

Discussion

This case raises the interesting problem of the possible causes of hyperglobulinaemia and consequently raised E.S.R. According to Wintrobe (1956) the common causes are myelomatosis, lymphogranuloma venereum, sarcoidosis, disseminated lupus erythematosus, kala-azar, subacute bacterial endocarditis, cirrhosis of the liver, leukaemia, and chronic nephritis. To this list can be added "essential hyperglobulinaemia" as coined by Waldenström (1943, 1946, 1952), but the case for the existence of this condition does not seem to be fully established. Two of Waldenström's cases had macroglobulinaemia, which has now been shown by Martin and Close (1957) not to be a specific disease.

The finding of an increased number of plasma cells in the sternal marrow (13%) in December, 1952, certainly suggested myelomatosis as the correct diagnosis, because the upper limit of normal is usually regarded as being 1%–2% (Wintrobe, 1956; Whitby and Britton, 1957). A moderate increase in plasma cells, however, is not necessarily diagnostic of myelomatosis, as this may occur in rheumatic fever, collagen diseases, hypersensitivity reactions, cirrhosis of the liver, and Hodgkin's disease.

In myelomatosis x-ray changes in the bones are usually regarded as an essential feature, but it is now realized that a diffuse infiltration may occur without specific isolated lesions. Thus Wallerstein (1951) describes three such cases, and Kubota *et al.* (1956) found four in a series of 60 cases of proved myelomatosis.

The present case is described because such a long period (four years) had elapsed between the time when the patient was first known to have hyperglobulinaemia and the development of symptoms of clinical myelomatosis. During this time she seemed to be in normal health and carried out all her duties as a housewife. The only clinical abnormality was anaemia, which did not increase during this period (see Table II). Electrophoretic analysis showed marked increase in gamma-globulin, with the sharp peak characteristic of myeloma-globulin. Ultracentrifugal analysis showed an excess of proteins with an S_{20w} of 6.7, but no components of higher molecular weight. Another interesting point is that it was nearly five years before Bence Jones protein could be detected in the urine. This observation supports the suggestion of Putnam *et al.* (1956) that Bence Jones protein is not the direct result of degradation of the circulating or tissue proteins. It is also in accord with the now well-known fact that marked hyperglobulinaemia and Bence Jones proteinuria occur in inverse ratio (Snapper *et al.*, 1953). The pleural effusion which brought the patient under observation is presumed to have been tuberculous and not related to the subsequent development of myelomatosis, as no further chest complications have occurred and the chest has remained radiologically normal.

Summary

A case of myelomatosis is described in which four years elapsed between the discovery of marked hypergammaglobulinaemia and the development of signs and symptoms of this disease.

FOOTNOTE

The patient died on September 23, 1958. Necropsy confirmed the diagnosis of myelomatosis, there being extensive medullary and extramedullary deposits of plasma cells. There was moderate oedema of the lungs, but no evidence of tuberculosis.

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SUPPOSITORY TREATMENT OF HAEMORRHAGIC PROCTITIS

BY

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Haemorrhagic proctitis is a condition of unknown aetiology in which the rectum is diffusely inflamed. Other names for the condition are idiopathic proctitis and granular proctitis. If the inflammation extends into the sigmoid colon the condition is often referred to as proctosigmoiditis. The cardinal symptom is the passage of blood, pus, and mucus per rectum. There may be bouts of diarrhoea, but in between these the motions are usually firm or even costive. Indeed, some sufferers seldom or never experience diarrhoea. Rectal bleeding is more likely to be heavy when constipation is present, because of increased trauma during defaecation, and the blood is then separate from the main mass of the stool, not intimately mixed with it as in the diarrhoeal stool of classical ulcerative colitis. In between the passage of stools there are commonly several passages of blood or blood-stained mucus each day.

Lower abdominal pain may occur, low back pain is common, rectal pain is sometimes experienced, and tenesmus may be a feature; but the general health usually remains good and severe loss of weight and other signs of constitutional disturbance do not occur, with the conspicuous exception of anaemia. The anaemia is of the iron-deficiency type usually found in chronic blood loss and is sometimes severe. On sigmoidoscopy it is often possible to get above the

inflamed area and to observe normal colonic mucosa. The barium-enema examination is sometimes negative, although a skilled radiologist will usually detect an abnormal rectal mucosal pattern. In effect, the illness is a minor one compared with classical ulcerative colitis, in which the general health is often much affected and the disease sometimes runs a dangerous course.

