group, despite its larger number of perforations, was roughly the same as in the group not receiving steroids. But naturally perforation, by leading to infection, is apt to complicate and prolong the convalescence enormously. I think that the apparent impairment of wound-healing and the high incidence of serious sepsis noted in the patients having steroids is to be attributed to this circumstance rather than to any specific interference with tissue vitality and resistance to infection. Certainly in my cases undergoing *interval* proctocolectomy there has been no noticeable difference in the incidence of wound complications whether steroids were given or not (see Table VI).

TABLE V.—*Emergency Colectomy or Proctocolectomy for Ulcerative Colitis* (1952–9 *Inclusive*)

	Cases Treated	Cases with Perforation			Operative Deaths	Severe Wound Sepsis or Delay of Wound Healing	Post-operative Hypotensive Collapse
		Total	Open	Sealed			
Steroids given	28	11	4	7	8	14	1
Steroids not given	13	1	0	1	4	4	0
All cases	41	12	4	8	12 (29·3%)	18	1

TABLE VI.—*Interval Colectomy or Proctocolectomy for Colitis* (1952–9 *Inclusive*)

	Cases Treated	Operative Deaths	Severe Wound Sepsis or Delay of Wound-healing	Post-operative Hypertensive Collapse
Steroids given	39	0	2	2
Steroids not given ..	65	3	1	2
All cases ..	104	3 (2·9%)	3	4

Our experiences with perforations certainly conflict with the findings of the first Medical Research Council trial (Truelove and Witts, 1954, 1955). They make it difficult to resist the conclusion that steroid administration in some way predisposes to this complication—either by a direct deleterious effect on the bowel wall or, as I believe is more probable, by prolonging the course of conservative treatment and thereby extending the period at which the patient is a risk. It is clear that the physician assumes a very serious responsibility when he essays remission with steroid therapy in these very urgent cases, and I consider that such attempts by him are only justifiable if he accepts a very definite time-limit to his efforts and, failing clear signs of improvement within 10 days, is prepared to invoke surgical aid without further heart-searching or delay.

Summary

This paper is concerned with two aspects of the surgical treatment of ulcerative colitis.

The value of colectomy and ileo-rectal anastomosis has been appraised. While excellent results have been obtained in patients with segmental colitis without rectal involvement, the results in diffuse forms of the disease have been disappointing and have failed in half the cases in which the operation was attempted. The use of the operation in diffuse colitis, therefore, is not recommended, and is only reluctantly undertaken at the patient's request where rectal involvement is slight or the patient seems mentally incapable of accepting or managing an ileostomy.

The results of the surgical treatment of the acute phases of colitis are reported in 41 patients with fulminating primary attacks or exacerbations of the disease. Here operative mortality was ten times greater than in patients with chronic or milder disease owing largely to the high frequency of pre-operative perforation, which occurred in nearly a third of these patients. The role of steroid therapy in relation to these results is discussed. It is felt that unless early improvement follows medical treatment in this type of case emergency surgery should not be delayed. Primary colectomy-ileostomy is still regarded as the operation of choice, though use of simple ileostomy in particularly ill patients might reduce the operative mortality.

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ULCERATIVE COLITIS PROVOKED BY MILK

BY

S. C. TRUELOVE, M.D., M.R.C.P.

Nuffield Department of Clinical Medicine, University of Oxford

(From the Radcliffe Infirmary, Oxford)

The aetiology of ulcerative colitis remains obscure. Infective, allergic, nutritional, and psychosomatic theories have been advanced, but there is no general agreement that any one of these is an adequate explanation. One result is that medical treatment has been forced to develop on the basis of trial and error. The lack of universal efficacy of our present medical measures is apparent from the fact that total colectomy is necessary in some patients. The need to find specific factors in the causation of the disease is obvious.

Present Study

During the last few years a group of patients with ulcerative colitis has been recognized in whom removal of milk (and protein milk-products such as cheese) from the diet has been followed by marked improvement in the clinical course of the disease. In several of these patients milk has been reintroduced into the diet, and in every instance this has been followed by a frank attack of ulcerative colitis. The object of the present article is to describe these observations and to discuss their implications.

Case 1

A housewife aged 29 developed ulcerative colitis in 1955 during her second pregnancy. On admission to another hospital for treatment, because of anaemia and weakness, the condition worsened, and she was transferred to the Radcliffe Infirmary on July 15, after preliminary transfusion with 5 pints (2.9 litres) of blood. At that time she was 36 weeks pregnant and was passing 8–12 loose bloody motions a day, but her general condition was reasonably good.

Four days after admission she went into labour and was delivered of a healthy baby. A few days after delivery there was a sharp exacerbation of the ulcerative colitis, with the frequent passage of bloody stools, colicky abdominal pain, fever, and leucocytosis (W.B.C. 30,000). A.C.T.H.-gel 80 units daily, was injected intramuscularly in addition to general medical measures. On this regime she gradually improved, but severe hypercortisonism developed. The A.C.T.H. was stopped after six weeks' treatment and the patient was discharged home, having about three loose stools a day with a small amount of blood present.

