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COELIAC DISEASE

HISTOPATHOLOGICAL FINDINGS IN THE SMALL INTESTINAL MUCOSA STUDIED BY A PERORAL BIOPSY TECHNIQUE

BY

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Villous atrophy, changes in the surface epithelium, mucosal thickening, and glandular hypertrophy were a feature of all the mucosal biopsies from the small intestine obtained from eight coeliac children. No histological differences were observed between the children previously treated with intermittent gluten-free diets and the untreated children. Serial biopsy studies were carried out on one coeliac child before and after treatment with a gluten-free diet over a period of two years. On the whole they confirmed the irreversible nature of the observed histopathological changes but minor improvements could not be excluded. Mucosal abnormalities in coeliac disease are the same as in adult idiopathic steatorrhoea, where they are observed in patients with or without a response to a gluten-free diet. It is concluded that the elimination of gluten from the diet has little if any influence on the histopathological abnormalities observed in coeliac disease.

The clinical picture of coeliac disease was well described by Samuel Gee as long ago as 1888. He emphasized the passage of loose, bulky, pale, and offensive stools as the first and foremost sign of the disease, accompanied by anaemia, muscular atony, wasting, and stunted growth.

The aetiology of coeliac disease has, however, remained obscure. An anatomical lesion of the small intestine had never been demonstrated until the first report by Sakula and Shiner (1957) in which they described villous atrophy of the intestinal mucosa of the smaller intestine obtained by peroral biopsy technique from an untreated coeliac child. This work has now been extended to embrace seven more coeliac children who are the subjects of this report. In addition, repeat biopsies, over a period of two years while the patient was on a gluten-free diet, were performed on the child originally reported by Sakula and Shiner.

METHOD

The child's intestinal biopsy tube (Fig. 1) is a modification of the adult suction biopsy tube (Shiner, 1956). It is of sufficiently small calibre to be used for intubating children of the age of 1 year. From half to one hour is required to take the biopsy.

The child is not usually sedated, but if necessary a mixture of pethidine, mg. 100, chlorpromazine, mg. 50, and promethazine, mg. 50, per 100 lb. of body weight may be administered intramuscularly. He should be fasting and the throat may be anaesthetized with a ½-1% amethocaine gargle. The tube is introduced in the left lateral position and its progress through the stomach and duodenum is followed fluoroscopically. The biopsy specimen is preferably taken from the first part of the jejunum but occasionally the head end of the tube will not travel further than the second or third part of the duodenum when the specimen is taken from these sites. A high negative pressure of 10 to 20 in. of mercury is necessary for adequate specimens to be sucked into the aperture. Several biopsy specimens can be obtained at any single intubation by varying the position of the tube. Once specimens are taken, the tube should be rapidly withdrawn and the specimens immediately fixed in 10% formol saline to avoid autolysis.

The method described has proved safe and no complications have occurred in the 18 children subjected to it. But it was not possible to obtain adequate specimens or to pass the tube beyond the pylorus in eight of these children.

MATERIAL

Of the 10 children in whom adequate mucosal specimens were obtained, eight had coeliac disease, one juvenile pernicious anaemia, and one idiopathic hypoproteinaemia associated with steatorrhoea.

The diagnostic criteria of coeliac disease, namely diarrhoea, steatorrhoea, anaemia, and muscular atony in a stunted, underweight child, were strictly adhered to by their physicians in charge when the patients first came under observation.

