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Patchy enteropathy in childhood

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SUMMARY Two hundred and seventy-eight duodenal biopsy specimens taken consecutively from children using either a single port paediatric Crosby capsule or a double port modification were examined both histologically and by dissecting microscopy, in order to determine the incidence of patchy mucosal lesions. One hundred and six specimens were abnormal and 49 of these were patchy. Patchy lesions occurred most commonly in cow's milk sensitive enteropathy where 66% of 33 specimens were patchy; in comparison all children with undiagnosed coeliac disease taking a normal diet showed a uniformly flat mucosa. Twenty-two per cent of specimens taken using the double port and 10% using the single port capsule were patchy, a statistically significant difference ($P = 0.01$) using standard errors. Where lesions were uniform, grading by dissecting microscopy correlated well with histological grading; 18 (37%) of specimens were, however, recognised as patchy only on gross appearance. The high incidence of patchy lesions of the proximal small intestine reflected the prevalence of cow's milk protein intolerance and the postenteritis syndrome in these children. The use of the double port capsule and of dissecting microscopy also contributed to the high incidence found.

Post-mortem studies of the mucosal morphology of the small intestine in children (Walker-Smith, 1972) and adults (Thompson, 1974) with gastrointestinal disease have demonstrated variation in severity of mucosal damage within a small area—that is, patchy enteropathy. A biopsy specimen of the proximal small intestinal mucosa obtained using the Crosby capsule (Crosby and Kugler, 1957), or its paediatric modification, may not, therefore, be fully representative of a diseased mucosa. Recently, patchiness on biopsy has been documented in adult coeliac disease and dermatitis herpetiformis (Scott and Losowsky, 1976), the authors using the hydraulic multiple biopsy instrument (Quinton Instruments, Seattle) a technique not easily applied to infants and young children. Other workers have described biopsy instruments, suitable for use in infants, which take two mucosal specimens (Latham *et al.*, 1969; Ament and Rubin, 1973). Since 1974, a double port modification of the Crosby capsule (Kilby, 1976), which provides two mucosal specimens has been used in our department. This allows more tissue to be obtained with safety from infants, and samples from a wider area.

The present study aims, firstly, to confirm the existence of a patchy enteropathy in children, secondly, to relate the incidence of patchy lesions to diagnosis, and, thirdly, to compare the 'pick up rate' of patchy lesions using the single port Watson modification of the paediatric Crosby capsule and the double port modification.

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Methods

Two hundred and seventy-eight proximal small intestinal biopsies (100 single port capsule and 178 double port capsule) taken over an 18 month period (1 July-31 December 1976), during routine investigation from children with a variety of gastrointestinal problems, were examined. Each specimen was removed from the capsule, placed villous surface upward on black filter paper, immersed in cold saline, and photographed using the Zeiss Tessovar photomacrographic zoom system. The specimens were then processed for histological examination. Specimens from a single port capsule were sectioned in a cryostat and the section stained with haematoxylin and eosin and with Scharlach R. Subsequently, the tissue was embedded in ester wax, sectioned, and stained with haematoxylin and eosin. When a double port capsule was used one specimen was processed as above, the second specimen being fixed directly in formal saline and embedded in ester or paraffin wax.

Each specimen was examined histologically and graded:

N: normal mucosa; villi at least twice as long as crypts.

+: a minor degree of partial villous atrophy (PVA), including mucosa with not more than two of the following features: shortening or thickening of villi; epithelial abnormality; increased cellular infiltrate in the lamina propria; elongation of the crypts.

++: severe PVA, short, frequently wide villi; most specimens in this grade showed an epithelial abnormality—increased intraepithelial lymphocytes and/or pseudostratified epithelium; a moderate increase in cells of the lamina propria; hyperplasia of the crypts.

+++: flat mucosa.

Each specimen was graded by a single observer (N.F.) who did not know the clinical condition of the patient at that time.

Morphometric observations were made in some biopsies but are the subject of a separate report (de Peyer *et al.*, 1978).

Photographic transparencies of the macroscopic appearance of the biopsies were examined without knowledge of histological grading and graded:

0: normal mucosa—tall, thin ridge-like villi, tongues, leaves and fingers.

1: minor degree of abnormality—shortening and thickening of villi and confluence of ridge-like villi.

2: severer abnormality—short thick ridges and/or convoluted ridges.

3: flat mucosa—featureless or with a mosaic pattern.