Two days after discharge she relapsed with about seven loose bloody stools a day and was readmitted to hospital. Sigmoidoscopy showed the changes of severe ulcerative colitis. She was moderately anaemic (Hb, 70%) and the E.S.R. was much raised (88 mm. in 1 hour). Cortisone by mouth, 25 mg. q.d.s., was given in addition to general medical measures, such as control of electrolyte balance, repeated blood transfusions (25 pints (14 litres) of blood during her stay), penicillin, and sulphonamides, high-protein diet, and vitamin supplements. After some weeks a further course of A.C.T.H. was tried and then a course of sulphasalazine ("salazopyrin"). The illness proceeded in spite of this intensive medical treatment, and after two months colectomy began to be considered as the next step.

At this point, in order to preserve the state of nutrition, she was put on to a nightly gastric drip of milk containing fresh eggs beaten up in it. However, this was followed by further exacerbation of the bowel symptoms. Therefore high-protein diet was given with rigid exclusion of milk and eggs in any form. Thereafter, steady improvement set in and she became entirely symptom-free. She was discharged home on January 21, 1956, six months after her original admission, on a diet excluding eggs and milk but on no other treatment.

When seen as an out-patient on February 13 she was feeling well, and was having two soft motions a day without blood. Haemoglobin was 109% (16.1 g./100 ml.) and the E.S.R. 7 mm. in 1 hour. On March 12 she was well, and the Hb was 105% (15.5 g./100 ml.) and E.S.R. 8 mm. in 1 hour. She was advised to try the effect of adding eggs and milk to the diet.

On April 9 she reported that she had eaten boiled and other cooked eggs without harmful effects. She had tried adding milk to tea, but this was followed the next day by diarrhoea which settled in a day or two, and the experiment had not been repeated. Cooked cheese had been eaten without harmful effect, but when uncooked cheese was tried she had four loose stools the next day. After a few more days she tried uncooked cheese again, with a similar result and, in addition, the passage of some blood per rectum. It was decided to study the effect of ingesting cheese in more detail.

On April 12 sigmoidoscopy showed some areas of scarring, but the mucosa was otherwise within normal limits. A mucosal biopsy specimen was taken from the lower sigmoid colon, approximately 7 in. (17.5 cm.) from the anus, by means of a Truelove–Salt biopsy instrument. Histological examination of this specimen showed near-normal appearances (Fig. 1). The blood was normal: Hb, 98% (14.5 g./100 ml.); E.S.R. 7 mm. in 1 hour; W.B.C., 12,000/c.mm.

After this examination on April 12 she waited a few days and then began, on April 17, to eat a helping of uncooked cheese each day. On April 19 there was some looseness of the motions and sigmoidoscopy showed definite hyperaemia. She continued to eat a daily helping of cheese. After one week on it she began to pass blood and large quantities of mucus per rectum and was having about three loose bloody stools a day. She continued on the cheese for a few more days and then stopped eating it. However, the bloody diarrhoea continued. When seen by me on May 3 she was generally unwell and the Hb was 78% (11.5 g./100 ml.), E.S.R. 26 mm. in 1 hour. Sigmoidoscopic examination showed active ulcerative colitis of moderate severity. Histological examination of a biopsy specimen from the lower colon showed the changes of active ulcerative colitis (Fig. 2).

[NOTE.—So far as the histological evidence of relapse is concerned, the sections have recently been submitted to Dr. W. C. D. Richards, a pathologist with a special interest in the gastro-intestinal tract. He reports:

"Section I (of April 12, 1956) (Fig. 1). The full thickness of the mucosa, the muscularis mucosae, and a portion of submucosa are present. No abnormality of the surface epithelium and glands is seen. There is mild congestion of the mucosal capillaries and the cellular content of the lamina propria is slightly increased. The cells are mainly plasma cells, lymphocytes, and eosinophil leucocytes. A follicular collection of lymphocytes is present at one end of the section and there are two small lymphocytic aggregates in the submucosa. A slight increase in cells is noted in the submucosa.

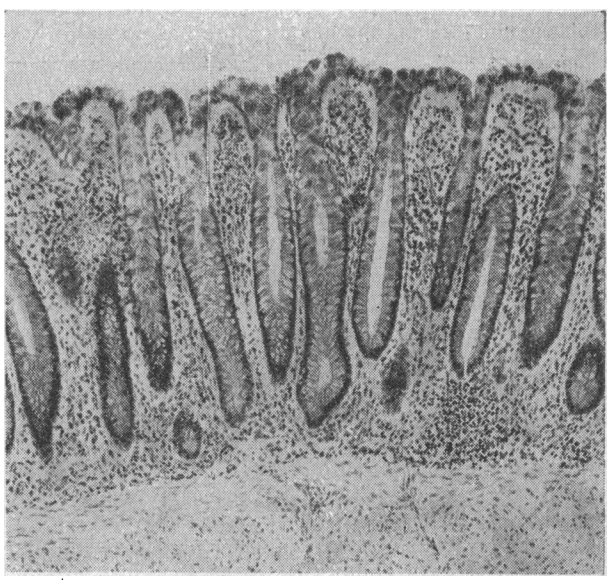

FIG. 1.—Case 1. Histological appearances of colonic mucosa before eating cheese.