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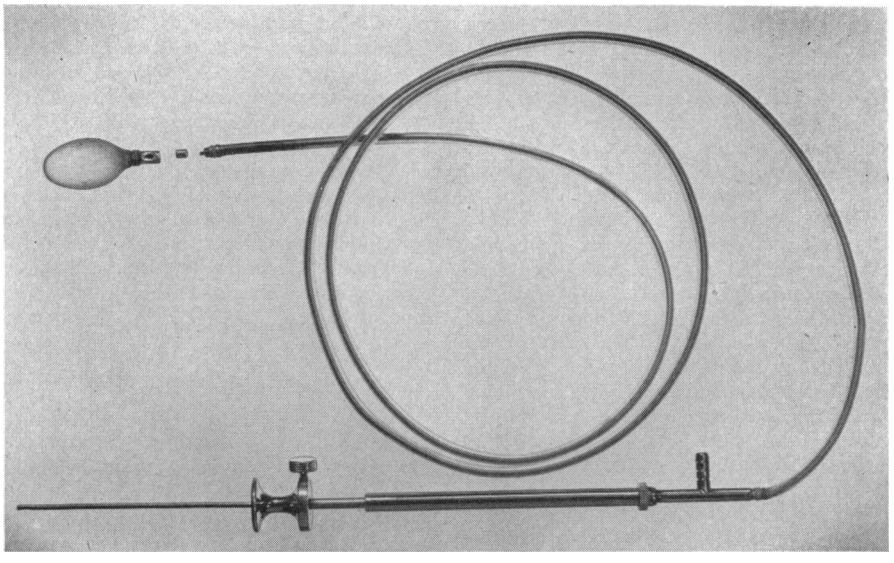

FIG. 1.—*The child's small intestinal biopsy tube.*

TABLE I

CLINICAL SUMMARY OF SERIES OF EIGHT COELIAC CHILDREN

No.	Name	Age (yr.)	Sex	Height (in.)	Weight (lb.)	Diarrhoea	Abdominal Distension	Steatorrhoea (Faecal Fats)	Haemoglobin (%)	Glucose Tolerance Curve
1	G.C.	10	Male	48¾	24	No	No	7·7 g./day	98	Normal
2	D.L.	9	Female	43⅞	38·8	Yes	Yes	91·5% absorption	42	Flat
3	P.K.	2¼	Male	30¼	22·3	Yes	Yes	87% absorption	86	Flat
4	J.B.	15	Female	57	81	No	No	—	52	Normal
5	L.P.	4½	Female	40	32	Yes	Yes	86% absorption	62	—
6	A.R.	13½	Male	52⅛	60·7	Yes	No	58% absorption	54*	Flat
7	J.N.	2½	Female	34½	24·1	Yes	Yes	13 g./day	80	—†
8	M.R.	7¾	Male	41¾	32	Yes	Yes	48% absorption	74	Flat

* = macrocytic anaemia † = xylose excretion low

TABLE II

AGES AT ONSET AND DIAGNOSIS AND TREATMENT IN EIGHT COELIAC CHILDREN

Case No.	Name and Age (yr.)	Age at Onset of Symptoms (yr.)	Age at Diagnosis (yr.)	Previous Treatment	Treatment at Time of Biopsy	Clinical Progress
1	G.C. (10)	Not known	6¾	Gluten-free diet for 4 years	No treatment for past 4 months	No gain in weight or increase in height during the past 4 months
2	D.L. (9)	2	3	Nil	No treatment	Good progress on gluten-free diet
3	P.K. (2¼)	1	2¼	Nil	On gluten-free diet for 3 days before biopsy	Under investigation
4	J.B. (15)	1	1½	Starch-free diet, then gluten-free diet for 2 years from age 11. Repeated blood transfusions	No treatment for 2 years before biopsy	Under investigation
5	L.P. (4½)	3½	4½	Nil	No treatment	Good progress on gluten-free diet
6	A.R. (13½)	6 months	6	Gluten-free diet at intervals from age 8 onwards	No treatment for 4 months before biopsy	Under investigation
7	J.N. (2½)	1½	2½	Nil	On gluten-free diet for 12 days before biopsy	Under investigation
8	M.R. (7¾)	Not known	5½	Nil	No treatment before first biopsy Five weeks on gluten-free diet before second biopsy One year, five months on gluten-free diet before third biopsy Two years, one month on gluten-fee diet before fourth biopsy	Good progress on gluten-free diet

