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MEDICAL MANAGEMENT OF ULCERATIVE COLITIS*

BY

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The medical management of ulcerative colitis is a difficult and diffuse topic, and the assessment of any therapeutic agent is a most complex task in a disease which varies greatly in severity and extent, not only from patient to patient but also in the same individual from attack to attack. Carefully planned controlled trials in colitic attacks of comparable severity are necessary for the evaluation of any remedy. No specific treatment has yet been found. The physician possesses a variety of drugs capable of inducing remission in perhaps half the cases treated and has no reliable means 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 fulminating attack or exacerbation of the colitis as speedily as possible; secondly, in preventing recurrence by some form of maintenance therapy; and, thirdly, realizing that his efforts may fail at both these stages, knowing when to call in the surgeon. In this regard he should constantly be critically asking himself if his therapeutic efforts are adversely affecting the outcome of surgery or the long-term well-being of the patient.

In trying to answer some of these problems I shall review the experiences of others, the results of the elegant therapeutic trials undertaken in colitis in recent years, and will draw on personal experience obtained in Leeds in the past ten years, where I have treated some 197 patients with colitis, who have received in all some 340 courses of treatment. The attacks of the disease were judged severe in two-thirds of the patients treated, and the clinical pattern of the illness was an acute fulminating attack in 36, chronic intermittent diarrhoea in 92, chronic continuous diarrhoea in 29, while 38 had a distal proctocolitis. Two cases resembling the non-specific enterocolitis described by Cooke and Brooke (1955) were included.

Space does not allow me to dwell on the important general principles of management of the acute attack—namely, the maintenance of water and fluid balance, of nutrition, the correction of anaemia, and the control of diarrhoea. Antibiotics have a real place in the febrile toxic case, but should only be given systemically in short courses, as prolonged usage predisposes to secondary monilial infection. Psychotherapy, particularly in acute disease, has proved singularly ineffective and occasionally harmful.

I shall describe in greater detail two groups of drugs which have been shown, after critical appraisal, to be capable of terminating the acute attack in a significant proportion of patients treated. These are sulphasalazine and the steroid group of compounds administered either systemically or topically.

Sulphasalazine Therapy

Sulphasalazine ("salazopyrin," "asulfidine") has been used extensively in Sweden and America since 1941 in the treatment of colitis. The drug has not been submitted to a proper controlled trial, but the excellent results in large series of patients reported by Professor Svartz, Dr. Bergen, and other American workers are some testimony of its value. These results

TABLE I.—Immediate Results of Treatment and Frequency of Drug Intolerance of Acute Colitic Episodes Treated with Sulphasalazine in 751 Patients Treated in Sweden, America, and England. Remissions were Induced in from One-half to Three-quarters of the Patients Receiving the Drug

	Patients Treated	Recovered or Much Improved	Showing Drug Intolerance
Svartz (1956)	439	75%	—
Morrison (1953)	60	70%	21%
Moertel and Bergen (1959)	183	64%	17%
Personal (1950-9)	69	47%	16%

are summarized in Table I, where the percentage remission rates are detailed; they varied between 64 and 75%. My own experience has been less favourable, only 47% of 69 attacks treated being remitted. Use of the drug is limited because of the occasional toxic effects it produces, which develop in between one in five and one in six of the patients treated. These effects include nausea, indigestion, headache, drug fever, skin rashes, and blood dyscrasias.

Systemic Steroid Therapy

Despite the regular use of steroids in ulcerative colitis for the past 12 years their value is still in doubt. The drugs have been received with enthusiasm in some quarters, but in others they are regarded as both ineffective and dangerous. It has been repeatedly asserted that the outcome of surgery is prejudiced by their use.

To some extent these controversial issues were resolved by controlled trials, conducted under the auspices of the Medical Research Council between 1950 and 1958, in which I had the privilege of participating. I would like briefly to remind you of the main conclusions reached.

*Based on a communication given to the Association of Surgeons of Great Britain and Ireland in April, 1960.