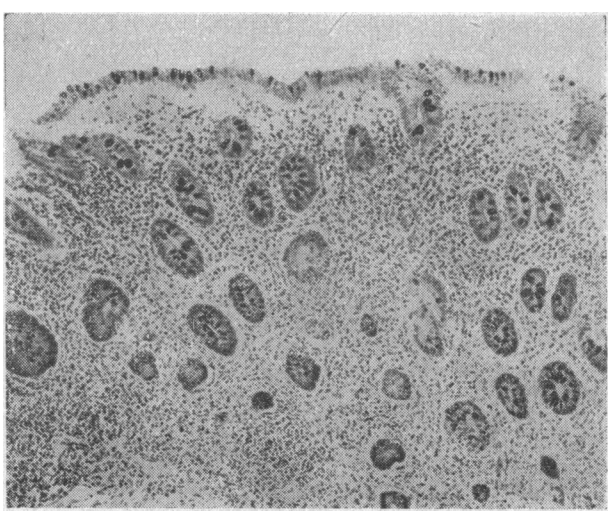

FIG. 2.—Case 1. Histological appearances of colonic mucosa after eating cheese regularly.

No diagnostic features of ulcerative colitis are present. The appearances are, however, consistent with ulcerative colitis in remission or in a quiescent phase.

"Section II (of May 3, 1956) (Fig. 2). Although the surface epithelium is intact, there is definite evidence of active ulcerative colitis. A moderately heavy cellular infiltrate of lymphocytes and plasma cells is present in the lamina propria. Eosinophil leucocytes are not more numerous than in the first biopsy. Several small crypt abscesses are present in gland tubules; some of these are in an early stage of formation and show neutrophil leucocytes accumulating in and around the gland epithelium; others are well developed and are sometimes associated with fragmentation or rupture of the glandular epithelium. When compared with the first biopsy, there is obviously a recurrence of the ulcerative colitis."]

Treatment with a rectal drip of hydrocortisone gave little benefit. Cortisone by mouth in a dose of 25 mg. q.d.s. brought definite improvement, although there was immediate relapse when she ran out of cortisone tablets for a day. She continued on cortisone as an out-patient, although requiring admission to hospital for one night for a blood transfusion of 4 pints (2.3 litres) because the haemoglobin level had fallen to 63% (9.3 g./100 ml.). There was gradual improvement, and symptoms were slight by September. In November cortisone was stopped, and in December she was symptom-free. When seen again in March, 1957, she was still symptom-free and the blood-picture was normal.

Since that time she has had no further frank attack of ulcerative colitis and has continued on the milk-free diet.

Comment.—There seemed little doubt at the time that this patient's sharp recurrence of ulcerative colitis was due to a reaction to ingested cheese. However, although scientifically gratifying, the results were dismaying to me as a physician, because of the severity of the recurrence and the difficulty of checking it. Before beginning the experiment of putting the patient on regular helpings of cheese, I had assumed—naively, as it transpired—that any attack induced by such feeding would rapidly clear up on avoiding ingestion of cheese.

During the next few years watch was kept for other patients with presumptive evidence of colonic sensitivity to milk and its products, but no further tests of reintroducing milk into the diet of such patients were carried out until 1959. By this time a series of studies on treatment had culminated in the finding that combination of oral prednisolone and local hydrocortisone hemisuccinate was a highly effective method for checking mild or moderate attacks of ulcerative colitis (Truelove, 1960). It was therefore judged safe enough to try further dietary tests on the following patients.

Case 2

A medical student aged 24 was first seen by me with an attack of ulcerative colitis in August, 1957. He failed to respond to prednisolone by mouth and to a rectal drip of hydrocortisone hemisuccinate when they were used separately, but responded promptly when they were combined. Early in 1958 he had another attack of ulcerative colitis, which again responded to combined corticosteroid treatment, and he remained well on stopping the oral prednisolone but continuing with the nightly rectal drip of hydrocortisone. This local treatment was continued until October, 1958, when the blood-picture, sigmoidoscopic appearances, and barium-enema appearances were normal. However, he had another sharp relapse in February, 1959, necessitating further combined corticosteroid therapy. At this time he was also put on a milk-free diet, and the oral prednisolone was stopped after one month and the local treatment after six weeks. Thereafter he remained symptom-free, with normal sigmoidoscopic appearances. In October, 1959, he went back on to milk in his diet and the events were as follows:

Date	Clinical State	Sigmoidoscopic Findings
October 9 ..	Entirely well Then started drinking ½ pint (284 ml.) of milk a day	Normal
October 16 ..	Entirely well	"? Excess of mucus"
,, 23 ..	Loose motions for past 4 days	"Hyperaemia and definite excess of mucus"
November 2 ..	Passing blood per rectum after defaecation and a sense of incomplete evacuation	"Diffuse inflammation of the mucosa with hyperaemia, granularity, multiple petechiae, and contact bleeding—mild but definite ulcerative colitis"

He was given combined corticosteroid treatment and rapidly showed improvement. It was a long time, however, before he became symptom-free; for in April, 1960, he still had haemorrhagic proctitis confined to the lower half of the rectum. At the time of writing he has become entirely symptom-free without treatment other than the dietary restriction.