The coeliac children (Table I) comprised four boys and four girls. Their ages ranged from 2 years 3 months to 15 years. All were in hospital at the time of the present investigation and were in relapse, clinically or biochemically. Their heights and weights were below normal for their respective ages. Cases 2, 3, 5, 7, and 8 were previously undiagnosed and either had not received any treatment or had started a gluten-free diet for up to three weeks before biopsy (Table II). In Cases 1, 4, and 6 the diagnosis had been made at an earlier age. Case 1 had been on a gluten-free diet for four years, but had received a normal diet for the past four months. Faecal fat estimations showed a return of steatorrhoea. Case 4 had been treated with a starch-free diet and later a gluten-free diet but had been on a normal diet for the past four years. The present admission was necessitated by severe iron deficiency anaemia. Case 6 had been on a gluten-free diet at intervals for five years but had received a normal diet for four months before biopsy. He relapsed both clinically and biochemically with steatorrhoea and macrocytic anaemia. Case 8 was followed up for two years after beginning a gluten-free diet. While on this diet his height increased from 41¾ to 48¼ in. and his weight from 32 to 51 lb. Faecal fats fell from 26 to 4 g. per 24 hours.

The diagnosis of juvenile pernicious anaemia in one child was supported by vitamin B_{12} absorption studies. Idiopathic hypoproteinaemia was diagnosed in the other child by studies with labelled serum albumin.

The biopsy specimens obtained from each of these children were examined. They varied in number from one to 10 and included full-thickness mucosa, muscularis mucosae, and sometimes a small amount of submucosa. They were more or less fragmented. The shape of the villi, the surface epithelium with nuclei, the mucosal thickness, the number of glands of Lieberkühn, the appearances of the glandular cells, and the amount of inflammatory reaction were examined in detail. Treatment, if any, with a gluten-free diet was related to the time of biopsy (Table II).

Results

Normal Small Intestinal Mucosa.—This (Figs. 2a and 2b) was found in the two children with juvenile pernicious anaemia and idiopathic hypoproteinaemia. In appearance it was comparable to adult small intestinal mucosa (Doniach and Shiner, 1957; Shiner and Doniach, 1959). The villi were long, slender processes covered by regular, tall columnar epithelium containing basally situated, elongated nuclei. A faint basement membrane could be identified. The lamina propria contained relatively

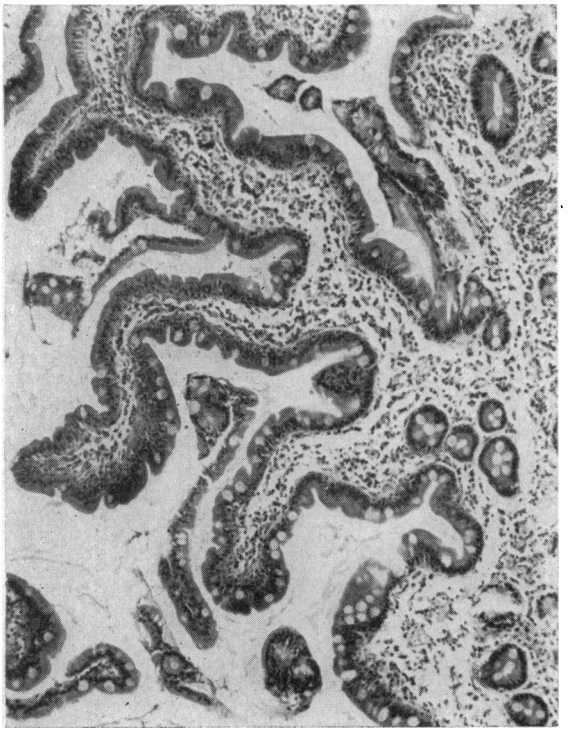

Fig. 2a.—*Biopsy of normal mucosa from patient with idiopathic hypoproteinaemia, showing villi and part of mucosa. Haematoxylin and eosin × 100.*