Firstly (Table II) it was shown that 109 patients treated with cortisone fared significantly better than 101 receiving inert therapy, the remission rates being

TABLE II.—*Results Obtained in Controlled Trials Conducted Under the Auspices of the Medical Research Council Between 1950 and 1958 into the Treatment of Colitis with Steroid Compounds*

	First Attacks		Relapses		Total	
	Total	% Remissions	Total	% Remissions	Total	% Remissions
Cortisone ..	45	42.2	64	40.6	109	41.3
Control ..	38	13.2	63	17.5	101	15.8
Cortisone ..	31	41.9	54	37.0	85	38.8
Corticotrophin	40	50.0	44	70.5	84	60.7

2 in 5 and 1 in 6 respectively (Truelove and Witts, 1955). First attacks 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 frequently and more completely than the controls, the numbers of patients treated and the precise frequency of remission being summarized in Table II. When the response to corticotrophin and to a larger comparable dose of cortisone was compared, the former was shown to possess a significant advantage, 3 in every 5 patients receiving it going into remission, as compared with 2 out of 5 receiving cortisone (Truelove and Witts, 1959). In this instance the response of first attacks to both agents was comparable, remissions occurring in 50% and 42% respectively. Relapsing cases treated with corticotrophin showed a significant advantage over those treated with cortisone, remissions occurring in 70.5% and 37% in each instance (Table II).

It will be seen from Table III that strikingly similar results have been obtained by groups of American and Canadian workers to those obtained in the M.R.C.

TABLE III.—*Percentage Remission Rates Induced in Colitic Attacks by Use of Steroids in Four Groups of Patients Treated in England and America*

Drug	Authors	Daily Dosage	No. of Patients Treated	Percentage Frequency of Remissions
Cortisone ..	Truelove and Witts (1955)	100 mg.	109	41.3
	Truelove and Witts (1959)	200 "	85	38.8
	Kirsner <i>et al.</i> (1959)	300 "	45	38.0
Corticotrophin	Truelove and Witts (1959)	80 units	84	60.7
	Kirsner <i>et al.</i> (1959)	160	166	50.0
	Malby <i>et al.</i> (1956)	160-300 units	109	64.0

trials. In my own hands either method seems to have about an even chance of success. It will also be seen from this table that the heavier dosage of steroids employed by the American and Canadian workers achieved no better results than did the more modest dosage employed in England.

Results which to my mind are not quite as good have been obtained by many workers with prednisone and triamcinolone used in comparable dosage. Thus Truelove (1960) could induce remissions in only 35% of 40 patients treated with prednisone; I personally observed remissions in 12 of 36 patients receiving prednisone and in only 6 of 22 receiving triamcinolone.

Topical Treatment

The favourable results reported from the topical use of hydrocortisone in skin, eye, and joint diseases

prompted Truelove in 1955 to apply steroids in the form of retention enema of hydrocortisone hemisuccinate sodium or prednisolone 21-phosphate, and later as prednisolone suppositories, to patients with ulcerative colitis of mild to moderate severity with predominantly distal colonic involvement. This treatment has been shown by a series of controlled trials to induce significantly more remissions than saline applied in the same way (Watkinson, 1958; Truelove, 1958). The dosage of, indications for, and method of administration of the various steroid compounds used topically in colitis are summarized in Table IV. In

TABLE IV.—*Types of Steroid Compound Used in Topical Treatment of Colitis, Together with Their Indications, Dosage, and Method of Administration*

	Dosage	Vehicle	Comment	Indications
Hydrocortisone hemisuccinate sodium	100 mg.	Retention* enema 100 ml.	Liquid unstable. Must be freshly prepared	Distal ulcerative colitis and proctocolitis
Prednisolone 21-phosphate	20 "	Saline nightly	Tablet stable	
Prednisolone suppositories	5 "	Suppository nightly	Convenience	Distal proctocolitis of short duration

* Retention facilitated by use of propantheline 15-30 mg. half an hour before enema.

patients with diarrhoea, retention of enema can be facilitated by the preliminary administration of propantheline by mouth or intravenously.

