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Case reports

Collagenous colitis

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SUMMARY Clinical and pathological aspects of six patients with collagenous colitis are presented. These patients have been observed for between four and 15 years and the evolution of the condition is documented in three (cases 1, 3 and 5). Management and possible pathogenetic mechanisms of this enigmatic condition are discussed.

The term collagenous colitis was introduced by Lindstrom[1] in 1976 to describe the microscopical changes seen in the rectal biopsies of a patient with longstanding watery diarrhoea. Since then over 20 isolated cases have been reported mainly from continental Europe.[2–20] The clinical and pathological descriptions have all been similar. The patients are predominantly middle aged women, essentially well apart from watery diarrhoea and abdominal pain. Clinical examination, including sigmoidoscopy, is usually unremarkable as are laboratory investigations. The condition is unresponsive to conventional treatment used in inflammatory bowel disease. The cause of the abnormally thick band of collagen underlying the colonic epithelium is speculative as is its relationship to the diarrhoea, but it is tempting to attribute the latter to the former. Some have proposed[2 10 12 14 19] that the pathogenesis lies in the abnormal differentiation of the pericryptal fibroblastic sheath,[21] but the primary aetiology is obscure. The paucity of published cases implies this condition to be exceptionally rare. One of us has seen and followed six new cases in the past 13 years in the course of general gastroenterological practice, which suggests collagenous colitis to be commoner than generally supposed. We report the clinical and pathological aspects of these six patients.

Case histories

CASE 1

This woman born in 1912 was first seen in 1971 with a severe watery diarrhoea, present intermittently for two years, but persistently for six weeks, with the bowels open up to 15 times each day and daily stool output of over 1 litre. No abnormalities were found on external examination. Sigmoidoscopy revealed copious fluid faeces, but a macroscopically normal mucosa. The only abnormalities found on laboratory tests of stool, urine and blood were a white blood count of 16×10^9/litre (82% neutrophils) and ESR of 45 mm/hour. Barium studies of stomach, small intestine and colon were normal. Initial treatment with opiate antidiarrhoeals had little effect, but a course of oral prednisolone, 45 mg/day, given because the rectal biopsy showed inflammatory changes (*vide infra*), led to rapid and complete remission with the white cell count and ESR falling to normal. Over the ensuing 12 years she experienced three or four attacks yearly of several weeks' duration usually controlled by opiates. A more severe attack in 1983 required a further course of corticosteroids to produce a remission. Biopsies of the colonic mucosa initially showed patchy inflammation with minimal thickening of the collagen plate; the more recent biopsies showed marked thickening of the plate, less, though now diffuse, inflammation and fibrosis of the lamina propria (Table 1).

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CASE 2

At presentation in 1976 this woman, born in 1941, she was asymptomatic, but gave a 25 year history of intermittent watery diarrhoea with the bowels open up to six times a day at times of stress. No abnormalities were found on examination. Sigmoidoscopy showed normal rectal mucosa to the naked eye and formed stool. A diagnosis of irritable