A lesion was counted as patchy if histological sections or gross appearance showed variation of one or more grades in severity in a single biopsy specimen or between biopsy specimens obtained by the double port capsule. A variation of 0/1 in gross appearance was disregarded later if histological grading was normal, in order to avoid over-interpretation of minor abnormalities apparent only with the dissecting microscope.

Most specimens obtained with both the Watson paediatric capsule and also the double port capsule did not include muscularis mucosae. Perera *et al.* (1975) have stated that biopsies which do not include the muscularis mucosae may have villi that appear to be shortened and broad. Such a possible artefact was allowed for in interpretation of this material. Moderate shortening of villi alone was not regarded as evidence of abnormality unless some other feature was present—for example, increased cellular infiltrate.

Results

The results of examination of all 278 biopsy specimens are set out in Table 1. One hundred and six of the 278 biopsies were abnormal, and, of these, 49 showed some degree of patchy abnormality. Examples of patchy lesions are shown in Figs 1 and 2.

Two degrees of patchy abnormality were recognised: (1) minor: a difference of one grade on histological and/or gross appearance; (2) major: a difference of two or more grades on histological and/or gross appearance

Table 1 *Results of biopsy in relation to capsule used*

Grade		*Single biopsy capsule*	*Double biopsy capsule*	*Total*
Normal		66	106	172
Abnormal	Uniform	24	33	57
	Patchy	10	39	49
Total		100	178	278

PATCHY ENTEROPATHY AND DIAGNOSIS

The diagnosis of all children biopsied are listed in Table 2, together with those who had a patchy enteropathy of minor or major degree.

Sixty-six per cent of 33 biopsy specimens from infants with cow's milk protein intolerance (cow's milk sensitive enteropathy, Walker-Smith *et al.*, 1978) showed a patchy enteropathy, which was of major degree in 39%. Forty-four per cent of 23 specimens from infants with postenteritis syndrome showed patchy lesions, although this was of major degree in only 9%. In children with coeliac disease only after challenge with gluten (for periods of one to four months) was patchiness found at a comparable level to children with the postenteritis syndrome and cow's milk protein intolerance; 35% of 20 biopsy specimens showed patchiness, although mostly of a minor degree. All children with untreated coeliac disease on initial biopsy, while taking a normal diet, showed uniformly flat mucosae. Where children had been on a gluten-free diet for a period of more than two years and were biopsied before gluten challenge, only two of 20 biopsy specimens were abnormal but both of these were patchily abnormal.

COMPARISON OF SINGLE AND DOUBLE PORT CAPSULES

A major degree of patchiness was seen in 17 of the 49 patchy biopsies, four taken using the single port and 13 the double port capsule (Table 3).

Thirty-four of 100 biopsy specimens obtained by the single port capsule were abnormal and of these 10—that is, 29·4% of abnormal biopsies—showed a patchy abnormality.

In comparison, 72 of the 178 biopsies taken using

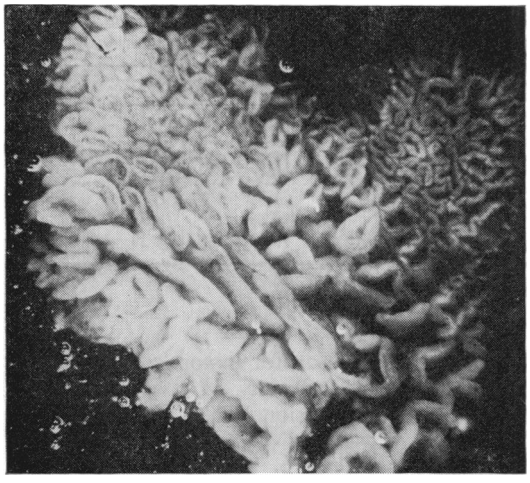

Fig. 1 *Patient I. J. Macroscopic appearance of a biopsy specimen from patient with the postenteritis syndrome. In the upper left and right hand corners are convoluted ridges giving a brain-like appearance; the remainder of the specimen consists of tall thin ridge like villi of normal appearance (graded 2/0).*

the double port capsule were abnormal and of these 39—that is, 22% of all biopsies taken using the double port capsule or 54% of the abnormal biopsies—showed a patchy abnormality (Tables 1 and 3). The difference is statistically significant ($P = 0.01$).

A simple method of demonstrating the effectiveness of the double port capsule was to count those biopsies where one specimen was graded as normal and the other abnormal—that is, where a single biopsy might have missed the lesion completely. There were 12 such biopsies.