Results of treatment with topical steroids are summarized in Table V. Truelove, in the course of various trials, conducted between 1958 and 1960, reported remissions in between 69% and 75% of patients treated with topical hydrocortisone and in 64% of patients afflicted by milder proctocolitis receiving suppositories. Excellent results have been obtained by Matts (1960), who used prednisolone phosphate solution delivered from a disposable plastic enema bag (Table V). In my hands, 73 colitic attacks were treated with

TABLE V.—*Frequency of Symptomatic Remission and Improvement After Topical Treatment of Colitic Attacks with Various Steroid Preparations. Patients Treated with Prednisolone 21-Phosphate had Milder Attacks of Haemorrhagic Proctocolitis*

	Courses Treatment	Percentage Showing	
		Rapid Remission	Improvement
Hydrocortisone hemisuccinate sodium	{ 58* 20* 73†	69 70 52	18
Prednisolone 21-phosphate	{ 20* 32‡	75 94	
Prednisolone suppositories	{ 22* 36†	64 44	39
Prednisone orally, hydrocortisone enema	{ 20* 23†	100 83	

* Truelove (1958, 1959, 1960). † Watkinson (1956-60). ‡ Matts (1960).

rectal drips of hydrocortisone. Although 70% improved, only 52% showed complete remissions; while only 44% of 36 patients with haemorrhagic proctocolitis showed temporary remissions after treatment with prednisolone suppositories.

Combined Topical and Systemic Treatment

Truelove (1960) has suggested that *combined* systemic and topical treatment might be the treatment of choice in ulcerative colitis. By a combination of oral prednisone, 20 mg. daily, and rectal hydrocortisone he obtained remissions in all of the first 20 cases so

treated. Continued evaluation of this combined therapy is continuing by a controlled trial which Dr. Truelove and I are making together, employing sequential analysis; to date 19 of 23 patients so treated have remitted (Table V).

Complications of Systemic Steroid Therapy

The complications of steroid therapy occurring in the two M.R.C. trials are summarized in Table VI. It

TABLE VI.—Percentage Frequency of Complications During Systemic Treatment with Steroids are Summarized, Together with the Mortality and Number of Patients Requiring Surgical Treatment

	Trial 1950-5		1955-8	
	Cortisone	Inert	Cortisone	Corticotrophin
No. of patients	109	101	85	84
Early deaths	4.6	10.9	5.8	8.3
Perforation of bowel	0	2.0	3.5	3.5
Suppurative perianal or skin conditions	6.3	2.0	8.2	1.2
Hypercoricismism	0	0	2.3	18.3
Early surgery necessary	8.3	14.9	8.3	

will be seen that in the first trial both the mortality and the frequency of recourse to early surgery were halved by the use of steroids. In the second trial mortalities were appreciably higher, though they did not differ to a significant degree between the treatments adopted, and the overall recourse to surgery was similar.

The reputed production of colonic perforations by steroids has featured widely in the literature, clinicians tending to blame therapy rather than the course of the disease for this disastrous complication. When such perforations as were observed in the first trial occurred in patients who were not receiving steroids with an overall frequency of under 1%, I felt quite certain that steroids were blameless in this regard. My conviction was further strengthened by the work of Goldgraber *et al.* (1957) in Chicago, who showed, by a carefully retrospective study, that colonic perforation occurred twice as often in the 20-year period before steroid therapy was first used in 1949 as in the seven subsequent years 1950-6, when the compounds were in regular usage, relative frequencies in these periods being 2.5% and 1% respectively.

My convictions were somewhat shaken by the increased frequency of perforation in the second trial at 3.5% in both groups treated, and when I analysed my own experience in Leeds the perforation rate in 106 attacks of colitis treated with steroids was 7%. It is likely, however, that this high frequency may be due to the large proportion of acute fulminating attacks treated in Leeds, which are known to carry much higher mortality and morbidity rates. I think insufficient evidence exists to suggest that an increased prevalence of perforation accompanies the exhibition of steroids, but doubt about this issue is another reason for careful thought before the initiation of and careful supervision during steroid therapy.

