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Distribution of collagenous colitis: utility of flexible sigmoidoscopy

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Abstract

We investigated the distribution of the collagen band in 33 patients with collagenous colitis to estimate the likelihood of the disease being diagnosed in biopsy specimens from the left side of the colon, such as those obtained using flexible sigmoidoscopy. To be included in this study patients had a subepithelial collagen band ≥10 μm, an increase in chronic inflammatory cells in the same specimen, and diarrhoea for which there was no other apparent cause. In 17 patients undergoing full colonoscopy with a thickened collagen band, collagenous colitis was frequently patchy, even though overall the thickened collagen band was almost equally distributed throughout the colon. Rectal biopsy specimens showed a normal collagen band in 73% of patients, while a thickened collagen band was found in 82% of patients in at least one specimen from the left side of the colon. Three patients had a thickened collagen band only in the caecum. In three of eight rectal biopsy specimens with a normal collagen band there was no mucosal inflammation to raise the possibility of proximal disease, although all but one specimen with a normal collagen band from the sigmoid and descending colon were inflamed. Rectal biopsy alone is therefore a relatively poor method of making the diagnosis. Flexible sigmoidoscopy with multiple biopsy specimens from several sites is a reasonable initial investigation but not sufficient to exclude collagenous colitis when based on the presence of a thickened collagen band alone. Should left sided biopsy specimens show a normal collagen band but an inflamed mucosa, total colonscopy with multiple specimens including the caecum may be required to establish the diagnosis.

Collagenous colitis is an uncommon condition of unknown cause affecting the large bowel, with characteristic histological changes of a thickened eosinophilic and hypocellular subepithelial collagen band and an increase in inflammatory cells in the lamina propria, primarily plasma cells, often with an increase in intraepithelial lymphocytes, and often intraepithelial and lamina propria, neutrophils or eosinophils.[1–13] Colorectal biopsy specimens are required for diagnosis from patients suspected of having collagenous colitis, because there is usually no radiographic or endoscopic abnormality.[6 8 14–16] Several reports have suggested that the disease may be focal, but its precise distribution remains unclear.[2 5 10 15 17] It is also unclear whether collagenous colitis is accompanied by diffuse inflammation throughout the large bowel even in patients without a diffuse diagnostic collagen band, in which case flexible sigmoidoscopic biopsy specimens could reasonably exclude proximal disease.

The purpose of this study was to investigate the distribution of the disease, and to estimate the value and the limitations of proctoscopic or flexible sigmoidoscopic biopsy.

Methods

Patients were identified by review of the surgical pathology files of McMaster University Medical Centre and the record of weekly gastrointestinal biopsy conferences from 1985 to early in 1990. Clinical records were also reviewed to exclude patients with other conditions which may cause diarrhoea, such as radiation, infective and pseudomembranous colitis, and inflammatory bowel disease. Two patients who also had coeliac disease which had not fully responded to treatment were included in this study.

The thickness of the subepithelial collagen band was measured at two points in well oriented parts of the biopsy specimens at the thickest points of each colorectal specimen. Each measurement was carried out by two pathologists independently, using haematoxylin and eosin slides (and trichrome stain if needed) and a calibrated eye piece graticule. When there were capillaries with a thickened wall within the collagen band, band thickness was measured at the part not affected by the capillaries (Fig 1). Interobserver variation was almost exclusively due to different points of the specimens being measured rather than to techniques of measurement. Agreement was obtained after verifying which points were appropriate for measurement. The mean thickness of the collagen band was calculated from both readings at each site in the large bowel, which was divided into caecum, ascending colon to hepatic flexure, transverse colon to splenic flexure, descending colon, sigmoid colon, and rectum. Multiple specimens (up to four) taken from the same site were analysed collectively as a single specimen using a mean collagen band thickness which was evaluated as an average of all specimens at this site. To compare flexible sigmoidoscopic specimens with full colonoscopic specimens, the large bowel was divided into the left colorectum including the rectum to the descending colon and the proximal colon including the splenic flexure to the caecum.