Table 1 *Biopsy review*

	Material reviewed	*Biopsy date*	*Histological findings*	*Comment*
Case 1	2 sigmoidoscopic biopsies	1971	Patchy mucosal inflammation. Minimal thickening of collagen plate, minimum 3 μm, maximum 7 μm.	Differs from other cases in initial patchy inflammation and later more diffuse fibrosis of lamina propria.
		1983	Mild diffuse inflammation including prominent eosinophils. Thick collagen plate, minimum 12 μm, maximum 120 μm. Increased collagen, throughout lamina propria.	
Case 2	1 sigmoidoscopic biopsy	1982	Mild diffuse inflammation of lamina propria and thickened collagen plate – minimum 6 μm, maximum 15 μm.	Typical collagenous colitis.
Case 3	7 sigmoidoscopic biopsies – latest with electron microscopy	1978 to 1984	Initially mucosa diffusely heavily inflamed with collagen plate <3 μm. Then less inflamed and collagen plate patchily thickened, 3 to 18 μm. Then similar mild inflammation with diffusely thickened collagen plate 6 to 10 μm. Electron microscopy showed excess collagen immediately below normal epithelial basement membrane.	Non-specific diffuse inflammation ↓ patchy ↓ Typical diffuse collagenous colitis.
Case 4	1 sigmoidoscopic biopsy	1981	Mild diffuse inflammation and thickened collagen plate, minimum 4 μm, maximum 10 μm. (Also mild diffuse increase in collagen in lamina propria).	Typical mild collagenous colitis.
Case 5	4 sigmoidoscopic biopsies and 1 set of 4 colonoscopic biopsies	Feb–June 1981	Initially diffuse heavy inflammation with surface ulceration, fibrinous surface exudate, crypt abscesses and no thickening of collagen plate → less inflamed with collagen plate ill-defined but up to 12 μm thick → similarly inflamed with collagen plate in last 2 biopsies throughout 12–30 μm thick.	Actively diffusely inflamed and superficially ulcerated ↓ Typical collagenous colitis.
Case 6	3 sigmoidoscopic biopsies, 1 set of 4 colonoscopic biopsies.	1982 to 1983	All biopsies similar: mild diffuse inflammation and thickened collagen plate – minimum 5 μm, maximum 60 μm.	Typical collagenous colitis.

bowel syndrome was made. In 1982 she attended again because of gradual worsening and increasing frequency of the attacks of diarrhoea and in addition nocturnal diarrhoea with occasional incontinence. She was seen during an attack. External examination was normal. Sigmoidoscopy showed profuse watery stools with an apparently normal mucosa which on biopsy showed the features of collagenous colitis (Table 1). Laboratory blood, stool, and urine tests were normal as were barium meal, follow through, and enema. Treatment with opiate anti-diarrhoeal drugs afforded only minimal benefit. Two years later her diarrhoea persists, but her general health remains good. The colonic biopsies remain abnormal.

CASE 3

The watery diarrhoea started suddenly in 1974. This was of such severity that on several occasions this woman, born 1935, was admitted to hospital with dehydration. Barium studies of the small and large intestine were normal. She was first seen by us in 1978 at which time the bowels were open up to 20 times during the day and night with stool volumes approaching 5l/24 hours. She had lost 6·3 kg in weight, but was otherwise well. She has two sisters one of whom suffers from ileal Crohn's disease. On external examination she was dehydrated. Sigmoidoscopy and colonoscopy showed normal mucosa and liquid faeces. Laboratory investigations of the blood revealed a normochromic, normocytic

anaemia (Hb 10·9 g%), low values of sodium (126 mmol/l), potassium (2·9 mmol/l), chloride (80 mmol/l) and albumin (27 g/l) and a slightly raised urea (10·6 mmol/l). Stool and urine tests were normal. Barium meal, follow through and enema, thyroid and gut hormone profile, tests of small gut function, gastric secretion and a small bowel perfusion study to assess absorptive and secretory status were all normal. Biopsies of the rectum and colon initially showed diffuse heavy mucosal inflammation without significant thickening of the collagen plate. Within six months the appearances had developed into those of typical collagenous colitis with mild diffuse inflammation and a thickened collagen plate (Table 1). These features have persisted since. Treatment with opiate antidiarrhoeal drugs, corticosteroids, sulphasalzine and indomethacin were tried without success. After several months she went into spontaneous but incomplete remission and regained the weight she had lost. The abnormal blood tests returned to normal. Since that time her diarrhoea has been constantly present to a greater or lesser degree with the bowels open between three and 15 times daily, always liquid. Her general health has not suffered and her blood tests remain normal.