It also appeared that suppurative perianal and skin conditions were more

common in the cortisone-treated group in each trial, making it desirable to combine short courses of antibiotic therapy with cortisone administration. Complications resulting from steroid therapy itself in the way of electrolyte disturbances, gain in weight, facial mooning, and mental illness were much more apparent with treatment with corticotrophin, and constituted a serious contraindication to its use.

Management of the Acute Attack

In treating the acute attack of moderate severity in addition to the general supportive measures detailed, I use sulphasalazine initially. If no improvement occurs in 7 to 10 days, topical steroid therapy is then tried for a further 10-day period. Finally, systemic steroids are given for two to three weeks. I still think that cortisone is the drug of choice, corticotrophin being reserved for resistant cases or fulminating attacks, and prednisone for the milder case or for out-patient usage. In the severe fulminating case I usually try a combination of systemic and topical steroid therapy or a combination of systemic steroids with sulphasalazine for 7 to 10 days, considering early surgery seriously if deterioration continues or a sudden worsening occurs. The high mortality and complication rate in the acute first attack has made me advise surgery at a much earlier stage than I did previously.

Maintenance Treatment

Little well-controlled information on the long-term results of treatment of colitis is available. Many patients stay well on a maintenance dosage of sulphasalazine, Svartz (1956) claiming that three-quarters of 119 patients followed for five years were still in remission, and Moertal and Bergen (1959) that 57% of 183 patients were well a year later after prolonged treatment with sulphasalazine.

As to maintenance treatment with steroids, rather damning evidence of its value was obtained in the M.R.C. trial conducted between 1955 and 1958. No significant difference in relapse rates could be demonstrated between a group of patients maintained for a year on a small dose of cortisone and one on inert therapy, relapses occurring in nearly one-half in each group, those who had received corticotrophin initially

Long-term results of treatment with sulphasalazine, cortisone, and topical steroids summarized at periods of 6, 12, 24, 36, 60, and 120 months. Numbers of patients remaining in remission at these times are indicated in the histogram above the zero line, while cumulative medical failures are shown in the hatched line below it. Darker areas indicate the patient in whom surgery was advised.

seeming to relapse earlier and more frequently than those treated initially with cortisone (Truelove and Witts, 1959). Better results have been claimed from prolonged steroid therapy by Kirsner *et al.* (1959), more than two-thirds of their patients remaining well for periods up to two or more years. Here larger maintenance doses were used, and the incidence of complications and side-effects was appreciable.

My own experience of maintenance treatment in colitis is shown in the Chart, where the long-term results with sulphasalazine and systemic and topical steroids are summarized for periods of up to 10 years. Of 57 patients showing remission or improvement after treatment with sulphasalazine, after four early failures and one recourse to surgery, 31 have continued in remission for periods up to six years.

Of 65 patients receiving maintenance treatment with steroids, 12 medical failures and 10 recourses to surgery occurred in the first six months, 18 by the end of one year, of whom 12 required operation, and at the end of the 10-year follow-up period there had been 30 failures of medical treatment, 20 requiring operation. In 35 patients, however, remissions have continued for periods of up to 10 years, in a few instances accompanied by surprisingly dramatic radiological and sigmoidoscopic improvement, though in the majority structural damage has persisted and even progressed during symptomatic remission. After topical treatment with hydrocortisone in 49 patients showing initial improvement, 13 failures occurred within six months and 24 within two years. However, remissions exceeding three years have been observed. There seems some evidence, therefore, to suggest that the long-term results of treatment with sulphasalazine are better than with steroids. The occasional prolonged remission obtained after maintenance treatment with sulphasalazine or cortisone has made me continue maintenance treatment for at least six months after symptomatic remission of the disease, when the respective treatment is then tailed off.