The normal collagen band is less than 7 μm thick,[5 8 11 18 19] and in reported cases of collagenous colitis the collagen band is thicker than 10 μm and accompanied by mucosal inflammation.[2 5 8 14 16 19] On the basis of these data, we used a mean thickness of 10 μm or more and an

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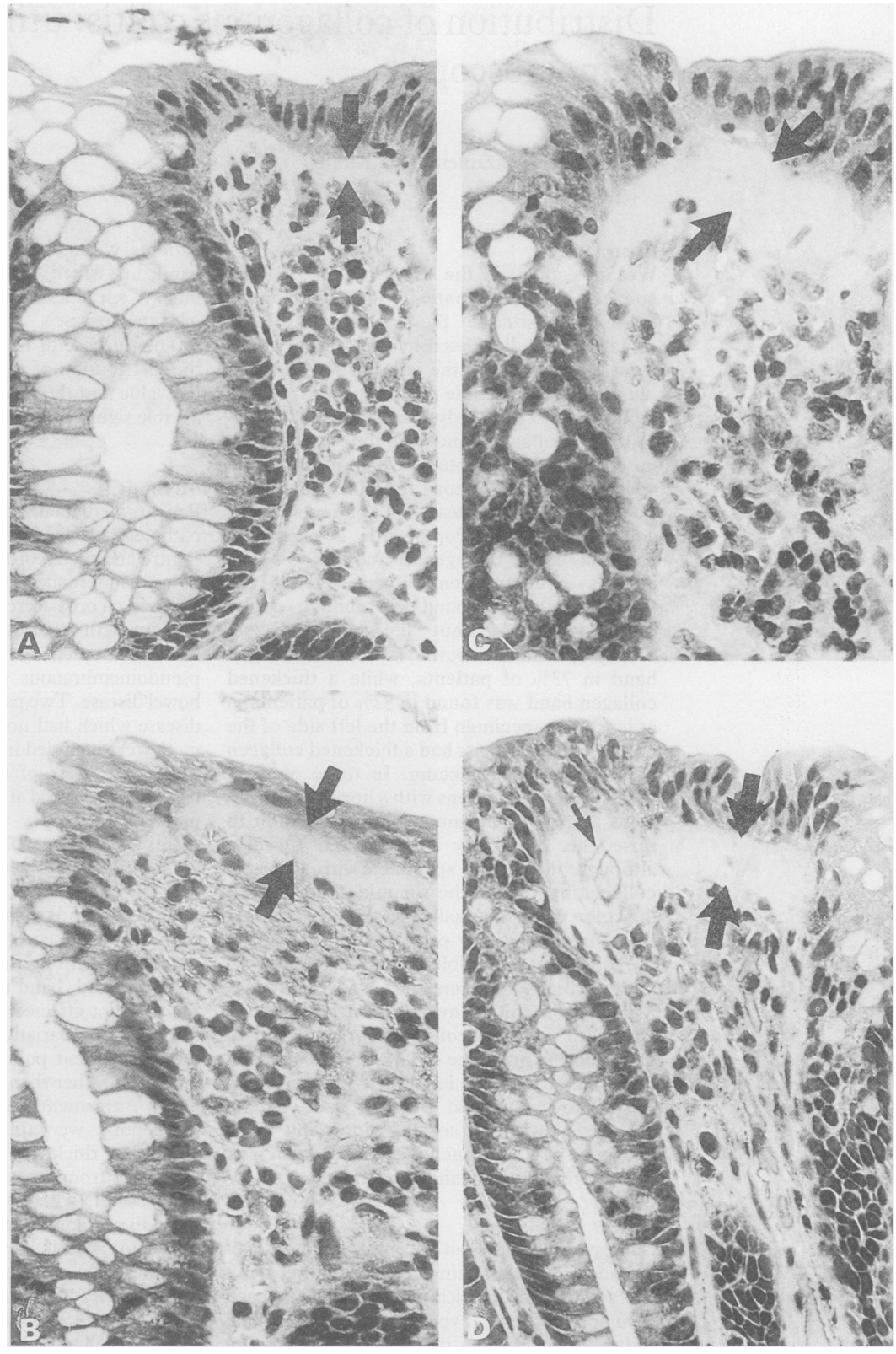

Figure 1: The subepithelial collagen band between the arrows is 7 μm (upper limit of normal) (A), 10 μm (B), and 20 μm (C). (D) When capillaries (arrow) existed within the collagen band the thickness of the collagen band was measured at the part without the direct effect (between the arrows). (Haematoxylin & eosin, original magnification ×460).

increase in chronic inflammatory cells in the same specimen as the diagnostic criteria for collagenous colitis.