Comment.—This patient was considerably slower than Case 1 in showing manifest evidence of colitis, it being 10 days after starting milk before symptoms began and two weeks before definite sigmoidoscopic abnormalities could be seen.

Case 3

A housewife aged 35 was admitted to the Churchill Hospital in August, 1955, with an attack of ulcerative colitis. The condition was first diagnosed in 1943, and she was discharged from the Women's Auxiliary Air Force because of it. An attack in 1949 involved the whole colon. Thereafter intermittent bouts of symptoms occurred, but they were relatively mild until the few weeks preceding her admission in 1955.

Cortisone, 50 mg. q.d.s., was given without response. She was then treated with hydrocortisone in a rectal drip, being one of the first patients to be so treated at Oxford; there was no response. Then intramuscular A.C.T.H. was given, likewise without response. The A.C.T.H. was stopped and, as she was not severely ill, she was sent home in December, 1955, for out-patient supervision.

When seen one week later in the out-patient department she was having about seven loose motions a day with small amounts of blood present and with urgency of defaecation. Sigmoidoscopy showed evidence of ulcerative colitis of moderate severity. Two weeks later she was symptomatically worse and sigmoidoscopy still showed active disease. Sulphasalazine was given without benefit and the sigmoidoscopic appearances worsened. The bowel symptoms continued and she was moderately anaemic, the haemoglobin being 70% (10.5 g./100 ml.).

In February, 1956, she was instructed to avoid milk and eggs in all forms. By March she was symptomatically improved though sigmoidoscopy showed doubtful improvement, while the haemoglobin value of the blood had risen to 80% (11.8 g./100 ml.). By April she was greatly improved symptomatically and the sigmoidoscopic appearances were only slightly abnormal. By June she was symptom-free and feeling well, the sigmoidoscopic appearances were normal, and the haemoglobin was 95% (14.1 g./100 ml.). Thereafter she was kept under regular observation. In August she went back on to eggs without ill effect, the sigmoidoscopic appearances remaining normal.

In November, 1959, further sigmoidoscopy showed normal appearances, while a barium enema showed no evidence of active ulceration, the only abnormality (if, indeed, it can be called an abnormality) being absence of haustra in the distal colon. She went on to milk on November 28. For six weeks there was no harmful effect, but then she developed bloody diarrhoea, while sigmoidoscopy showed evidence of active ulcerative colitis of moderate severity. She continued

on milk for one more week and became worse, with general malaise, liquid motions, and heavy bleeding from the bowel. Sigmoidoscopy showed active ulcerative colitis, while repeat barium enema showed ulceration of the sigmoid and descending colon.

When treated with oral prednisolone, 5 mg. q.d.s., a nightly rectal drip of hydrocortisone hemisuccinate, and a milk-free diet she became entirely symptom-free after one week, and after two weeks the sigmoidoscopic appearances were nearly normal. The oral prednisolone was tailed off and the rectal drip stopped after another week. However, she then relapsed and needed a further course of combined corticosteroid treatment before she became symptom-free. She continues well on a diet containing no milk.

Comment.—This patient resisted medical treatment for several months before being tried on a diet not containing eggs or milk. Eggs were returned to the diet without ill effect, but, after being symptom-free for three and a half years on a milk-free diet, she suffered a sharp relapse six weeks after starting on milk again. This relapse responded promptly to treatment with combined oral and local corticosteroids, but she relapsed when treatment was stopped after two weeks and needed further treatment. A notable feature in this patient was that no harmful effect was apparent for several weeks after the reintroduction of milk into the diet, and this may be connected with the long period for which she was symptom-free while abstaining from milk.

Case 4

A housewife aged 28 was admitted to the Churchill Hospital in February, 1954, with an attack of ulcerative colitis. Since 1952 she had been liable to pass blood and mucus per rectum, without diarrhoea. During the six weeks preceding admission she had moderately severe bloody diarrhoea and griping abdominal pains. She was anaemic, the haemoglobin value being 66%. Sigmoidoscopy showed ulcerative colitis, and barium enema showed that the ulceration extended proximally as far as the mid-transverse colon. She was treated with general medical measures, including blood transfusion, and improved but did not become symptom-free. However, she was unhappy in hospital and was discharged to attend as an out-patient.

The symptoms persisted, though they were not severe. In April, 1955, in view of the persistent symptoms and sigmoidoscopic evidence of active disease, oral cortisone was given; this brought definite symptomatic improvement, but had little effect on the sigmoidoscopic picture. In the middle of May, while still on cortisone, she had a flare-up of symptoms with frank bloody diarrhoea. Questioning revealed that before this flare-up she had had some dental extractions and had drunk a lot of milk to keep her strength up. She believed that the milk had upset her and had cut it out of her diet before being seen, and the symptoms were then abating. She was advised to eliminate milk completely from her diet. She continued to improve and was almost symptom-free in June, 1955, while the sigmoidoscopic picture showed improvement. The cortisone was stopped and she became entirely symptom-free. She remained symptom-free, and in February, 1956, was put back on to milk. This was followed in two days by loose motions and the passage of purulent material per rectum, while sigmoidoscopy showed moderate inflammation. Six weeks after beginning milk she developed bloody diarrhoea with sigmoidoscopic appearances of severe ulcerative colitis.