CASE 4

In 1975 this woman, born 1938, had suffered watery diarrhoea which continued intermittently for two years. She lost 6·3 kg in weight. She was seen for the first time by us in late 1980 because of a recurrence of the same symptoms. The bowels were open up to 12 times daily and twice at night, with occasional incontinence. Measured stool volume was 500 ml/day. There was associated colicky abdominal pain. Externally there was no abnormality to find, but sigmoidoscopy produced a torrent of fluid stool. To the naked eye the mucosa of the colon at sigmoidoscopy and colonoscopy appeared normal, but biopsies all showed features of collagenous colitis (Table 1). Blood tests showed a slightly raised white count ($12{\cdot}9\times10^9$/l, 75% neutrophils), but no other abnormality. Stool and urine tests and barium studies of the stomach, small bowel and colon were normal. Treatment with antidiarrhoeal drugs and subsequently mepacrine had no useful effect. The diarrhoea has persisted, but her general health has remained good. The white blood count has returned to normal.

CASE 5

This woman, born 1917, had experienced watery diarrhoea up to eight times daily with episodes of incontinence which suddenly started in 1980. There was associated colicky lower abdominal pain and she lost 9 kg in weight. When examined in early 1981, no abnormality could be found other than copious liquid stool in the rectum. The rectal mucosa had lost its normal vascular pattern, but was neither visibly ulcerated nor friable. A similar appearance was noted throughout the colon at colonoscopy. Initial biopsies showed diffuse severe inflammation, superficial ulceration though no thickening of the collagen plate, but within 15 weeks the appearances were typical of collagenous colitis (Table 1, Figs 1, 2). Blood tests showed a slightly raised white count (12×10^9/l, 80% neutrophils) and a platelet count (800×10^9/l), but stool and urine tests were normal. Two barium enemas showed a rather long, patulous and ahaustral colon without ulceration. Barium meal and follow through were normal. Treatment with antidiarrhoeal drugs, corticosteroids, sulphasalazine and mepacrine was ineffectual. She was eventually seen by a homeopathist in 1981 and a complete remission was achieved with Natrum Mur.

CASE 6

This woman born 1951 travelled extensively in the Middle East, the Indian subcontinent and Central America. She assumed this was the cause of her chronic intermittent diarrhoea of four years standing. She sought a medical opinion in 1982 because her symptoms were worsening. The bowels were open four times daily and sometimes at night. The stools were always liquid with daily volumes around 600 ml. She appeared fit on examination; sigmoidoscopy revealed an apparently normal mucosa and a profuse flow of watery faeces. Colonoscopy similarly showed a normal mucosa, but biopsies of the rectum and colon showed collagenous colitis (Table 1). Her white count was initially slightly raised ($11{\cdot}6\times10^9$/l, 79% neutrophils), but other laboratory tests of blood and urine were normal. Barium studies of the upper and lower gut were also normal. Her diarrhoea has been improved somewhat, but by no means cured, by regular codeine phosphate.

CLINICAL PRESENTATION

The major symptom was watery diarrhoea, either intermittent or persistent, with daily stool volumes from 500–5000 ml. Nocturnal diarrhoea, faecal incontinence, and colicky abdominal pain were all common. General health was usually unaffected, but in three patients the diarrhoea and malaise were sufficiently severe to interfere with nutrition and led to weight loss. In two of these three vomiting accompanied the most severe attacks of diarrhoea. The possibility of purgative abuse was considered in all six cases, but there was no supportive evidence for this in terms of personality, search of personal