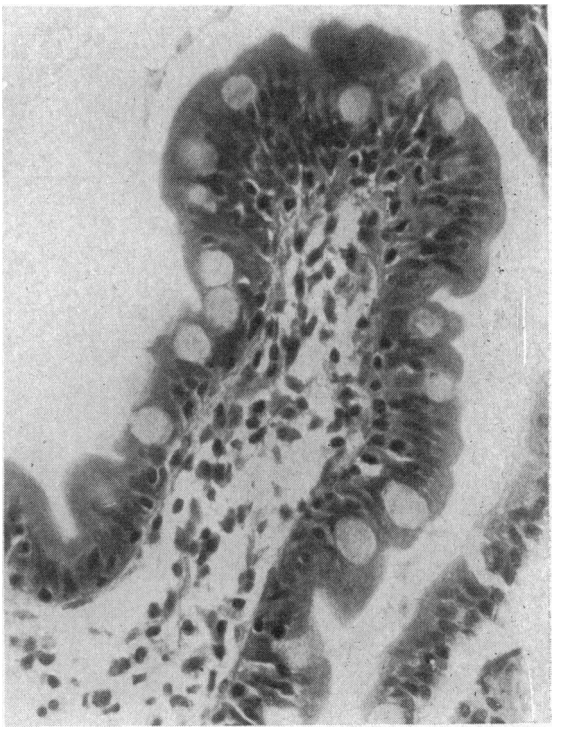

Fig. 2b.—*High-power view of villus from same biopsy. Haematoxylin and eosin × 370.*

TABLE III

HISTOLOGICAL FINDINGS IN EIGHT CASES OF COELIAC DISEASE

Histological Details	Case 1	Case 2	Case 3	Case 4	Case 5
Site of biopsy	Duodeno-jejunal junction	Low duodenal	Duodeno-jejunal junction	Jejunum	Jejunum
No. of specimens	3	3	4	5	8
Villi	Absent	Absent	Absent	Absent	Absent
Surface epithelium	Reduced in height	Not well preserved	Reduced in height	Reduced in height	Reduced in height
Nuclei of surface epithelium	Irregular	—	Irregular, large, pale	Irregular, large, pale	Irregular, large, pale
Mucosal thickness	Increased	Increased	Increased	Increased	Increased
No. of glands of Lieberkühn	More numerous	More numerous	More numerous	More numerous	More numerous
Glandular cells	Normal	Normal	Normal	Normal	Normal
Interstitial cell infiltration	Increased, chronic type	Not excessive	Not excessive	Increased, chronic type	Not excessive

Histological Details	Case 6	Case 7	Case 8			
			First Biopsy	Second Biopsy	Third Biopsy	Fourth Biopsy
Site of biopsy	Low duodenal	Jejunum	Duodenum	Duodenum	Duodenum	Duodenum
No. of specimens	1	6	4	10	4	3
Villi	Almost absent, few short and broad villi	Absent	Broad, flat, or absent	Short, broad, or slender	Short and more slender	Short and broad or slender
Surface epithelium	Reduced in height	Reduced in height	Reduced	Reduced	Reduced	Reduced in height
Nuclei of surface epithelium	Irregular	Irregular, large, pale	Irregular	Irregular	Irregular	Irregular
Mucosal thickness	Increased	Increased	Increased	Increased	Less increased	Less increased
No. of glands of Lieberkühn	More numerous	More numerous	More numerous	More numerous	Less numerous	Less numerous
Glandular cells	Normal	Normal	Normal	Normal	Normal	Normal
Interstitial cell infiltration	Not excessive	Some increase, chronic type	No excess	No excess	No excess	No excess

few glands of Lieberkühn and inflammatory cells were moderate in number, consisting mainly of lymphocytes and plasma cells. Mitosis was observed in the glandular cells but not in the villous cells. The ratio between lamina propria and villi was similar to that found in adults, the villi being about two-and-a-half times the height of the glandular layer.

THE MUCOSA IN COELIAC DISEASE.—Normal villi were not seen in any biopsy specimens from the eight children with coeliac disease (Table III). Surface appearances were either flat or showed occasional broad and short villi (Figs. 3a and 3b). The surface epithelium stained poorly, the cells were reduced to low columnar or cuboidal epithelium with their nuclei arranged in a disorderly pattern within the cells. Many of these nuclei, instead of being elongated and darkly staining, were pale and large. The basement membrane appeared interrupted in places or could not be seen at all. The mucosal thickness was invariably increased and the glands of Lieberkühn appeared more numerous than normal. An increase in inflammatory cells was noted in only three biopsies.