VALUE OF DISSECTING MICROSCOPY IN DIAGNOSIS OF PATCHY ENTEROPATHY

Table 4 shows that 18 (37%) specimens were recognised as patchy only by their gross appearance, and patchiness would have been missed if only routine histological had been performed. Moreover major degrees of patchiness were more likely to be recognised by dissecting microscopy as a larger area is examined. Where patchy lesions were demonstrated by both gross and histological means, major degrees of patchiness were recognised grossly

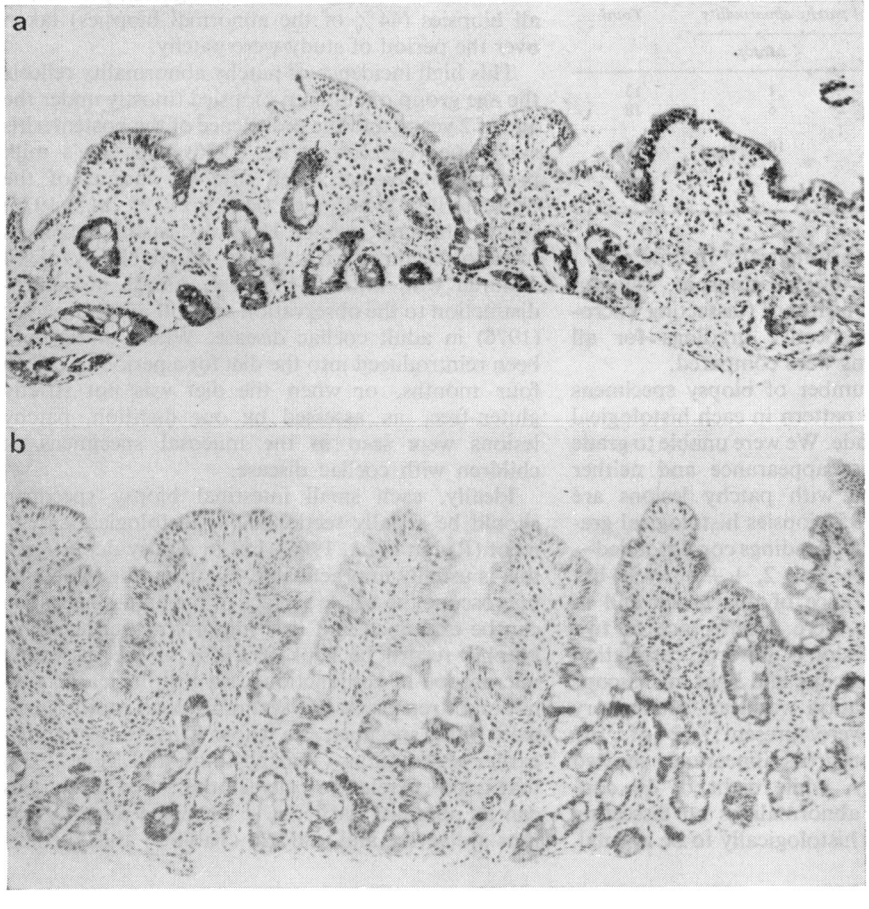

Fig. 2 *Patient S. S. Histological sections of biopsy specimens taken using the double port capsule from patient with cow's milk sensitive enteropathy. H. and E. (×110). (a) specimen 1: graded ++. (b) specimen 2: graded ± (possible shortening of villi).*

Table 2 *Patchy enteropathy—correlation with disease*

Diagnosis	*Degree of patchy abnormality*		*Biopsies (no.)*		*Total*
	Minor	*Major*	*Patchy*	*Uniform*	
Cow's milk protein intolerance	9	13	22	11	33
Postenteritis syndrome	8	2	10	13	23
Coeliac disease:					
at diagnosis	0	0	0	14	14
on gluten-free diet	1	1	2	18	20
at challenge	6	1	7	13	20
Others	8	0	8	160	168
Total	32	17	49	229	278

Table 3 *Patchy abnormality and biopsy capsule*

Capsule	*Degree of patchy abnormality*		*Total*
	Minor	*Major*	
Single port	6	4	10
Double port	26	13	39
Total	32	17	49

Table 4 *Degree of patchy abnormality seen with each examination technique*

	Degree of patchy abnormality		*Total*
	Minor	*Major*	
Histology alone	12	1	13
Gross appearance alone	12	6	18
Histology and gross appearance	8	10	18
Total	32	17	49

in all 10 specimens but histologically in only six.