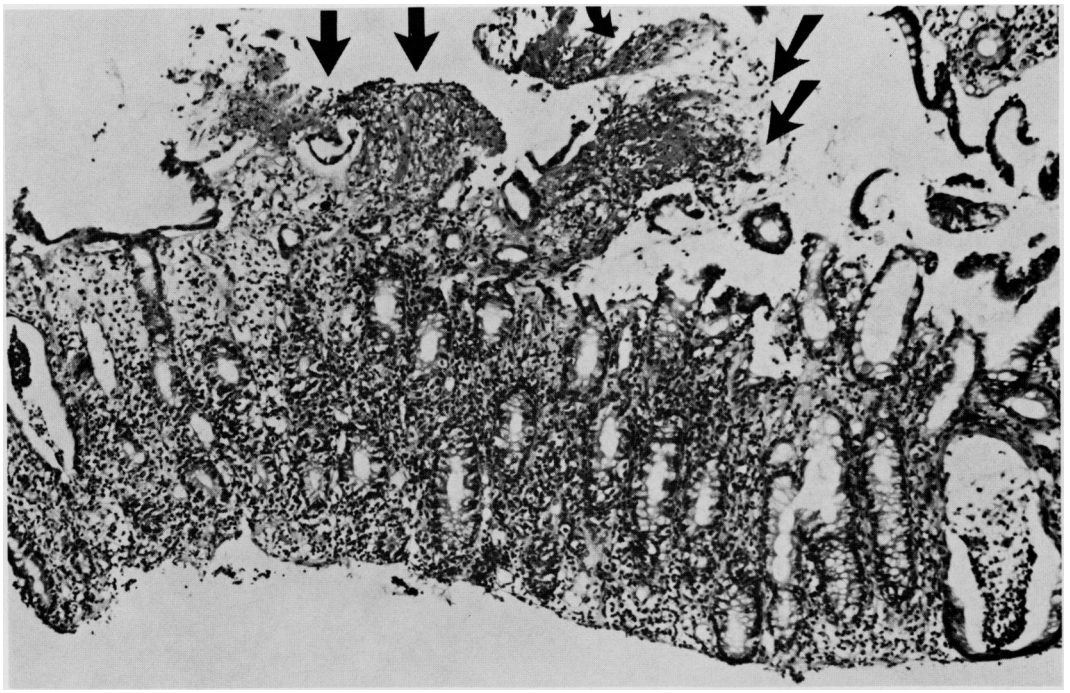

Fig. 1 *Initial sigmoidoscopic biopsy from Case 5. There is superficial ulceration with attached surface fibrinous exudate (arrows) and heavy inflammation of the lamina propria, but no thickened collagen band here or elsewhere. H and E ×100 (orig. mag.).*

belongings, stool examination for phenolphthalein, urine analysis for anthraquinones or rectal biopsy findings.

HISTOLOGICAL METHODS AND RESULTS

All specimens were fixed in 10% formalin and paraffin embedded in the normal manner. Sections were stained with H and E, van Geison, and Congo red and were taken from several levels of all blocks. Part of the most recent biopsy from Case 3 was fixed in 2·5% glutaraldehyde in 0·IN cacodylate buffer (pH 7·3), post fixed in 10% osmium tetroxide and embedded in araldite; ultrathin sections were examined in a Jeol 100 CX transmission electron microscope. All the above material was viewed independently by two pathologists (BCM and DAL) and the findings correlated. The thickness of the collagen plate was measured using a calibrated eyepiece graticule; the best orientated part of each section was identified; measurements were made under x16 and x40 objectives of the thinnest part of the plate and the thickest part of the plate; the average of the two readings of the thinnest part and the average of the two readings of the thickest part of the plate were recorded. The nature of the colonic biopsy material available for actual review and the salient histological features are summarised in Table 1, representative appearances from case 5 are illustrated in Figures 1 and 2, Figure 2 showing typical appearances of collengous colitis, and reference to the histological appearances is made in the individual case presentations above. Jejunal biopsies, only done on cases 3 and 6, were normal.