The first, pre-treatment biopsy, of Case 8 showed broad, flat villi with abnormal surface epithelium (Figs. 4a and b). The mucosal thickness was increased and the glands of Lieberkühn appeared more numerous than normal. The first repeat biopsy (Fig. 5) five weeks after the beginning of a gluten-free diet showed a similar picture but a few more slender though short villi could be identified. The surface cells showed no improvement. Three of the four specimens obtained at the second repeat biopsy 17 months later (Figs. 6a and b), while the child was still on a gluten-free diet, showed more attempts at villous formation. Though the villi still appeared rather short they were more slender and the normal indentations at the sides of these villi were noted. More crypts opening into the surface were seen. Though the surface epithelium showed little improvement at the tips and sides of the villi, it appeared more normal at the base of the budding villi and in the crypts. The third repeat biopsy showed a similar picture to the previous one. A few short but slender villi (Fig. 7a) were again noted but broad and short villi or a completely flat surface were also present (Fig. 7b). No further change in the surface epithelium was seen. The mucosal thickness was much increased in the region of overlying broad villi but it was less thick in the region of more normal villi. The glands of Lieberkühn appeared slightly less numerous.

DISCUSSION

From the study of the small intestinal mucosa in adults in a wide variety of diseases affecting the alimentary tract it was observed that mucosal