Milk was again stopped from her diet and she improved steadily until she caught influenza in May, when bloody diarrhoea occurred. Treatment with a rectal drip of hydrocortisone had a dramatically beneficial effect on the symptoms but the sigmoidoscopic picture was not normal. At this stage, dietary restrictions were stopped and attacks were treated, as they arose, by local hydrocortisone, to which she repeatedly responded rapidly. However, in January, 1958, she had an attack sharp enough to necessitate admission to hospital. She was treated with combined oral and local corticosteroids and did well, but she was also put on to a rigid milk-free diet.

She then remained symptom-free until January, 1960. At this time a barium enema showed no evidence of active ulceration, although there was absence of haustration in the descending colon. Sigmoidoscopy showed the typical changes of a very mild ulcerative colitis. On January 8, she began to drink half a pint (284 ml.) of milk daily. Seven days later she started to pass blood and pus per rectum several times a day, and sigmoidoscopy showed marked worsening of the inflammation. She was left on milk and kept under close observation. One week later she was still passing blood and the sigmoidoscopic appearances were unchanged. Another week later she was worse, with bloody diarrhoea and frequent passages of blood and mucus per rectum. After a further week, with no improvement, she returned to a milk-free diet and was treated with combined oral and local corticosteroid. There was immediate cessation of the rectal bleeding, with rapid lessening of the diarrhoea. When seen two weeks later she was symptom-free and the sigmoidoscopic appearances were nearly normal. The corticosteroids were stopped but the diet was continued with. However, there was rapid return of rectal bleeding which proved resistant for some weeks to treatment with prednisolone and sulphasalazine, while the haemoglobin value fell to 60%. Treatment with a rectal drip of hydrocortisone hemisuccinate was rapidly beneficial and the anaemia responded to intravenous iron.

Comment.—This patient has twice shown sharp recurrences of ulcerative colitis when put on to milk after a period of abstention. In the second recurrence, it is interesting that the response to combined corticosteroid treatment was rapidly beneficial as in Case 3, but that both these patients rapidly relapsed when the corticosteroids were stopped after two weeks, and thereafter both needed further energetic treatment for several weeks even though they were already on a milk-free diet. A notable feature is that a milk-free diet does not cause completely normal sigmoidoscopic appearances in this patient even though treatment with local hydrocortisone hemisuccinate will do so. This suggests that some factor additional to milk plays a part in this particular case.

Case 5

A schoolgirl, aged 14 in 1960, first developed diarrhoea and abdominal pain in September, 1958, for which she was admitted to hospital in Cheshire, where the diagnosis of ulcerative colitis was made on sigmoidoscopy and barium-enema appearances. She was moderately anaemic (Hb, 70%) and the E.S.R. was 82 mm. in 1 hour. Treatment with sulphonamides and general medical measures, and also psychotherapy, was given. As she did not respond well to sulphonamides a rectal drip of hydrocortisone hemisuccinate was instituted and brought a prompt response, and she was discharged home symptom-free, with the haemoglobin level 100%, although the E.S.R. remained high. A few weeks later she relapsed and was readmitted to the same hospital. A course of sulphasalazine had no effect on the condition. In May, 1959, she was again treated with a rectal drip of hydrocortisone together with oral prednisolone 5 mg. b.d., and she responded well to this. The oral prednisolone was stopped but she continued with the rectal hydrocortisone on alternate nights. On this treatment she remained well until September, when she again relapsed, and putting her back to nightly treatment with local hydrocortisone failed to check the attack. The E.S.R. remained elevated at over 40 mm. in 1 hour.

In October, 1959, she was referred to me and was admitted to the Radcliffe Infirmary. Sigmoidoscopy showed evidence of mild ulcerative colitis, and the barium-enema examination showed fine contour irregularities extending from the descending to the ascending colon.

Oral prednisolone 5 mg. q.d.s., a nightly rectal drip of hydrocortisone hemisuccinate, and a milk-free diet were prescribed. She became symptom-free almost immediately, and was sent home after two weeks on the same regime except that the oral prednisolone was reduced to 5 mg. t.d.s. On her discharge, sigmoidoscopy still showed evidence of mild ulcerative colitis. When seen as an out-patient in December, 1959, she was entirely symptom-free and the sigmoidoscopic appearances were normal. The oral prednisolone was then tailed off. In January, 1960, she was well and the sigmoidoscopic findings were normal. The rectal drip of hydrocortisone was discontinued but she continued on a milk-free diet. In April she was entirely well and sigmoidoscopy showed normal appearances.

At the beginning of July she was readmitted to the Radcliffe Infirmary for reintroduction of milk into the diet, it being judged wise to have her under supervision in view of Cases 1–4 and her home being too distant for supervision as an out-patient. On admission she was in robust health. Sigmoidoscopy showed entirely normal findings, while barium-enema examination showed only very minor abnormalities. Arrangements were made for regular estimation of the total eosinophil count of the blood because of the study by Riisager (1959) showing that eosinophilia usually precedes and accompanies an attack of ulcerative colitis. Three days after admission milk was added to the diet. The motions became soft but remained only one a day and she felt entirely well. Sigmoidoscopy after three days showed entirely normal appearances. One week later she was symptom-free, but sigmoidoscopy showed a slightly inflamed mucosa. My report was: "The colon contains porridge-like faeces with tiny flecks of blood on the surface. The mucosa is hyperaemic and finely granular. The vascular pattern can still be seen but less plainly than last week. Conclusion: Mild sigmoidoscopic relapse."

