frequent surveys of marrow and liver function. While no fatalities occurred in the group, marrow depression was common, and, if not recognized, could have led to severe consequences in patients in whom nutrition was poor and serious infection a not uncommon cause of death. It is particularly hazardous to begin therapy with an inadequate dose and then increase it after one to two weeks' unsuccessful therapy.

I believe that while these agents are capable of producing improvement which at times seems little short of miraculous, they are not suitable for general use ; in fact the most significant contribution of this therapy may well be its aetiological implications. The following facets appear worth further investigation —namely, the relative freedom from infections, both bacterial and viral, which these patients have enjoyed during treatment ; the lack of any consistent change in either polymorphonuclear cells or lymphocytes ; the consistent effect of therapy upon the platelets ; and the long remissions which have followed the use of busulphan. A disconcerting feature has been the inevitability and severity of relapse when treatment has been discontinued. This course is in sharp contrast with that in the control group of patients. The latter are rarely without symptoms, and experience a varying degree of morbidity, with frequent relapses. On the other hand, these relapses are far less severe and incapacitating than those which have occurred in the treated group after the suspension of therapy, and on the great majority of occasions they spontaneously remit.

The nature of ulcerative colitis remains a challenging problem. Many authorities consider that an immunological disturbance plays a primary part in the disease. Some of my observations seem to be at variance with this view. These are, first, the failure of some drugs, recognized as effective immune-suppressants, to influence favourably the course of the disease ; secondly, the lack of any consistent change in lymphocytes or other cells during successful therapy ; and, thirdly, the part played by platelets in this and other so-called autoimmune diseases. There is an undoubted link between ulcerative colitis

and carcinoma of the colon, and it may not be too far-fetched to suggest a common cause. Megakaryocytes and platelets have been shown to play an important part in viral multiplication in certain forms of cancer in animals (de Harven and Friend, 1960 ; Gross, 1963), and more recently thrombocytosis has been reported in human cancer (Levin and Conley, 1964). My own observations are in agreement with the views of the latter worker. In these circumstances the immune-suppressant role of these drugs may well be a disadvantage, and perhaps provide an explanation for both the failure of these drugs to cure and the severity of the relapses. The beneficial action of the drugs could then be attributed to an antiviral action.

Further support for this view comes from recent observations on cancer chemotherapy in animals (Groupé and Rauscher, 1965) and the therapy of Burkitt's lymphoma in man (Burkitt *et al.*, 1965).

Summary

Observations on a small group of patients suffering from ulcerative colitis and treated with antimetabolites are reported. While the effect of chemotherapy is at times dramatic, the successful use of the drugs requires adequate facilities and careful control.

While most patients have shown a steady return to normal in all parameters, the failure to achieve cure has been disappointing.

The role of the platelet is discussed, and it is suggested that these observations support a viral infection rather than an autoimmune basis for the disease.

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Comparison of Three Methods for Treatment of Congenital Clubfoot

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It is one of the paradoxes of modern surgery that although therapeutic facilities have never been so plentiful disappointing results still occur. In particular, this is true in the treatment of congenital clubfoot.

Brockman (1930) pointed out that everyone agreed that in the infant the proper treatment is repeated manipulation combined with some form of fixation of the foot. The method by which fixation is carried out varies according to the surgeon, and, as Sir Robert Jones (1894) remarked, different methods can give the same result.

In the past ten years three principal methods of fixation have been used in the treatment of clubfoot at the Hospital for Sick Children. None was entirely satisfactory, but the impression that one method was more successful than the others indicated the need for a detailed analysis. A comparison of three different methods of treatment of clubfoot has not hitherto been published ; most reports are concerned with one method in the hands of one surgeon. The results presented here form part of a much larger survey designed to show the causes of failure in each of these methods.

Present Series

Among the 140 patients reviewed boys (96) were more commonly affected than girls (44). There were 81 bilateral cases (59 in boys and 22 in girls) and 59 unilateral cases (37 in boys and 22 in girls). An analysis of the patients is shown in Table I.

Criteria for Selection of Patients.—Only patients with idiopathic talipes equinovarus were included in the series (Brockman's (1930) type 1 deformity). Children with overt neurological abnormalities such as spina bifida or muscular disorders such as arthrogryposis were excluded. All the elements of congenital talipes equinovarus must have been present. In addition, if correction of all the deformities was obtained at the first treatment the child was excluded. In all children in the series initial treatment started within one month of birth, in our clinics, and the method must have remained unchanged. Children qualified for assessment only when they were walking, which is better than taking a certain age as the criterion. In fact the youngest children in the series were over two years of age ; the eldest was 10.

Criteria of Correction.—The aim of treatment is to obtain a foot with active eversion and active dorsiflexion at the ankle above the right angle. The term "overcorrection" was not used ; what is called "overcorrection" is no more than the valgus and calcaneus position that the normal foot can be made to assume. Likewise, the term "relapse" was considered to indicate a foot that had never been fully corrected by primary treatment. The hallmark of success is a child walking on a mobile plantigrade foot with the heel down and in neutral or slight valgus position and a satisfactory longitudinal arch.

TABLE I

			Denis Browne Splint		Robert Jones's Strapping		Serial Plasters	
			Cases	Feet	Cases	Feet	Ca ses	Feet
			63	105	62	96	15	20
Age at follow-up	Average age–years		7		5		6	
	Minimum age ..		2		2		2	
	Maximum „ ..		10		6		8	
Male (96)	Unilateral	Right	6	11	11	19	3	7
		Left	5		8		4	
	Bilateral		31	62	26	52	2	4
Female (44)	Unilateral	Right	3	10	5	9	3	3
		Left	7		4		0	
	Bilateral		11	22	8	16	3	6

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