DISTRIBUTION OF COLLAGENOUS COLITIS

To determine the distribution of the disease, specimens obtained at full colonoscopy were examined retrospectively in patients with the disease as defined above. Full colonoscopic examinations in which at least one specimen had a mean collagen band thickness of 10 μm or more and in which biopsy specimens were taken from both the proximal and the left colorectum were selected. The proportion of positive specimens (mean thickness ≥10 μm) at each site overall was also investigated.

Fisher's exact probability test was used for

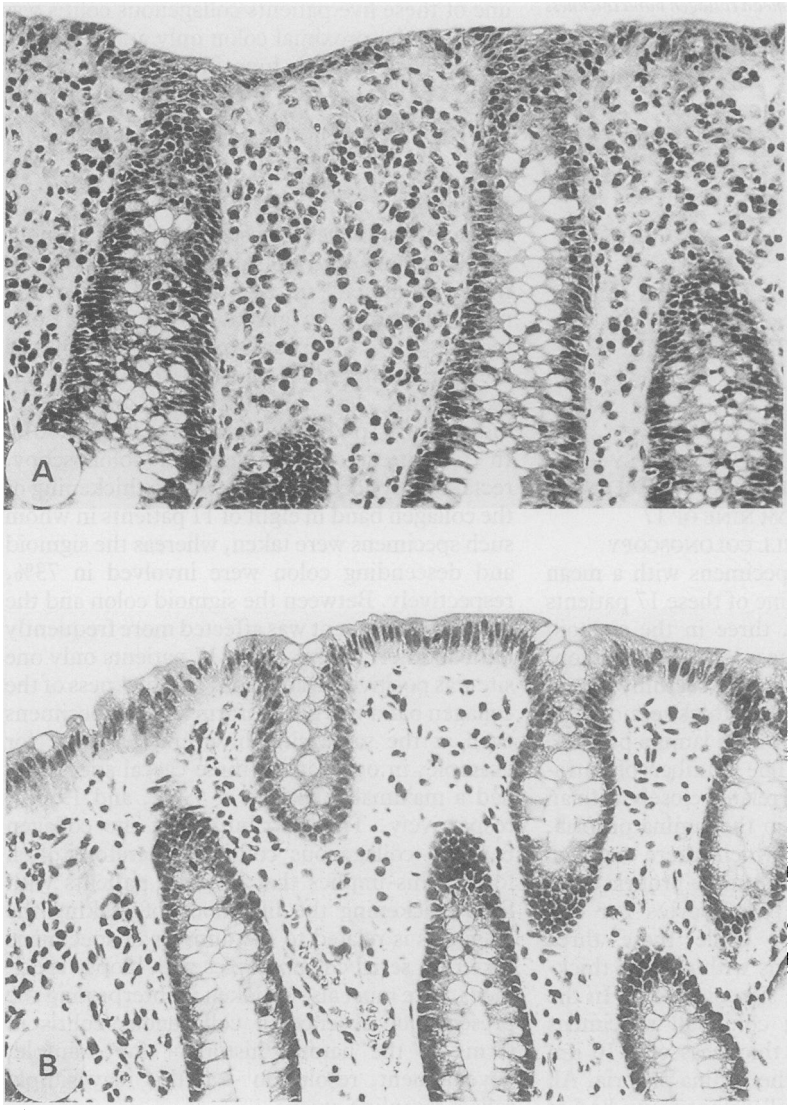

Figure 2: Sample of increased (A) and normal (B) cellularity in the lamina propria (Haematoxylin & oesin, original magnification ×180).

statistical analysis of independent variables of positive and negative biopsy specimens between different sites.

PROBABILITY OF DIAGNOSING COLLAGENOUS COLITIS

Using the same study group as that selected above, colonoscopic specimens were examined to estimate the chance of making the correct diagnosis in specimens sequentially by site. The proportion of the cumulative positive specimens (mean thickness ≥10 μm) to each site was investigated.