At this point the patient went home. She remained essentially symptom-free for three days, when diarrhoea occurred and continued. Milk was stopped from the diet after three more days, but the diarrhoea continued and became more severe with about six fluid motions daily. Ten days after the onset of diarrhoea she was readmitted to the Radcliffe Infirmary. On sigmoidoscopy, the mucosa was hyperaemic, coarsely granular, and dotted with petechiae, and it bled on being rubbed with gauze. A barium enema showed a sharp deterioration since the previous examination, with evidence of ulceration throughout the entire colon and with irritability and much-reduced size of lumen (Fig. 3). The total eosinophil count was abnormally high, being 386, 416, and 392 on three consecutive counts during the first two days of her stay in hospital.

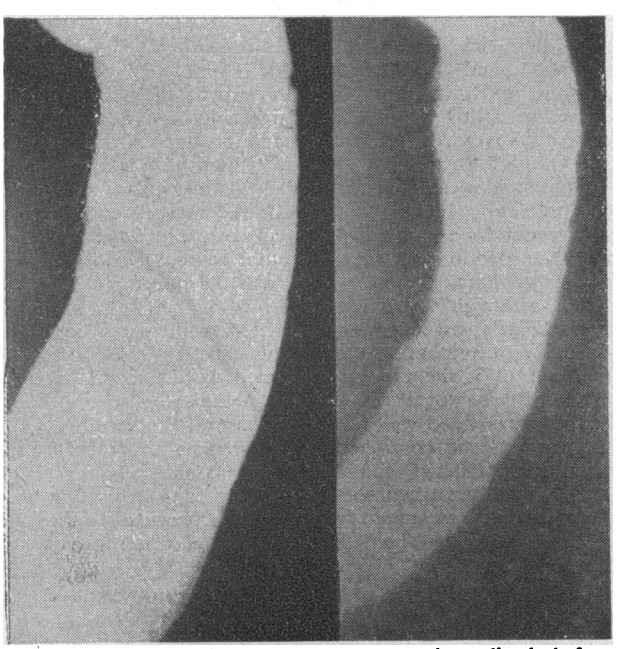

FIG. 3.—Case 5. Barium-enema appearances immediately before and three weeks after reintroduction of milk into diet. Corresponding portions of descending colon.

She was then put on combined local and systemic corticosteroid treatment and a milk-free diet. She rapidly improved and was discharged almost symptom-free after eight days of treatment, although she continued on the same course of treatment at home. Ten days later, on July 21, sigmoidoscopy showed very mild inflammation, while a barium enema showed marked improvement although the appearances were not entirely normal.

She has been advised to remain indefinitely on a milk-free diet, but obviously time must elapse before the success of this restriction can be judged.

Comment.—The course of events strongly suggests that reintroduction of milk into the diet was responsible for this patient's relapse. In one sense it was unfortunate that it was judged necessary, because of the distance of her home from Oxford, to admit her to hospital for the actual reintroduction, because protagonists of the psychosomatic theory of the causation of ulcerative colitis would possibly regard the fact of readmission as sufficient reason for the relapse. On the other hand, the patient felt entirely well in hospital and was herself convinced that milk was harmless to her when she left the hospital, although by that time sigmoidoscopic relapse had occurred, antedating frank bowel symptoms by four days.

Discussion

The likelihood of a relapse of ulcerative colitis occurring by chance alone in the course of a few days or weeks after the reintroduction of milk into the diet would be too small to account for the occurrence of relapse in all five of the patients now reported. Some estimate of the natural expectation can be obtained from controlled trials of maintenance treatment aimed at preventing relapses among patients in clinical remission, in which "dummy" preparations were used to treat some of them. In one of these trials, 13 of 31 patients (42%) on "dummy" cortisone tablets relapsed in the course of one year (Truelove and Witts, 1959). In another, when 13 patients were on "dummy" local treatment to the colon, 5 (or roughly 40%) relapsed during the six-months trial period (Truelove, 1958).

If we take 30% as an outside estimate for the chance of a relapse occurring spontaneously in a patient with ulcerative colitis within a few weeks from a time chosen at random, it is a simple matter to calculate the probability that six consecutive patients would relapse within six weeks. (I count Case 4 as two patients for this argument as she relapsed on two separate occasions when milk was reintroduced into the diet.) The probability of such a run of relapses would be $(3/10)^6 = 0.000729$, giving odds of more than 1,000 to 1 against this run occurring by chance alone. It can therefore be taken as sufficiently proved that in this group of patients the reintroduction of milk (or milk-products such as cheese) into the diet had a direct connexion with the recurrence of disease. The one proviso that should be made is that the possibility exists that the reintroduction of milk caused the relapse to occur through psychosomatic mechanisms. Apart from the inherent improbability of this explanation in the circumstances of this particular study, there is the additional circumstance that in two of the patients (Cases 1 and 3) reintroduction of eggs into the diet after previous abstention was not followed by harmful consequences.