In order to assess the relationship between histological and gross appearance (dissecting microscope) gradings, the respective gradings for all uniform biopsy specimens were compared.

Table 5 shows the number of biopsy specimens with a uniform mucosal pattern in each histological and gross appearance grade. We were unable to grade nine specimens on gross appearance and neither these nor 49 specimens with patchy lesions are shown in the table. In 195 biopsies histological gradings and gross appearance gradings corresponded—that is, N = 0, + = 1, ++ = 2, +++ = 3—but in 24 there was a difference of one grade and in only one specimen was there a difference of two grades. Thus, when the lesion is uniform, correlation between dissecting microscope and light microscope grading is good. Correlation was least satisfactory when minor lesions were present; 12 of 167 thought to be normal on gross appearance showed histological abnormality, while eight of 16 considered to show minor abnormalities on dissecting microscopy were shown histologically to be normal.

Table 5 *Relationship between histological and gross appearance gradings in uniform biopsy specimens*

Gross appearance	*Histology*				*Total*
	N	+	++	+++	
0	155	11	1*	0	167
1	8	7	1	0	16
2	0	1	7	1	9
3	0	0	2	26	28
Total	163	19	11	27	220

*Difference of two grades.

This lack of correlation for minor lesions was due principally to the difficulty in assessing villous height from two-dimensional photographs.

Discussion

This biopsy study demonstrates the occurrence of patchy lesions in gastrointestinal disease affecting the proximal small intestinal mucosa in children and confirms previous post-mortem studies (Walker-Smith, 1972; Thompson, 1974). Eighteen per cent of all biopsies (44% of the abnormal biopsies) taken over the period of study were patchy.

This high incidence of patchy abnormality reflects the age group of children biopsied (mostly under the age of 2 years) and the prevalence of the postenteritis syndrome (Gribbin *et al.*, 1976) and cow's milk protein intolerance, itself often a variant of the postenteritis syndrome (Harrison *et al.*, 1976) within this age group. However, such patchiness was not demonstrated in the initial biopsy of 14 children with untreated coeliac disease in contradistinction to the observation of Scott and Losowsky (1976) in adult coeliac disease. Where gluten had been reintroduced into the diet for a period of one to four months, or when the diet was not strictly gluten-free, as assessed by our dietition, patchy lesions were seen in the mucosal specimens of children with coeliac disease.

Ideally, each small intestinal biopsy specimen should be serially sectioned for histological assessment (Rubin *et al.*, 1965), but in a busy department this is usually impracticable. By using the dissecting microscope the whole surface of the biopsy specimen can be examined and it is important that a photographic record be kept. The use of the dissecting microscope in conjunction with histological examination of representative sections allows rapid assessment of the specimen as a whole. This study confirms earlier observations (Walker-Smith and Reye, 1971) that good correlation between these two techniques can be obtained particularly when the mucosal lesions are severe and uniform (Table 5) and, further-

more, dissecting microscopy is of major importance in assessing mucosal patchiness (Table 4).

We have recognised two degrees of patchiness—namely, a major degree where there was a difference in grading of two or more grades on histological and/or gross assessment and a minor degree where there was a difference of only one grade.

We believe a minor degree of patchiness is of particular significance in paediatric practice where the diagnosis of the postenteritis syndrome or cow's milk protein intolerance for example, may depend upon the presence of a mild partial villous atrophy (grade +). Confirmation of the significance of minor abnormality, and of our grading system has been obtained using the morphometric techniques of Dunhill and Whitehead (de Peyer *et al.*, 1978).

The double port capsule was introduced into our department in order to provide with safety more tissue for investigation; at the same time the capsule samples from a larger area of mucosa. The likelihood of this capsule picking up more variation in mucosal damage than would a single port capsule when there is a patchy enteropathy was confirmed by the present study. Using both histological and gross appearance criteria, 22% of biopsies taken with the double port capsule were patchy compared with 10% of biopsies taken using the single port capsule. In addition, in 12 instances an abnormal mucosa might have been missed by a biopsy taken using a single port capsule. Since patchiness of mucosal damage does occur and lesions may, therefore, be missed, biopsies should be taken from as wide an area as possible. In infants and small children the double port modification of the Crosby capsule is an easily usable and inexpensive advance of the single port capsule. It is important also to appreciate that biopsy provides a sample only of the proximal small intestinal mucosa and post-mortem studies have shown that gastroenteritis, for example, may damage distal small intestine to a variable degree, with sometimes the ileum being most severely damaged (Walker-Smith, 1972).

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