Some workers regard haemorrhagic proctitis as entirely distinct from ulcerative colitis. For example, Hess Thaysen (1934) described it as "a morbid condition which, when present in a very mild degree, as a rule is mistaken for haemorrhoidal bleeding, while in its severe form it is usually regarded as ulcerative colitis, *although it has nothing to do with these two conditions*" (my italics). Similarly, Brooke (1953, 1954) distinguishes the condition of proctosigmoiditis from classical ulcerative colitis affecting a large part or the whole of the colon. Other authorities regard the condition as no more than ulcerative colitis which is localized to the rectum or to the rectum and the lower pelvic colon. Goligher (1953) stated that "it is certainly incorrect to describe ulcerative colitis and proctosigmoiditis as fundamentally different diseases." Among the reasons for this opinion he gave "our finding in a number of cases of mild granular proctosigmoiditis that the pathological process subsequently spread proximally to involve the entire colon and to produce severe symptoms requiring colectomy."

A study by Newell and Avery Jones (1958) revealed that 8% of patients with haemorrhagic proctitis when first seen had subsequently developed extensive ulcerative colitis. To quote their own words: "The view was firmly established from this survey that idiopathic proctitis was one and the same disease as ulcerative colitis but in a localized and milder form." My own experience is also strongly in favour of this view, for the following reasons: (1) Haemorrhagic proctitis has been observed to progress into extensive ulcerative colitis, exactly as described by Goligher and by Newell and Avery Jones. (2) Patients with classical ulcerative colitis have subsequently been seen with the symptoms and sigmoidoscopic signs of haemorrhagic proctitis. In some patients this has been merely a stage in the evolution of a severe attack of ulcerative colitis. (3) In the course of extensive biopsy studies of patients with rectal and colonic disease, now amounting to about 800 biopsy examinations, the histological appearances have proved to be similar in the two conditions.

There can therefore be little doubt that haemorrhagic proctitis is sometimes the precursor of ulcerative colitis and sometimes a sequel to an attack of it. We must inevitably conclude that, in at least some patients, haemorrhagic proctitis is merely a localized form of ulcerative colitis. The treatment of haemorrhagic proctitis therefore assumes importance for two distinct reasons: (1) the condition is troublesome and disagreeable to the patient and deserves to be treated on its own merits; and (2) if it can be successfully treated there is the possibility that some attacks of ulcerative colitis will be averted.

During recent years considerable success in treating ulcerative colitis has been obtained by the use of hydrocortisone solutions applied locally to the colon by means of a nightly rectal drip (Truelove, 1956, 1957). This form of treatment has been shown to be effective in a large proportion of patients by two independent

studies each employing the "double-blind" technique (Truelove, 1958; Watkinson, 1958). Some of the patients included in my own studies have been examples of disease localized to the rectum and recto-sigmoid region, because I have never regarded this type of disease as basically different from more extensive ulcerative colitis.

The use of a nightly rectal drip has certain disadvantages in the case of patients with disease limited to the rectum and recto-sigmoid area. First, it involves some degree of inconvenience for the patient, which is a small price to pay if it relieves the symptoms of ulcerative colitis but is worth avoiding if equally good results can be obtained more simply. Secondly, a characteristic of the rectal drip is that the solution travels widely through the colon, a property which is unnecessary in the case of localized distal disease. Thirdly, the treatment involves the use of comparatively large quantities of hydrocortisone, so that long-term treatment is expensive.

Use of Suppositories in Treatment

In 1957 suppositories containing 10 mg. of hydrocortisone in the form of the hemisuccinate sodium ester were used to treat a case of post-radiation proctitis and were found to be highly successful. In consequence the use of these suppositories was extended to patients with distal forms of ulcerative colitis and proctitis. More recently, experience has been gained with suppositories containing prednisolone 21-phosphate, a compound resembling hydrocortisone hemisuccinate sodium in so far as it is highly soluble in water and would therefore be expected to enter the mucosa of the rectum and colon if brought into contact with it. The results with both these types of suppository have been encouraging, and the purpose of the present article is to present them.