A further item of evidence supporting the idea of a direct causal connexion between the reintroduction of milk and the subsequent relapse comes from studying the relationships between the period of abstention and the time taken for clinical relapse to occur after reintroduction. The Table contains the relevant data which show that there is a highly significant positive correlation between these two variables. In general terms, it can be said that the longer a patient was symptom-free on a milk-free diet the longer it took for clinical relapse to occur after reintroduction of milk into the diet. Such a finding is much more in keeping with the concept of an immunological type of reaction, with the patient's reactivity varying according to how long ago he was last exposed to the antigen, than it is with the concept of these relapses being psychosomatic in origin. If an immunological type of response is the true explanation, it is likely to be a reaction to the proteins of milk and cheese. Butter has been included in the diet of these patients, and lactose is not likely to be a sensitizing agent. An additional point is that in Case 1 cooked cheese was harmless whereas uncooked cheese was detrimental, a finding compatible with the idea that denaturation of the proteins may have altered their antigenicity.

Relationship Between the Time the Patient was Symptom-free on a Milk-free Diet and the Time to Clinical Relapse After Reintroduction of Milk Into Diet

Case No.	No. of Months Symptom-free on Milk-free Diet	No. of Days after Starting Milk to First Definite Bowel Symptoms	Coefficient of Correlation
1	3	2	$r = +0.95$
2	7	10	The exact test of significance recommended by Fisher (1950) for use when the number of pairs of variables is small, gives $P < 0.01$
3	41	42	
4a	8	2	
4b	14	7	
5	9	13	

There is nothing new in the idea that particular foods may play an important part in the aetiology of ulcerative colitis. Andresen (1942) considered that ulcerative colitis was often due to food allergy, giving the figure of "at least 66% of the cases." Among the items of food which he considered had been responsible among his patients milk was outstanding, being incriminated as one factor in 84% of the patients whom he judged to be suffering from food allergy, and being, in his opinion, the sole factor in 40% of them. Other offending items of food were eggs, wheat, potatoes, oranges, and tomatoes. He advised the use of special allergy-test diets in order to detect the harmful items of food. Likewise, Rowe (1942) considered that ulcerative colitis might be caused by severe allergic reactivity in the colonic mucosa, similar to that which in the skin is responsible for atopic dermatitis. He found that skin tests were useless and recommended elimination diets not greatly dissimilar from those used by Andresen. He obtained remissions in 10 out of 14 patients by these diets.

In spite of the fact that these views have been widely published, few physicians have accepted the idea of food allergy as an important cause of ulcerative colitis. The difficulty has been to assemble proof of the hypothesis on the one hand or to disprove it completely on the other. The use of elimination diets as a sole method of treatment cannot be justified in patients with an acute attack of ulcerative colitis, because the illness is so severe that it must be halted without delay if this is possible. Consequently, it is difficult to devise a situation which is safe for the patient and yet capable of yielding evidence of scientific value. The classical method of studying allergic diseases is to show benefit on removal of the offending allergen and deterioration on its return. So far as the first part of this approach is concerned, my own observations seem to show that mere removal of the allergen is not sufficient to bring about immediate improvement, so that additional treatment is necessary with consequent blurring of the evidence. So far as the second part of this approach is concerned, which is the crucial part of the test, few such observations have been adequately described. It appears from the present study that deliberate provocation of an attack of ulcerative colitis is reasonably safe provided that early treatment with combined systemic and local corticosteroids is given if an attack occurs. This treatment should be continued for several weeks because of the risk of sharp relapse if discontinued prematurely (Cases 3 and 4).

If milk is indeed an important, if not the sole, factor in the causation of ulcerative colitis in a certain proportion of patients, it will be of consequence to know whether this is true of many or few of the patients. In addition to the five cases described I have at present eight other patients who have shown an apparent clinical improvement in the course of their disease since milk was eliminated but in whom the crucial test of reintroducing milk into the diet has not yet been tried. If these be taken provisionally as examples of patients sensitive to milk, making a total of 13 in all, they still represent a small proportion of the patients with this disease attending me regularly at present, who number more than 200. Nevertheless, it must be remarked that my own energies have been directed chiefly towards the study of drugs, especially corticosteroids, in the treatment of this disease, and, until recently, elimination diets have been tried on only a few patients who were proving resistant to conventional medical therapy or who relapsed frequently.

Experimentally, it has proved possible to sensitize the rectal mucosa to reagins (Gray and Walzer, 1938; Gray *et al.*, 1940). A human serum containing reagin antibodies for the peanut was injected locally into the rectal mucosa. Ingestion of peanut antigen 24–48 hours later was followed in a few minutes by an inflammatory reaction at the site of passive transfer, with oedema, hyperaemia, and excessive secretion of mucus. These changes were of brief duration. In spite of the theoretical interest of Gray and Walzer's work, the reaction they describe is unlikely to bear any close relationship to the type of change observed in my own patients, in whom the pathological response was much more greatly delayed.

