

Histological abnormalities in biopsies from macroscopically normal colonoscopies

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SUMMARY One hundred and nineteen children with gastrointestinal symptoms underwent colonoscopy during the course of one year. Out of 39 children that were reported as yielding normal results on endoscopic examination, six had disease detectable only by histology. The pathology included cases of microscopic colitis, Crohn's disease, and indeterminate colitis. To exclude large bowel inflammation as a cause of gastrointestinal symptoms biopsy specimens should always be taken at endoscopy.

Colonoscopy is now used as an important diagnostic technique in paediatric gastroenterology. It may even be used safely in infants. It is performed using sedation and not under general anaesthesia.¹⁻⁴ Multiple biopsy specimens can be taken at the time of colonoscopy. In adult practice a group of patients with chronic watery diarrhoea have been described who, in the presence of normal endoscopic appearances, have an infiltration of excess chronic inflammatory cells in the colonic mucosa.⁵ The aim of this paper is to report the histological findings in biopsy specimens taken from a series of children with normal appearance at endoscopy and so to determine whether biopsy specimens are necessary to evaluate the mucosa when the endoscopic appearances are normal.

Methods and materials

Children with symptoms suggesting chronic inflammatory bowel disease who underwent colonoscopy at St Bartholomew's Hospital and the Queen Elizabeth Hospital for Children, London, between September 1983 and September 1984 were entered into the study. The macroscopic appearances were reported at the time of the procedure. Children whose colonoscopy was reported as showing a normal vascular pattern throughout were selected. Biopsy specimens were taken from the caecum, transverse colon, sigmoid colon, and rectum for fixation in formal saline. They were embedded in paraffin, sectioned at 5 μ , and stained with haematoxylin and eosin. Each case was reported by one pathologist and independently reviewed by another (SB).

Stools were cultured in every child for pathogenic bacteria and examined for ova, cysts, and parasites. Serology was taken to detect yersiniosis or amoebiasis. Tuberculosis was tested by Mantoux test and chest x ray film.⁶ The small bowel was investigated by barium follow through and, when appropriate, by proximal small bowel biopsy. Barium enema, which yields no more information than colonoscopy,⁷ was not performed.

Results

One hundred and nineteen children underwent colonoscopy between September 1983 and September 1984. Of these, 39 had a normal endoscopic appearance. Biopsy specimens from six of these were histologically abnormal.

The clinical features of these children (Table 1) are those commonly seen in a paediatric gastroenterology practice. Four children had profuse diarrhoea, which in one case was associated with rectal prolapse. Four weighed less than the third centile for their age. The three oldest children complained of abdominal pain.

Histological findings. The histological abnormalities found in the six children are given in Table 2.

Three patients (cases 1, 2, and 3) had severe diffuse inflammation in the lamina propria (Fig. 1) with degeneration of the surface epithelium. Increased numbers of lymphocytes, plasma cells, histiocytes, and eosinophil polymorphs were found in the lamina propria. Intraepithelial neutrophils, crypt abscesses, and mild distortion of the glands

Table 1 *Clinical features and diagnosis in six children with normal appearances at endoscopy*

Case No	Age (years)	Sex	Symptoms	Diagnosis of colonic disease	Other diagnosis
1	1	M	Diarrhoea; failure to thrive	Indeterminate colitis	Autoimmune enteropathy
2	5	M	Diarrhoea; failure to thrive; rectal prolapse	Campylobacter colitis	Untreated coeliac disease (provisional)
3	6	F	Diarrhoea; weight loss	Indeterminate colitis	(1) Probable coeliac disease (2) Thyrotoxicosis
4	8	M	Abdominal pain; diarrhoea	Indeterminate colitis	
5	13	M	Short stature; weight loss; abdominal pain	Indeterminate colitis	Untreated coeliac disease (provisional)
6	14	F	Abdominal pain	Crohn's disease	

Table 2 *Histological features of the colonic biopsies*

Case No	Mucosal inflammation	Intraepithelial polymorphs	Crypt abscesses	Crypt architecture	Other features
1	Moderate	+	+	Gland distortion, dilatation, and branching	Goblet cell depletion; thin surface epithelium
2	Heavy	+	+	Minor gland distortion and branching	Goblet cell depletion
3	Heavy with eosinophils	+	-	Normal	Goblet cell depletion; thin surface epithelium
4	Mild and patchy	+	-	Minor gland distortion and branching	
5	Mild and patchy	-	-	Minor gland distortion	
6	Mild and patchy	-	-	Minor gland distortion	Non-casating granulomas