Problems for the Physician in Prolonged Maintenance Treatment of Colitis

The physician handling large numbers of colitic patients through the years does not sleep easily at night. He is haunted by the high frequency of carcinomatous transformation reported by his surgical colleagues in colitis of prolonged duration (Slaney and Brooke, 1959). Symptomatic exacerbation is of little value in predicting this complication, because misleading clinical quiescence, as Svartz and Ernberg (1949) have emphasized, often precedes the development of the carcinoma. I try to enforce yearly radiological examinations to detect neoplastic changes, but many patients are reluctant to undergo this unpleasant investigation and claim it may precipitate relapse. I still cannot bring myself to advise a purely prophylactic colectomy in a symptomless patient on the grounds that his colitis is of prolonged duration and that he may have a 1 in 5 chance of developing a carcinoma as has been suggested by Slaney and Brooke (1959). I think even the most persuasive of surgeons would have great difficulty in "selling" such an operation to a patient of this type. However, I readily advise surgery in symptomatic relapse or pathological worsening in these circumstances. To date I am aware of only two patients developing carcinomata under my care. While it may be that the physician's estimate of this complication is too low, I feel the surgeon's is too high in that he tends to collect chronic cases of

prolonged duration in which the complication is most likely to develop.

The second problem for the physician is the management of segmental or right-sided colitis where, because of initial symptomatic remission on medical treatment, he may allow the process to spread distally to involve the rectum, rendering more extensive and less desirable surgery necessary (Watkinson *et al.*, 1960).

A third problem is the management of the adolescent affected by the disease, where the severe retardation of physical and endocrine maturation which often accompanies the disease, the long-term poor prognosis, and the high rate of neoplastic change may make colectomy necessary, however undesirable it seems in so young a subject (Rosenqvist *et al.*, 1959). Finally, despite the control of the diarrhoea, in a few patients continued systemic complications, such as arthritis or skin lesions, may enforce colectomy.

Relation of Steroid Therapy to Surgery

I would finally like briefly to examine the evidence that steroid therapy adversely affects the outcome of surgery, in the light of operations for colitis performed by my surgical colleague, Professor J. C. Goligher. Our joint experience in this regard is reported elsewhere (Goligher, 1960), but a few general remarks seem appropriate. Firstly, it is quite certain that alarming operative and post-operative hypotensive crises do develop in patients who have had steroids, that no reliable biochemical tests exist for their prediction, and it is obligatory that any patient who has ever received steroids be given supportive therapy throughout the operative and post-operative period. Secondly, analysis of our experience at Leeds, and the adverse experience of others, has convinced us of the very serious prognosis of the acute fulminating attack, particularly in the elderly subject. Although this group contains some of the physician's most dramatic and most lasting successes, it also contains some of his most disastrous failures. This is well illustrated in Table VII, where it will be seen that in the 36 acute fulminating attacks of the disease the perforation rate, mortality, and recourse to early surgery were between two and four times greater than the exacerbations of chronic disease; indeed, I was glad to have Professor Goligher's help in treating nearly a quarter of these patients, and in several instances I felt that I had been guilty of postponing operation for too long.

TABLE VII.—*Outcome of Medical Treatment in 36 Acute First Attacks of Colitis Contrasted with Results of Treating 108 Chronic Relapsing Patients. The Frequency of Perforation, Early Surgery, and Death was Between Two and Four Times Greater in the Acute Group*

	No. of Patients	Remissions	Perforations	Deaths	Early Surgery
Acute fulminating first attacks . .	36	40%	8%	14%	23%
Chronic continuous or intermittent disease . .	108	52%	2.7%	2.7%	12%

In this type of case the physician should bring his most potent therapeutic weapons to bear immediately and be prepared to admit failure after two to three weeks if deterioration has continued. Only in this way will the surgeon receive the better operative material he deserves.

It is my opinion, therefore, that at all stages of colitis there is scope for a combined medical and surgical approach to the problem. The physician should initiate

treatment but keep the possibility of surgery in constant review with a surgeon particularly interested and experienced in this field. I have been fortunate in having the tolerant and enthusiastic support of Professor Goligher at a combined medical and surgical follow-up clinic which we have run together in Leeds for the last five years, and in which the medical and surgical fortunes of our patients have been reviewed together.

Summary

Medical treatment of the colitic patient is described. The results of treatment and the relative merits and disadvantages of treatment with sulphasalazine and steroid compounds administered topically and systemically are detailed. Problems arising in the long-term medical treatment of colitis are touched upon, notably the risk of carcinomatous transformation, of distal extension in segmental colitis, and the physical retardation of the child affected by the disease.