Finally, the theoretical implications of the present findings are worth mention. The observations are compatible with several different views of the aetiology of ulcerative colitis. One is that ulcerative colitis is not a single disease but a family of different diseases, in which case allergy to a particular foodstuff such as milk would represent one member of the family. Another is that ulcerative colitis is always a hypersensitivity reaction but that the antigens are various and diverse, with milk proteins acting as one of them. A third is that the colonic mucosa is basically abnormal in ulcerative colitis, for example, because of a deficiency of a specific nutritional factor, and that this abnormal mucosa readily becomes the seat of allergic responses which are secondary to the basic abnormality. These various possibilities deserve to be kept in mind when planning future work.

Summary

During the last few years it has proved possible to recognize a group of patients with ulcerative colitis in whom removal of milk and protein-containing milk products from the diet has been followed by marked improvement in the clinical course of the illness. In five of these patients milk has been reintroduced into the diet, and on every occasion this has been followed in a few days or weeks by a frank attack of ulcerative colitis. One patient was tested twice on separate occasions, so that there were six such events in all.

From previous studies in which patients in clinical remission were being treated with "dummy" tablets, it is possible to arrive at an estimate of the risk of spontaneous relapse in a patient with ulcerative colitis. Taking an outside figure for this risk, it can be shown that it was very unlikely that the six relapses would have occurred by chance alone. In other words, there was almost certainly a causal connexion between the reintroduction of milk into the diet and the subsequent relapse.

There was a highly significant positive correlation between the time a patient was symptom-free while on a milk-free diet and the time taken to clinical relapse after reintroduction of milk into the diet. This finding is compatible with the notion of these relapses representing an immunological type of response to milk proteins, with the reactivity of the colonic mucosa varying according to the length of time since it was last exposed to the allergen.

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ULCERATIVE COLITIS

A FOLLOW-UP INVESTIGATION WITH MUCOSAL BIOPSY STUDIES

BY

A. P. DICK, M.D., F.R.C.P.

AND

M. J. GRAYSON,* M.B., M.R.C.P.

Addenbrooke's Hospital, Cambridge

The object of this study has been to follow up an unselected series of cases of ulcerative colitis, including proctosigmoiditis, after an interval of 5 to 10 years, with particular reference to the presence of mucosal histological abnormalities in relation to the clinical state of the patient. It seemed of especial interest to find out what proportion of patients, apparently recovered, showed persistent abnormalities in the mucosa. It was also felt that the follow-up results of an unselected series would be of value. Of the many large reported series of ulcerative colitis, in some instances followed up for long periods, the majority come from a special centre (Sloan, Bargen, and Gage, 1950) or hospital dealing with diseases of this type (Cullinan and MacDougall, 1957), which would tend to draw the more severe cases or, alternatively, is concerned with in-patients only, such as the series of Rice-Oxley and Truelove (1950). Cases of proctitis and proctosigmoiditis have been included because there does not appear to be any fundamental distinction between such cases and those with more extensive involvement of the bowel.

The cases in our series were all referred to a provincial hospital centre, serving a mixed rural and urban population, and which was, for part of the area, the only hospital available. Some of the cases were seen initially at smaller local hospitals.

The series consisted of 94 patients, first seen by one of us (A.P.D.) between 10 and 5 years ago (April, 1949, to September, 1954).

Type of Case

The types of case comprising the series are summarized in Table I. The cases were classified according to the extent of disease into three groups—namely, proctosigmoiditis, left-sided colitis, and total colitis—and into three grades of severity—mild, moderate, and severe. There were no cases of right-sided or segmental colitis, although some may have started in this way before they were seen. Two cases in which typical total ulcerative colitis was associated with regional ileitis (Crohn's disease), proved by laparotomy and histological section, were seen for the first time during the same period as the cases under review. Whether regional ileitis represents a different type of tissue reaction to a similar mucosal disturbance or whether it is in fact an entirely different disease—a problem discussed by Lumb (1951) and Crook (1957)—is uncertain, but to avoid controversy these two cases have been excluded.

TABLE I.—*Type of Case*

	Total No. of Cases		Mild		Moderate		Severe	
	M	F	M	F	M	F	M	F
Proctosigmoiditis	9	36	6	21	3	14	—	1
Left-sided colitis	7	14	2	4	3	9	2	1
Total colitis ..	8	20	1	1	1	3	6	16

The extent of the disease was determined mainly by barium-enema examination. Cases were classified as "left-sided" when there were no changes in the barium enema proximal to the splenic flexure, although some of these may have had more extensive mucosal abnormalities. Cases where more than the left side of the colon was involved were classified as "total," although in some the whole colon was probably not involved. In cases of "proctosigmoiditis," in which group are included those with proctitis only, radiological abnormality was either absent or limited to the sigmoid region. In some of these patients, in whom there was no doubt on sigmoidoscopic grounds that the disease was confined to the rectum, a barium enema was not performed.

It appeared that some of the cases of total and left-sided colitis had begun as proctitis, and in a few, seen early in the disease, sigmoidoscopic and radiological evidence of this retrograde progression was available. A history of rectal bleeding, without diarrhoea, usually implies that the disease is confined to the rectum; and, indeed, of our 36 female cases of proctosigmoiditis, nine had no diarrhoea at any stage and in every instance the disease was confined to the rectum. Of the 28 patients

*Now at St. George's Hospital, London.