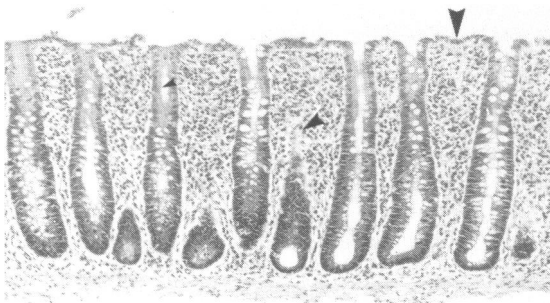


Fig. 1 *Case 3—Colonic biopsy specimen showing severe diffuse inflammation of the lamina propria (medium sized arrow), goblet cell depletion (small arrow), and attenuation of the surface epithelium (large arrow). Haematoxylin and eosin. Original magnification $\times 125$.*



Fig. 2 *Case 1—Colonic biopsy specimen showing severe diffuse inflammation of the lamina propria (medium sized arrow) with gland distortion, crypt abscesses (large arrow), and goblet cell depletion (small arrow). Haematoxylin and eosin. Original magnification $\times 270$.*

with goblet cell depletion were present in cases 1 and 2 (Fig. 2).

In two patients (cases 4 and 5) there was patchy mild chronic inflammation in the lamina propria (Fig. 3). The inflammatory cells consisted of lymphocytes, plasma cells, histiocytes, and eosinophil polymorphs. There was minor gland distortion with a normal goblet cell population. No granulomas were seen.

In another patient (case 6) whose biopsy specimen showed mild and patchy inflammation, non-casating, epithelioid granulomas were present in the lamina propria (Fig. 4).

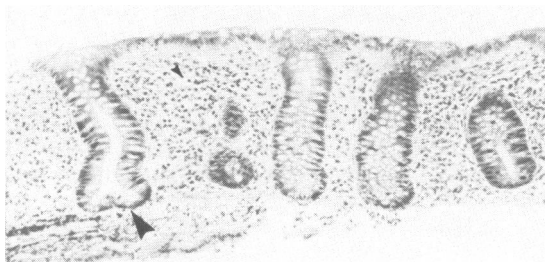


Fig. 3 Case 4—Colonic biopsy specimen showing mild chronic inflammation of the lamina propria (small arrow) and mild distortion and branching of the glands (large arrow). Haematoxylin and eosin. Original magnification $\times 125$.

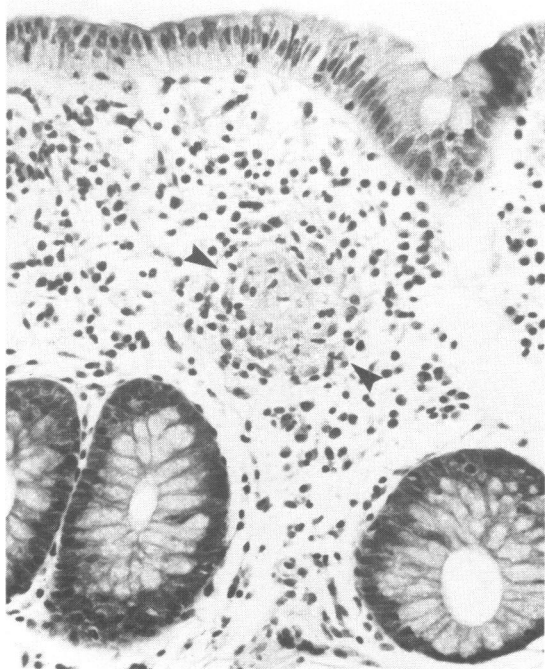


Fig. 4 Case 6—A non-caseating epithelioid granuloma (arrows) in the lamina propria of the colon. Haematoxylin and eosin. Original magnification $\times 325$.

Children with abnormal small bowel morphology. Four of the six patients had abnormal proximal small bowel biopsy specimens (Table 3).

Subtotal villous atrophy with crypt hyperplasia was reported in case 1. This child was still an infant and had never ingested gluten. He gained weight only on parenteral nutrition. Serology showed an autoantibody to small intestinal epithelial cells.

In two patients (cases 2 and 5) the jejunal biopsy specimen showed subtotal villous atrophy consistent with untreated coeliac disease. Both responded to a gluten free diet. Stool culture from case 2 showed a growth of *Campylobacter jejuni*.