BARIUM STUDIES AND ENDOSCOPY

Full radiological examinations of the stomach, small intestine and colon were normal with one minor exception. In case 5 the colon was large, tortuous, and capacious and lacked a normal haustral pattern. Sigmoidoscopy was done on several occasions on each patient. The striking finding was the quantity of watery stool which poured forth from the 'scope'. In only one case did the rectal mucosa look mildly abnormal with loss of the vascular pattern but without friability or ulceration. Colonoscopy was done in four patients; in three the appearances were

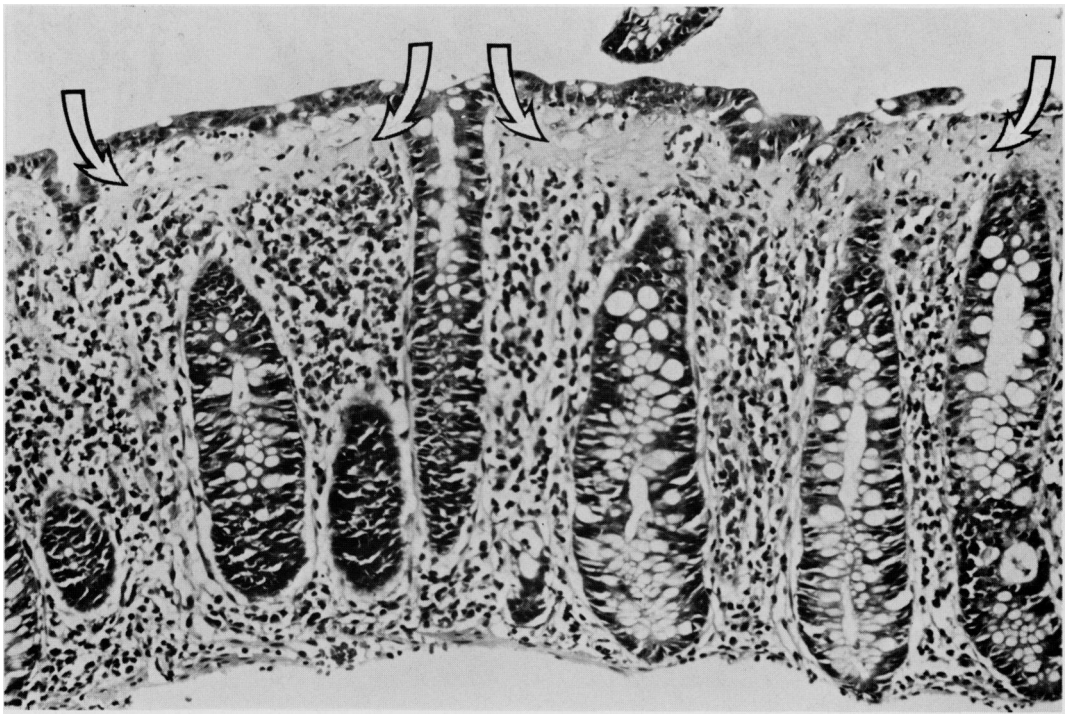

Fig. 2 *Same case as Fig. 1, sigmoidoscopic biopsy 15 weeks later. Prominent collagen band below the surface epithelium (arrows) varied from 12–30 μm in thickness. Lamina propria less inflamed. H and E ×175 (orig. mag.).*

Table 2 *Summary of clinical features*

Case	*Sex*	*Age at onset (yr)*	*Duration of symptoms (yr)*	*Recorded stool vol. (ml/24h)*	*Radiological features*	*Sigmoidoscopic colonoscopic appearances*	*Treatment and response*
1	F	57	15	1100	Barium meal, Follow through, Enema – NAD	Fluid faeces; Normal mucosa	Opiates – slight improvement; Systemic steroids – remission ×2
2	F	10	33	—	Barium meal, Follow through, Enema – NAD	Fluid faeces; Normal mucosa	Opiates – minimal benefit
3	F	39	10	5000	Barmium meal, Follow through, Enema – NAD	Fluid faeces; Normal mucosa	Opiates, Systemic steroids, Sulphasalazine, Indomethacin – No Effect
4	F	37	9	500	Barium meal, Follow through, Enema – NAD	Fluid faeces; Normal mucosa	Opiates, Mepacrine – No effect
5	F	63	4	—	Barium meal, Follow through – NAD; Enema – patulous ahaustral pattern	Fluid faeces; Loss of vascular pattern	Opiates, Systemic steroids, Sulphasalazine, Mepacrine – No effect; Natrum Mur. – Remission
6	F	27	6	600	Barium, Follow through, Enema – NAD	Fluid faeces; Normal mucosa	Opiates – some improvement

normal, but in one the loss of vascular pattern noted at sigmoidoscopy was seen to extend throughout the colon.