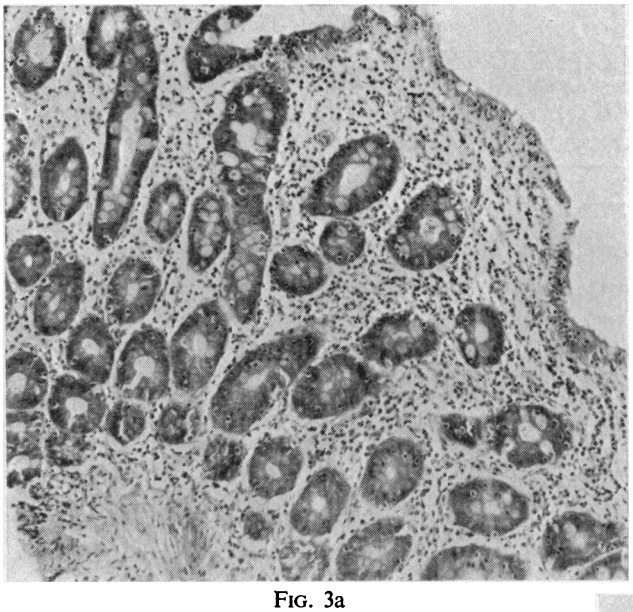

FIG. 3a

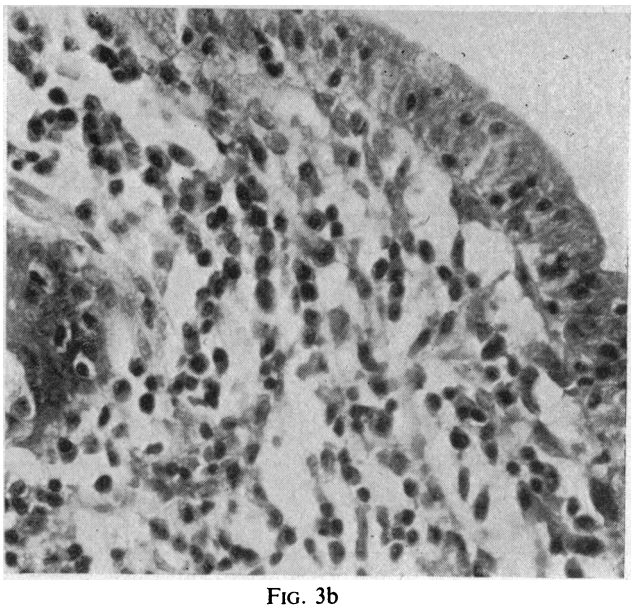

FIG. 3b

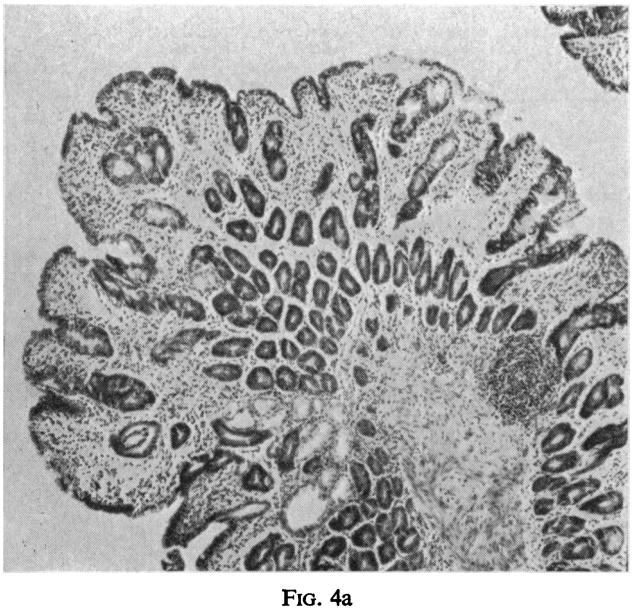

FIG. 4a

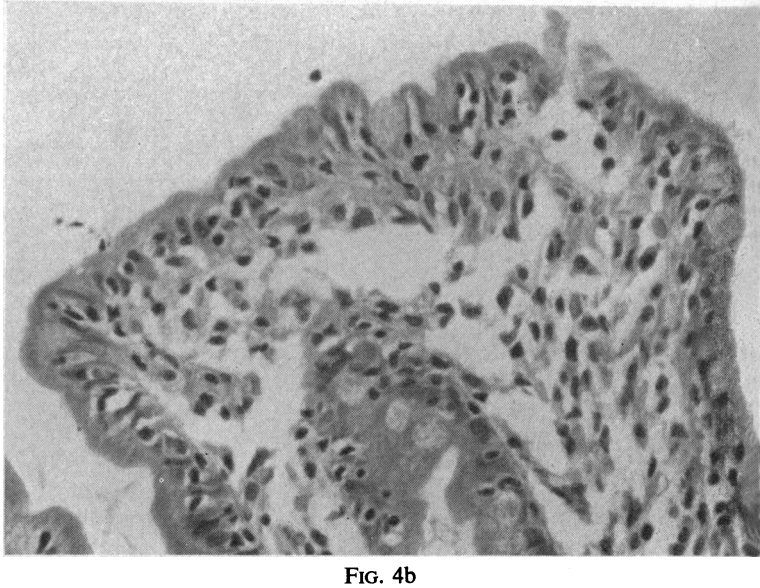

FIG. 4b

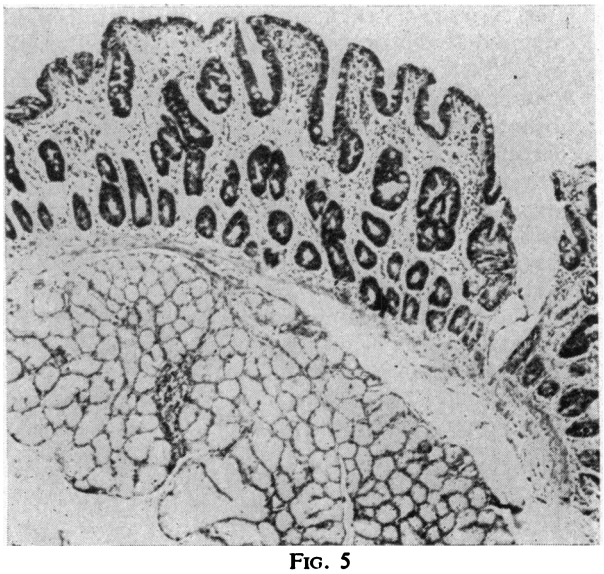

FIG. 5

FIG. 3a.—*Biopsy from coeliac patient P.K. aged 2 years 3 months, showing complete absence of villi. Haematoxylin and eosin × 100.*

FIG. 3b.—*High-power view of surface epithelium from same biopsy. Haematoxylin and eosin × 370.*

FIG. 4a.—*Original, pre-treatment biopsy from patient M.R. Haematoxylin and eosin × 50.*