MUCOSAL INFLAMMATION IN LEFT SIDED SPECIMENS WITH A NORMAL COLLAGEN BAND

Using the same study group specimens with a mean thickness of <10 μm in the left colorectum were examined to determine whether cellularity in the lamina propria was increased or normal (Fig 2). In left sided specimens without a thickened collagen band, and in which the diagnosis of collagenous colitis could not therefore be made, the number of intraepithelial lymphocytes (number/100 epithelial cells) were counted to determine whether they were present in increased numbers in specimens with and without an increase in inflammatory cells, and therefore whether they would be a better predictor of the presence of collagenous colitis elsewhere.

PROBABILITY OF DIAGNOSING COLLAGENOUS COLITIS AT INITIAL ENDOSCOPY

To estimate the probability of making the correct diagnosis on the initial endoscopy, specimens from the initial endoscopy (proctosigmoidoscopy or full colonoscopy) were examined. The test selected depends on the differing practices for endoscopy and biopsy of several gastroenterologists and trainees. The cumulative proportion of positive biopsy specimens (mean thickness ≥10 μm) to each site was determined.

Results

Thirty three patients were identified with collagenous colitis defined by diarrhoea, minimal or no endoscopic abnormality, and a mean collagen band thickness of 10 μm or more with an increase in chronic inflammatory cells. Altogether 60 large bowel endoscopies were carried out. This study group consisted of 30 females and three males, mean (SD) age 61·0 (16·1) years, range 2–87 years. Two patients had coeliac disease which had failed to respond fully to a gluten free diet.

DISTRIBUTION OF THE THICKENED COLLAGEN BAND IN 17 PATIENTS UNDERGOING FULL COLONOSCOPY WITH MULTIPLE BIOPSY SPECIMENS INCLUDING AT LEAST ONE POSITIVE SPECIMEN

The proportion of positive specimens at each site is given in Table I. The number of biopsy specimens taken at each site varied from one to three, with a mean (SD) number of 1·4 (0·7). The proportion of patients with positive specimens was significantly less for the rectum (27%) than for other sites (60%–83%) whether compared with other sites individually ($p<0·05$) or collectively ($p<0·01$). In five of 17 patients in whom only one specimen was positive, three were taken from the caecum, one from the descending colon, and one from the rectum. In addition, the thickness of the collagen band was not uniform among the specimens even at the same site in several patients.

PROBABILITY OF DIAGNOSING COLLAGENOUS COLITIS IN 17 PATIENTS UNDERGOING FULL COLONOSCOPY

The cumulative percentage of positive sequential specimens by site in 17 patients undergoing full colonoscopy with positive specimens is given in Table II. Had proctoscopy only been carried out, the yield from rectal specimens alone would have remained low, but had flexible sigmoidoscopy been carried out, this would have increased the yield to 82% of patients. In three of 17 patients the diagnosis was only apparent in the caecal biopsy specimen.

TABLE I *Proportion (and percentage) of biopsy specimens with a mean collagen band thickness of ≥10 μm at each site in 17 patients undergoing full colonoscopy*

	Rectum	*Sigmoid colon*	*Descending colon*	*Transverse colon to splenic flexure*	*Ascending colon hepatic flexure*	*Caecum*
Proportion (%)	3/11 (27)	8/11 (73)	8/11 (73)	9/11 (82)	6/10 (60)	10/12 (83)
	p<0·05					
	p<0·05					
	p<0·005					
	p<0·05					

Fischer's exact probability test.

MUCOSAL INFLAMMATION AND NUMBER OF INTRAEPITHELIAL LYMPHOCYTES IN BIOPSY SPECIMENS FROM THE LEFT SIDE WITH A MEAN THICKNESS OF <10 μM FROM NINE OF 17 PATIENTS UNDERGOING FULL COLONOSCOPY

The number of biopsy specimens with a mean thickness of <10 μm in nine of these 17 patients was eight in the rectum, three in the sigmoid colon, and three in the descending colon, respectively (Table III). In the rectum, five of eight specimens with a mean thickness of <10 μm showed inflammation of the lamina propria, primarily plasma cells. The number of intraepithelial lymphocytes correlated closely with an increase in inflammation in the lamina propria. In three specimens in which there was no increase in cellularity of the lamina propria there were ≤6 intraepithelial lymphocytes per 100 epithelial cells (normal), while these three patients also had specimens with a mean thickness of ≥10 μm from the sigmoid colon. In the sigmoid and descending colon all specimens except one with a mean thickness of <10 μm showed inflammation of the lamina propria. All 17 patients undergoing full colonoscopy had at least one specimen from the left side with either a thickened collagen band or mucosal inflammation.