LABORATORY INVESTIGATIONS

The normality of most tests was noteworthy. The most frequent abnormality, albeit modest, was the neutrophilic leucocytosis which was present initially in four of the six patients. This neutrophilia probably reflects the colonic inflammation rather than a response to dehydration as the patient with the most profound dehydration (Case 3) had a normal white cell count. In two the ESR was initially raised, in one of whom the haemoglobin was low, and in another the platelet count was raised.

All of the haematological abnormalities were transient, settling with partial remission of the diarrhoea. They did not necessarily reappear with clinical relapse. One patient had electrolyte depletion and mild uraemia at the time of very severe diarrhoea, again completely reversible. Tests for endocrine abnormalities (gut hormone profile, thyroid function) and absorptive function (serum B12 and folate, faecal fat, Schilling test) were normal. One patient underwent extensive tests of gastric and small intestinal function without any abnormality being found. Bacteriological investigation of faeces in all cases and jejunal contents in two of six was unhelpful.

TREATMENT

The response to treatment was disappointing. Only one of six patients responded to conventional treatment used in inflammatory bowel disease with complete remission being achieved on two occasions with full dose systemic corticosteroids. None responded to sulphasalazine, in fact the diarrhoea was made worse by this drug in Cases 1 and 3. One patient was markedly and one minimally improved by opiate antidiarrhoeal drugs. Mepacrine was used unsuccessfully in 2 cases and indomethacin in one. The most striking success was the response of case 5 to Natrum Mur prescribed by a homeopathist.

FOLLOW UP

The six patients have had their symptoms for between four and 33 years and have been regularly followed up for between two and 13 years since diagnosis (median six years). The condition remains essentially unchanged in three of six, but has been modified to a modest degree by drugs in the other three. None has suffered any lasting ill effects as judged by body weight, physical appearance, and laboratory tests, although one (case 3) is still prone to dehydration if she allows her fluid intake to fall below 5l/day. Notably there has been no evidence of psychiatric or emotional disturbance in these patients disproportionate to their disease.

Discussion

To define collagenous colitis as a distinct entity requires that the width of the subepithelial collagen table is outside the normal range, and that such widening is a specific abnormality not encountered in other colonic diseases. On the first score, there is little in the way of morphometric data to give a normal range and most pathologists simply recognise the collagen table as being normal or excessive. A few recent studies, however, have provided some figures.

Bogomoltz *et al*[3] found the collagen band in 30 normal subjects – that is, rectal biopsies reported as normal, to be 4·6–6·9 μ thick, whereas Gledhill and Cole[22] give a figure of up to 3 μ in 10 autopsy specimens. Van den Oord *et al*[12] looked at 564 rectal biopsies made up of normal material (200), inflammatory bowel disease (104) and miscellaneous colonic disorders (260), and reported a range of 0·4–4·6 μ. Gledhill and Cole[22] have examined the second aspect – namely the specificity of a thick band of collagen – by reviewing rectal and colonic biopsies of 457 patients with various colonic diseases. In the great majority the table width was less than 10 μ, but in 19 (4%) it was between 10 and 22·5 μ. The diagnoses in these 19 patients were non-specific colitis (four), carcinoma (six), polyps (six), megacolon (two) and diverticulosis (one). Of the seven patients with the widest collagen band, six had watery diarrhoea, although the diagnosis in these six was not given. From their findings Gledhill and Cole[22] conclude that a thickened collagen band is a rare, but non-specific feature of several colonic disorders, but that a band wider than 15 μ correlates strongly with watery diarrhoea. It is still not clear though from that paper what was the diagnosis in these six patients. If, for instance, they included the four with non-specific colitis, these would qualify as collagenous colitis, or if they fell among the seven with polyps or diverticulosis, they would be collagenous colitis with a coincidental finding of a polyp or diverticulosis.