The small bowel biopsy specimen of case 3 showed a severe partial villous atrophy with crypt hyperplasia. The child had, however, been on a strict gluten free diet for five years as a small bowel biopsy performed during infancy had shown severe villous atrophy. She initially responded to the removal of gluten from her diet but despite strict adherence to the diet deteriorated three years later. She also developed thyrotoxicosis at this time.

Diagnoses. In one child the inflammation in the colon was due to Crohn's disease. The remaining five patients had an indeterminate colitis.⁸

Case 1 had an autoimmune enteropathy. Anti-epithelial cell antibodies have been detected in other children^{9, 10} and found to cause small bowel disease. The colonic inflammation found in this child is probably also of autoimmune aetiology.

In cases 2 and 5 a provisional diagnosis of untreated coeliac disease was made from the jejunal biopsy specimen, the presence of an antigliadin antibody, and the response to a gluten free diet. The inflammation in the colon in case 2 could have been due to the campylobacter infection.

Case 3 fulfils the diagnostic criteria of microscopic colitis.^{5, 11} Firstly, histology of the large bowel showed diffuse inflammation; and, secondly, no cause was found for the chronic diarrhoea that continued after the child's thyrotoxicosis had been treated and after the small bowel morphology had returned to normal with treatment with steroids.

Table 3 Results of small bowel biopsies in four of the six cases

Case No	Villi	Crypts	Lamina propria	Intraepithelial lymphocytes	Other features
1	Subtotal villous atrophy	Hyperplastic	Excess plasma cells; eosinophils	Normal	Anti-epithelial cell antibody
2	Subtotal villous atrophy	Hyperplastic	Excess plasma cells	Raised	Positive antigliadin antibody
3	Severe villous atrophy	Hyperplastic	Excess macrophages; eosinophils; plasma cells; lymphocytes	Raised	
5	Subtotal villous atrophy	Hyperplastic	Increased plasma cells	Raised	Positive antigliadin antibody

The colitis found in case 4 was mild. He was the brother of a child with Crohn's colitis, but no diagnostic features of this condition were found. Case 6 had Crohn's disease.

Discussion

In six out of 119 children (5%) undergoing colonoscopy, disease was only found after histological examination. It has never previously been shown that total colonoscopy may fail to detect inflammation in children, although it is well known that in conditions causing visible patchy inflammation, such as Crohn's disease, inflammatory cells and even granulomas may be found in areas that appear normal. In performing colonoscopy it is important, therefore, not only to examine the whole colon but also to take biopsy specimens in all cases.

Although all six children had colonic disease detectable only on histological examination, the causes of the disease were diverse. Only one case completely fulfilled the criteria for microscopic colitis drawn up by Kingham *et al* that the inflammation be uniform and without identifiable cause.⁵

Three of the six cases described by Kingham had abnormal small bowel biopsy specimens. In our series a colitis was present in two children with probable coeliac disease. (A definite diagnosis of coeliac disease cannot be made until a formal gluten challenge has been performed to satisfy the criteria of the European Society for Paediatric Gastroenterology and Nutrition.¹²) Although in one child the inflammation could be attributed to an intercurrent infection with campylobacter, the other had no evidence of bacterial or viral infection. The question arises whether large bowel enteropathy can occur as a consequence of coeliac disease. No prospective study of large bowel disease in coeliac disease has been performed.¹³ In adults,¹⁴ however, inflammation of the large bowel, evident on endoscopy, has been reported to occur more often than the respective prevalences of coeliac disease and inflammatory bowel disease would predict. Colonic inflammation severe enough to cause rectal bleeding has also been described in two children with coeliac disease.¹⁵ Nevertheless, microscopic large bowel inflammation is not an invariable finding in children with coeliac disease as children with active coeliac disease in this unit have undergone colonoscopy and multiple biopsy without showing disease.

Kingham *et al* described one case of microscopic colitis occurring in a 56 year old woman

who had responded to a gluten free diet five years previously.⁵ Case 3 in our series similarly developed a microscopic colitis on a gluten free diet. The relation between coeliac disease and microscopic colitis, however, remains unclear.

In conclusion, it is essential to take biopsy specimens at colonoscopy, even when normal, if the causes of gastrointestinal symptoms in childhood are to be found. The results of histology, however, do not all fit a diagnosis of microscopic colitis but display varied disease.

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