Composition of the Suppositories.—Two types have been used. The first contains 10 mg. of hydrocortisone in the form of the hemisuccinate sodium ester which is incorporated in a base of oil of theobroma. The second contains 5 mg. of prednisolone 21-phosphate in a proprietary base.

Dosage.—Initially the suppositories were used twice a day, one being inserted at bedtime, the other after defaecation in the morning. In some patients in whom the response was excellent the dose was reduced after about three months to the nightly suppository only.

Results

The first 22 patients treated are now reported, brief individual details being given in Table I. Of these 22, 14 obtained complete relief from their symptoms, and this relief has persisted up to the time of writing, the suppositories having been discontinued in some of them or reduced to the use of one a day. In patients in whom the suppositories were effective the response was a decisive one, marked improvement occurring in the first few days, and the clinical response being complete in less than a fortnight. Favourable clinical responses were accompanied by corresponding improvement in the sigmoidoscopic appearances, which often became normal. In other words, if a definitely beneficial response is not apparent after two weeks at the outside, the suppositories can be considered to have failed and other therapeutic measures should be applied.

TABLE I.—Clinical Details and Response to Suppository Treatment (the First 10 Cases were Treated with Hydrocortisone Hemisuccinate Suppositories, the Remainder with Prednisolone Phosphate Suppositories)

Case No.	Sex and Age	First Attack or Relapse	Length of Immediate Symptoms	Total Length of History	Past History of Proctitis or Classical Ulcerative Colitis	Sigmoidoscopy before Treatment	Clinical Response	Sig-moidoscopy after Treatment	Subsequent Course	Length of Observation
1	M 37	F	3 months	3 months	—	Proctitis	Remission	Normal	Symptom-free	9 months
2	F 48	R	3 "	15 years	U.C.	" "	" "	" "	" "	9 "
3	F 17	F	4 "	4 months	—	" "	" "	" "	" "	9 "
4	M 22	R	1 month	11 years	U.C.	" "	Worse	Colitis	Other treatment	" "
5	F 42	R	1 "	6 "	P.	" "	Unchanged	Unchanged	" "	" "
6	M 67	R	1 "	11 "	U.C.	Proctosigmoiditis	Improved	Improved	" "	" "
7	F 23	R	2 years	2 "	P.	Proctitis	Remission	Normal	Symptom-free	7 months
8	M 30	R	6 weeks	1½ "	U.C.	" "	" "	" "	" "	7 "
9	M 23	R	4 months	2 "	P.	" "	" "	Near-normal	" "	7 "
10	F 32	R	1 month	5 "	P.	" "	" "	" "	" "	7 "
11	M 26	R	2 months	2 "	P.	" "	Unchanged	Unchanged	Other treatment	" "
12	F 36	F	11 "	11 months	—	Proctosigmoiditis	Remission	Normal	Symptom-free	6 months
13	M 37	R	1 month	11 years	P.	Proctitis	Unchanged	Unchanged	Other treatment	" "
14	M 25	F	1 "	1 month	—	" "	Remission	Near-normal	Symptom-free	6 months
15	F 31	R	1 "	1½ years	P.	" "	Unchanged	Unchanged	Other treatment	" "
16	F 41	R	1 "	5 "	U.C.	Proctosigmoiditis	" "	" "	" "	" "
17	M 47	R	2 months	3 "	P.	" "	" "	" "	" "	" "
18	M 34	R	2 "	9 "	P.	" "	Remission	Near-normal	Symptom-free	4 months
19	M 42	F	3 "	3 months	—	Proctitis	" "	" "	" "	4 "
20	F 40	F	8 "	8 "	—	" "	" "	" "	" "	4 "
21	F 23	R	1 month	3 years	U.C.	" "	" "	Normal	" "	4 "
22	F 78	F	2 months	2 months	—	" "	" "	Near-normal	" "	4 "