Despite these reservations, the striking clinical and histological similarity between all the cases so far reported suggests that collagenous colitis is a well defined entity. Chance alone is unlikely to dictate that almost 90% of patients on record are middle aged or elderly women with the same clinical features. The three different histological types of colitis which preceded the development of the condition in three of our patients favours the suggestion, proposed by Gledhill and Cole and

others that collagenous colitis is the end result of a variety of aetiological and pathological processes. We initially considered the diagnosis of infectious colitis in several cases and idiopathic inflammatory bowel disease in others (cases 1, 3, and 5), but bacteriological results and subsequent events did not support this. Nonetheless, the family history of Crohn's disease in case 3 cannot be discounted. The apparent transition from inflammatory to collagenous colitis in three of our cases has also been reported in two patients by Teglbjaerg.[19]

The relationship of collagenous colitis to the recently described microscopic colitis[23] is somewhat closer. Both conditions share two cardinal features – watery diarrhoea and an essentially normal endoscopic and radiological appearance of a microscopically abnormal colon. The microscopical appearances of the two conditions, however, are quite distinct.

The aetiology of collagenous colitis is entirely unknown, but it is possible to speculate on its pathogenesis. The most popular concept is that cell turnover is reduced, allowing fibrocytes to spend longer in the mature phase, hence producing more collagen and a thicker collagen plate. It is well known that in their immature replicative phase fibroblasts produce very little collagen, and in the colon it is only after they have moved up the crypt along with the epithelial cells that they are capable of collagen synthesis.[21] This suggested mechanism makes sense and also explains why in states where cell turnover is high – for example, active inflammation or inflammatory bowel disease, one does not find a thick collagen plate.

The histological findings in case 5 lead us to suggest that reduced turnover of fibroblasts/fibrocytes may not be the only factor involved in the development of a thick collagen plate. In this case the thick plate developed very rapidly (weeks) and at a site of preceding superficial ulceration and fibrinous exudate; possibly the plate resulted from organisation of the exudate. The initial stimulus for the ulceration and inflammation is unknown, but if it were a toxin impairing the blood supply, or ischaemia *per se,* then this might account for the development of a rather dense acellular area of scarring in the part of the mucosa known to be most susceptible to ischaemia.

Another possible mechanism of development of a thick plate of collagen at this site is the process of plasmatic vasculosis.[24] This term refers to the process whereby plasma proteins, including fibrinogen, seep into and through the walls of blood vessels even in the absence of obvious inflammation and is the probable mechanism for the development of the vessel wall fibrosis of hyaline arteriolosclerosis, in hypertension and diabetes. In these conditions the walls of the blood vessels initially stain histochemically and immunohistochemically as fibrin and other plasma proteins and then with time this material becomes converted to or replaced by collagen. We have noted the presence of prominent capillary sized blood vessels in the thickened collage plates in our patients and this has also been noted by others both histologically and electron microscopically.[13]

None of our patients, nor those previously reported, had evidence of gut involvement outside the colon. The subepithelial collagenisation would seem to be pancolonic as there have been no reports of collagenisation in the rectum in the presence of normal epithelium in the proximal colon. It seems likely then that this condition can be diagnosed on the basis of a rectal biopsy and that colonoscopy with biopsy merely confirms its pancolonic nature. Until this point is entirely certain though, it is prudent to take proximal colonic as well as rectal biopsies.

No firm recommendations for treatment can be given. Despite this lack of effective therapy, our study gives in some respects a fairly optimistic outlook for sufferers from this condition. On the debit side, the symptoms of watery diarrhoea continue to a greater or lesser extent in five of six, but on the credit side none has come to any harm as judged by physical and laboratory findings.

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