Finally, an analysis of the outcome of surgery in patients who have received steroids has emphasized the importance of supportive therapy in the operative and post-operative period. It is also emphasized that the vicious nature of the acute fulminating attack of the disease makes early recourse to surgery necessary unless medical treatment proves immediately successful.

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"In other words, much of the work that is being done and the papers that are being published are done and published for the wrong reasons: because someone had too much money to spend; or because a government official had to dispose of all the appropriated funds within the fiscal year; or because someone forced someone else to work in an area not of his own choosing; or because someone found it easier to drift along on fellowships than to strike off on his own; or because a practitioner thought it would 'look good' if he did some research; or because an assistant professor needed 'to publish' to get a promotion; or because of a thousand other reasons irrelevant to the advancement of medical knowledge. Shoddy reasons for doing research tend to produce shoddy research. This Foundation has no desire to contribute to the publication explosion. At no time have we brought any pressure to bear on Markle Scholars to publish. On the contrary, we have told them repeatedly that we believe there are other ways of evaluating the accomplishment of a man than counting the number of his publications. . . . Scientific papers should be the main means of communication between scientist and scientist, and between scientist and practitioner, but they should not be used for advertising purposes." (*John and Mary R. Markle Foundation Annual Report, 1959-60. Report of the President, Mr. J. M. RUSSELL.*)

SURGICAL TREATMENT OF ULCERATIVE COLITIS*

BY

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In this short paper only two aspects of colitis surgery are considered, but they are two of the outstanding issues at the present time in the surgical management of this disease. The first is the vexed question of colectomy with ileo-rectal anastomosis, which continues to provoke much discussion; the second is the surgical care of acute phases of colitis, which still remains a major problem.

Colectomy with Ileo-rectal Anastomosis

By comparison with Aylett (1959), the chief protagonist of this operation, who apparently employs it almost routinely in the surgical treatment of ulcerative colitis, my indications for its use have been extremely restricted, so that of the 145 patients with colitis on whom I have operated during the past seven to eight years only 22, or some 14%, have been given ileo-rectal anastomoses (Table I). My experience also differs from

TABLE I.—Methods Used for Primary Excision in 145 Consecutive Operations for Colitis (1952-9 Inclusive)

Proctocolectomy + ileostomy	104	} 123
Colectomy + ileostomy	19	
Colectomy + temporary ileostomy, followed by secondary ileo-rectal anastomosis	4	} 22
Colectomy + primary ileo-rectal anastomosis	18	

Aylett's in that my results have been much less consistently favourable than his, and in trying to reach a decision about this operation it may be of value to examine the record of my few successes and failures.

In considering colectomy and ileo-rectal anastomosis for colitis I believe it is important to distinguish clearly between segmental or so-called right-sided forms of the disease on the one hand and ordinary, diffuse, or primarily left-sided colitis on the other.

Segmental or Right-sided Colitis

I used to have considerable doubts about the existence of genuine right-sided ulcerative colitis and thought that most cases alleged to have lesions of this kind were really examples of Crohn's disease, affecting the colon alone or in conjunction with an ileal lesion. However, as a result of my experiences in the last few years I am now convinced that there is a brand of colitis that is macroscopically and microscopically indistinguishable from ordinary ulcerative colitis, except that it originates in the more proximal part of the colon and spares the rectum and possibly the distal colon in the first instance (Watkinson, Thompson, and Goligher, 1960). Actually some 7-8% of the cases of colitis coming under my care at the present time turn out to be of this variety. Clearly if surgical treatment should become necessary in such cases there is no need to sacrifice the normal rectum, and operation can take the very rational and attractive form of a colectomy with ileo-rectal anastomosis.

In segmental colitis there is a tendency for the condition to spread distally. This places the physician under a special obligation to resort to surgery without too much delay if the lesion is not being satisfactorily

*Being a paper read in the discussion on Ulcerative Colitis at the meeting of the Association of Surgeons of Great Britain and Ireland in Birmingham on April 9, 1960.