The finding that 14 out of 22 patients experienced symptomatic and sigmoidoscopic remission with the use of the suppositories makes the method of treatment appear moderately successful. A different slant is obtained by considering whether the cases were fresh ones or whether there was evidence of long-standing disease, either intermittent or continuous. Fresh cases have been defined as patients with symptoms beginning for the first time less than one year before suppository treatment was begun. When the patients are thus subdivided into fresh and chronic cases, an important finding emerges: *all the fresh cases responded well to the treatment.* All were symptom-free in less than a fortnight and with the sigmoidoscopic appearances either normal or near-normal. None of these fresh cases have relapsed up to the present time, although it must be mentioned that only two of them have ceased to use the suppositories. The uniformly successful results obtained with the fresh cases must be viewed with a certain reserve because there were only seven such cases (Nos. 1, 3, 12, 14, 19, 20, and 22), and from such a small sample any generalization should be made with caution. However, if we compare the results in these fresh cases with those obtained in the chronic ones, the results are significantly better for the former (Table II).

TABLE II.—Comparison of Results of Treatment in Fresh and Chronic Cases of Haemorrhagic Proctitis

	Effect of Treatment		Significance of Difference
	Failed	Successful	
Fresh cases	0	7	An exact test of significance gives a probability of approximately 0.04
Chronic "	8	7	

Further evidence about the type of case likely to be responsive to treatment can be sought by considering how successes and failures were distributed among the chronic cases. First, it does not seem to be important whether the previous history is of haemorrhagic proctitis or of classical ulcerative colitis. Thus there were six cases (Nos. 2, 4, 6, 8, 16, and 21) with a past history of more or less extensive ulcerative colitis, and three of these responded well; one of these three (Case 8) had previously had an extremely severe attack

of ulcerative colitis with the whole colon involved. In other words, the extent of past involvement of the colon does not seem to influence the response to suppository treatment in those patients who relapse with the haemorrhagic proctitis syndrome.

Secondly, the length of the immediate attack of symptoms does not seem to be important, for most of the chronic cases had had their present symptoms for only a few weeks or months before starting treatment. It is the chronicity of the disease as a whole which marks off the chronic cases from the fresh ones, rather than the duration of the immediate symptoms. The conclusion to be drawn is that early diagnosis is of cardinal importance so that fresh cases are treated as they develop. If the bulk of these can be treated successfully there is at least the possibility that far fewer cases will evolve into the chronic form.

Illustrative Case Histories

Example of a Fresh Case (Case 1, Table I).—A man aged 37 was first seen in February, 1958, when he was referred by a surgical colleague because of haemorrhagic proctitis. For the previous three months he had been passing bright red blood on defaecation every day. A barium-enema examination had shown evidence of some abnormality in the mucosal pattern of the rectum and sigmoid colon but no evidence of neoplasm. Sigmoidoscopy revealed sharp inflammation of the rectum and recto-sigmoid area, with hyperaemia, granularity, and contact bleeding, but above 6 in. (15 cm.) from the anal margin these changes shaded off into normality. He was given the suppositories to use twice a day. After two days' treatment the rectal bleeding ceased and did not recur. Some mucus was passed per rectum for a few more days and he then became entirely symptom-free. Sigmoidoscopy carried out one month after starting treatment showed the rectal mucosa to be within normal limits. He has remained entirely symptom-free during the succeeding nine months, having stopped treatment after three months.

Example of Ulcerative Colitis Relapsing as Haemorrhagic Proctitis (Case 8, Table I).—A man aged 30 developed his first attack of ulcerative colitis in 1956. The attack became very severe, with involvement of the entire colon. He was given intensive in-patient treatment and eventually became symptom-free, although in the course of treatment he developed Heinz-body anaemia due to salicylazosulpha-

pyridine ("salazopyrin") therapy (he was Case 1 of the article dealing with Heinz-body anaemia by Spriggs *et al.*, 1958). Thereafter he remained entirely symptom-free until 1958, when he was seen in March with a six-weeks history of passing blood when the bowels were opened. Sigmoidoscopy showed the typical appearances of haemorrhagic proctitis. He was given suppository treatment. Improvement occurred after the first suppository, and in two days he became symptom-free. The sigmoidoscopic appearances were normal when he was examined one month later. During the succeeding seven months he remained clinically and sigmoidoscopically normal, the dose of suppositories having been reduced to one nightly after the first three months.