PROBABILITY OF DIAGNOSING COLLAGENOUS COLITIS IN 33 INITIAL ENDOSCOPIES

Twenty three of 33 initial endoscopies were proctoscopy or flexible sigmoidoscopy and left sided biopsies alone; the remainder were full colonoscopy. The cumulative percentage of the positive specimens (mean thickness ≥10 μm) to each site at initial endoscopy is given in Table IV. From one to four biopsy specimens were taken at each site, with a mean (SD) number of 1·6 (0·8). A diagnosis of collagenous colitis was made in 78% of patients using the specimens from the left colorectum only, and in 85% using the specimens from the whole large bowel. Five patients in whom the diagnosis was not made had only one biopsy (three rectum, two sigmoid colon). In one of these five patients collagenous colitis was found in the proximal colon only at subsequent colonoscopy and in four it was subsequently found either in the left colorectum or both proximally and distally.

TABLE II *Cumulative proportion of biopsy specimens with a mean collagen band thickness of ≥10 μm in 17 patients undergoing full colonoscopy*

	Rectum	*Sigmoid colon*	*Descending colon*	*Transverse colon to splenic flexure*	*Ascending colon hepatic flexure*	*Caecum*
Proportion (%)	3/11 (27)	10/14 (71)	14/17 (82)	14/17 (82)	14/17 (82)	17/17 (100)

Discussion

Some reports have suggested that in collagenous colitis a thickened collagen band tends to be more prominent in the proximal colon and may sometimes be absent in the distal colorectum.[8 10 14 17 19] We confirm that this is indeed the case in this series and that the rectum was significantly less affected than other sites individually (p<0·05) or collectively (p<0·01). In 17 patients undergoing full colonoscopy, rectal biopsy specimens showed no thickening of the collagen band in eight of 11 patients in whom such specimens were taken, whereas the sigmoid and descending colon were involved in 73%, respectively. Between the sigmoid colon and the caecum no segment was affected more frequently than another. In five of the 17 patients only one site was positive. In addition, the thickness of the collagen band was not uniform among specimens even at the same site in several patients; for example, in one patient three caecal specimens had a maximal thickness of 9, 12, and 19 μm, respectively. The distribution of the collagen band in collagenous colitis is therefore often focal. This implies that in some patients with focal thickening the likelihood of making the diagnosis is related to the number of specimens taken. In serial colonoscopies with biopsy specimens, care must also be taken in interpreting the presence or absence of collagenous colitis in terms of the natural history – for example, development, resolution – as this may simply reflect sampling error.

The cumulative percentage of full colonoscopic examinations with a thickened collagen band in left sided large bowel specimens indicates a detection rate of collagenous colitis of 27% (3/11) for the rectum, 71% (10/14) for the sigmoid colon, and 82% (14/17) for the descending colon. These results imply that biopsies limited to the rectum and to the rectosigmoid only would have missed 73% and 29% of the patients with the disease, respectively, and that even when the descending colon was included in the distal biopsies, 18% of those with the disease would have remained undetected. Full and possibly multiple colonoscopies may therefore be required to make the diagnosis in some patients.

In 17 patients undergoing full colonoscopy three of eight rectal biopsy specimens with a mean collagen band thickness of <10 μm showed no increase in either cellularity of the lamina propria or intraerithelial lymphocytes,[1 20] although all specimens except one with a mean thickness of <10 μm from the sigmoid and descending colon showed an excess of plasma cells in the lamina propria. This implies that the rectal biopsy site is least likely to be positive, although in one of our patients it was the only site and therefore cannot be excluded from biopsy. However, biopsies in which the degree of inflammation in both the sigmoid and descending colon are normal are unlikely to be associated with

TABLE III *Lamina propria inflammation (LPI) and number of intraepithelial lymphocytes (NIEL/100 epithelial cells in left sided biopsy specimens with a mean thickness of collagen band <10 μm (each line is a different patient)*

Rectum		*Sigmoid colon*		*Descending colon*	
LPI	*NIEL*	*LPI*	*NIEL*	*LPI*	*NIEL*
+	22	+	25	+	34
+	25	+	24	+	21
+	20	NB		P	
+	12	NB		NB	
+	10	P		NB	
−	6	P		P	
−	4	P		P	
−	5	P		NB	
P		+	14	−	4

+=increased; −=normal; P=positive biopsy with a mean thickness of collagen band ≥10 μm; NB=no biopsy was taken from this site.

collagenous colitis elsewhere in the large bowel and may therefore be useful for screening purposes.

In one study the number of intraepithelial lymphocytes was found to be (mean (SD)) 24·6 (3·0) per 100 epithelial cells in cases with 'microscopic colitis.'[1] On the basis of this figure, among our 17 patients three patients showing left sided specimens with a mean thickness of <10 μm fulfilled this criterion. However, this correlated with inflammation of the lamina propria and was not a useful independent parameter for suspicion of collagenous colitis. Furthermore, an increase in intraepithelial lymphocytes is not specific for collagenous colitis or microscopic colitis, which is found in some patients with a similar clinical syndrome; it may also be seen in ulcerative colitis, Crohn's disease, coeliac disease and even in asymptomatic patients.[1]

The probabilities of making the correct diagnosis of collagenous colitis in this series at the initial endoscopy was 85% in 33 patients. In the remaining five patients a thickened collagen band was not detected at initial endoscopy presumably because affected areas in that part of the bowel were not sampled, because disease was not present in that part of the bowel, or conceivably because disease developed after the initial endoscopy. A high proportion (55%) of rectal biopsy specimens were positive at the initial endoscopy compared with 27% in the 17 patients undergoing full colonoscopy. This false higher proportion was due to a selection bias: in most of these patients only rectal biopsy specimens were taken; indeed there was no great difference between the 10 patients undergoing full colonoscopy as initial endoscopy and the 17 patients undergoing full colonoscopy. Another potential source of bias is that our series clearly consists only of patients diagnosed as having the disease; patients with collagenous colitis but with unremarkable rectal biopsy specimens alone might have been excluded from the study altogether. Such patients may, for instance, be managed as if they had irritable bowel syndrome.

Being retrospective, the study is subject to bias. While a prospective study with a standardised number of biopsy specimens and biopsy sites may have been preferable, practically this is difficult to achieve in a unit with many gastroenterologist, fellows, and residents carrying out colonoscopy in patients with an uncommon disease whose only presenting symptom is diarrhoea, in whom endoscopy is grossly normal and over a five year period. The retrospective study provides an indication of what actually happens in a gastrointestinal teaching unit, and is therefore much more likely to be representative of current clinical practice than a formalised prospective study.

In this series rectal biopsy alone was least reliable for making the diagnosis, although in some patients it may have been the only site of the disease. Flexible sigmoidoscopy with multiple biopsies including the rectum, sigmoid, and descending colon is effective to detect but not sufficient to exclude collagenous colitis when based on the presence of a thickened collagen band alone. But if entirely normal quantitatively regarding inflammation (primarily plasma cells) in these three sites, then collagenous colitis is unlikely to be found elsewhere. Flexible sigmoidoscopy with multiple biopsies from several sites is a reasonable initial investigation in patients suspected clinically of having collagenous colitis. Should these left sided large bowel biopsy specimens show a collagen band of normal thickness but an inflamed mucosa, total colonoscopy with multiple biopsies from every site including the caecum may be required to establish the diagnosis if there is a persistent clinical suspicion of this disease. An increase in intraepithelial lymphocytes was not found in the absence of an increased inflammatory infiltrate in the lamina propria and was therefore of little additional value.

TABLE IV *Cumulative proportion of initial endoscopic biopsy specimens with a mean collagen band thickness of ≥10 μm (23 flexible sigmoidoscopies and 10 full colonoscopies)*

Proportion (%)	*Rectum*	*Sigmoid colon*	*Descending colon*	*Transverse colon to splenic flexure*	*Ascending colon hepatic flexure*	*Caecum*
Flexible sigmoidoscopy	10/14 (71)	17/22 (77)	18/23 (78)			
Full colonoscopy	1/6 (17)	4/7 (57)	7/9 (78)	7/9 (78)	7/9 (78)	10/10 (100)
Total	11/20 (55)	21/29 (72)	25/32 (78)	25/32 (78)	25/32 (78)	28/33 (85)

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