Discussion

The present study has shown complete symptomatic relief in two-thirds of the patients with haemorrhagic proctitis treated with suppositories containing water-soluble compounds of hydrocortisone and prednisolone. Symptomatic relief is accompanied by notable improvement in the sigmoidoscopic appearances, which become normal or close to it. This method of treatment cannot be expected to be effective against widespread colonic disease, and the ideal case for its use is one in which it is possible to get above the inflamed area on sigmoidoscopy. In any event, if there is no clear-cut satisfactory response in a fortnight, this method of treatment should be abandoned and some more powerful therapeutic approach tried. However, for those who respond favourably the method offers a treatment which is easy to apply and one which carries no appreciable risks of any side-effects. In such patients it seems at present desirable to continue with the treatment for some months, and ideally it should not be stopped unless the sigmoidoscopic appearances are normal. The slightest return of symptoms should be the signal for immediate resumption of treatment, because histological and sigmoidoscopic relapse precede clinical relapse, so that mild symptoms usually indicate the existence of sharp inflammation.

It should hardly be necessary to add that precise diagnosis is a *sine qua non* for the employment of this type of therapy, but observation of several examples of faulty diagnosis prompts the following remarks. Severe attacks of ulcerative colitis seldom present much difficulty in diagnosis in this country, although they may temporarily be attributed to an infective dysentery. The mildest cases, which include those now spoken of as haemorrhagic proctitis, have to be separated from two other common conditions. On the one hand, the rectal bleeding, which is so often the salient feature, may be attributed to haemorrhoids; this error does little harm because treatment of any haemorrhoids present fails to give relief and the diagnosis is then reconsidered. On the other hand, the symptoms of haemorrhagic proctitis are identical with those occurring in many examples of rectal and lower colonic carcinoma, and it is a tragic blunder if a patient is labelled as suffering from haemorrhagic proctitis (or simply from haemorrhoids) when in reality a carcinoma is responsible for the symptoms.

External examination of the anus is of little diagnostic help. Digital examination of the rectum is likewise of limited value, although it permits positive diagnosis of rectal growths which are low down. Sigmoidoscopy permits direct inspection of the rectal mucosa, and in most cases the diagnosis of haemorrhagic proctitis is immediately apparent when this is done; so also is the

diagnosis of rectal and low colonic growths. A barium-enema examination should also be done to exclude a carcinoma or other lesions beyond the reach of the sigmoidoscope. That these elementary considerations deserve emphasis is apparent from a study by Muir (1956) from which it appears that the diagnosis of carcinoma of the rectum and colon is often unnecessarily delayed, the patient having symptoms for an average time of six months before he arrives at hospital. Similar findings by Swinton and Counts (1956) from America show that the problem is not confined to our own country.

With this proviso—namely, that the diagnosis of haemorrhagic proctitis has been confidently made on sigmoidoscopy and other lesions excluded by this examination and by barium enema—the use of the suppositories seems likely to bring relief to a large proportion of patients with the condition. This is especially likely to be so with fresh cases, for in these this treatment has so far proved uniformly successful.

Summary

Haemorrhagic proctitis is a disease of unknown aetiology in which the rectum is diffusely inflamed so that bleeding occurs spontaneously or with slight trauma, as, for example, during defaecation. If the inflammation extends into the sigmoid colon, the term proctosigmoiditis is employed. In our present state of knowledge it is best to regard haemorrhagic proctitis and proctosigmoiditis as localized distal forms of ulcerative colitis.

Suppositories containing water-soluble compounds of hydrocortisone and prednisolone have been used to treat 22 patients with the condition.

Rapid and complete symptomatic relief was obtained in 14 of these patients, such relief being accompanied by notable improvement in the sigmoidoscopic appearances, which usually became normal.

The best results were obtained in fresh cases of the condition, the treatment being uniformly successful in the seven patients of this type included in the series.

The treatment has the virtues of easy application and low dosage of steroids, so that side-effects are most unlikely to occur.

Some comments are made on the necessity for precise diagnosis before this form of treatment is used.

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