FIG. 4b.—*High-power view of short villus from same biopsy. Haematoxylin and eosin × 370.*

FIG. 5.—*Repeat biopsy from same patient after five weeks on gluten-free diet. Haematoxylin and eosin × 50.*

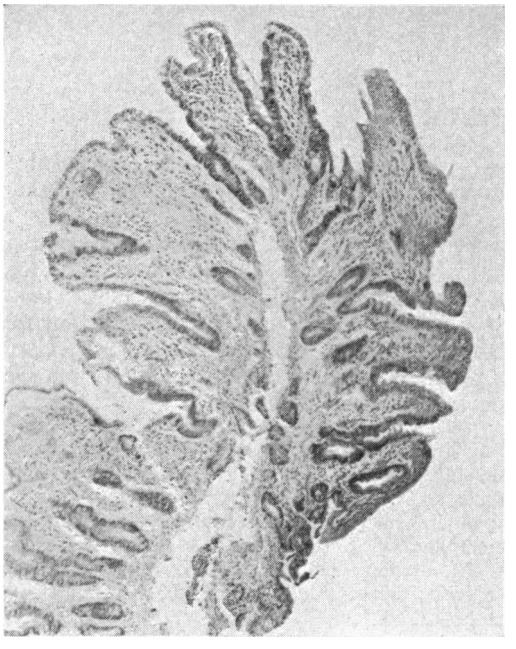

FIG. 6a

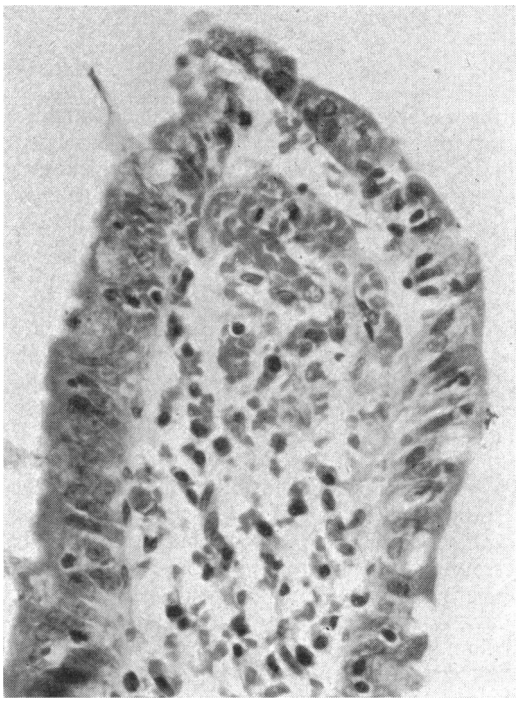

FIG. 6b

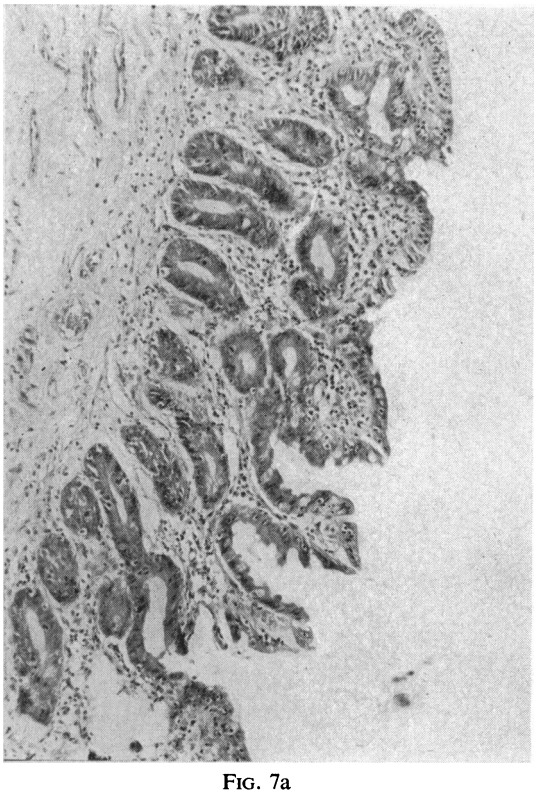

FIG. 7a

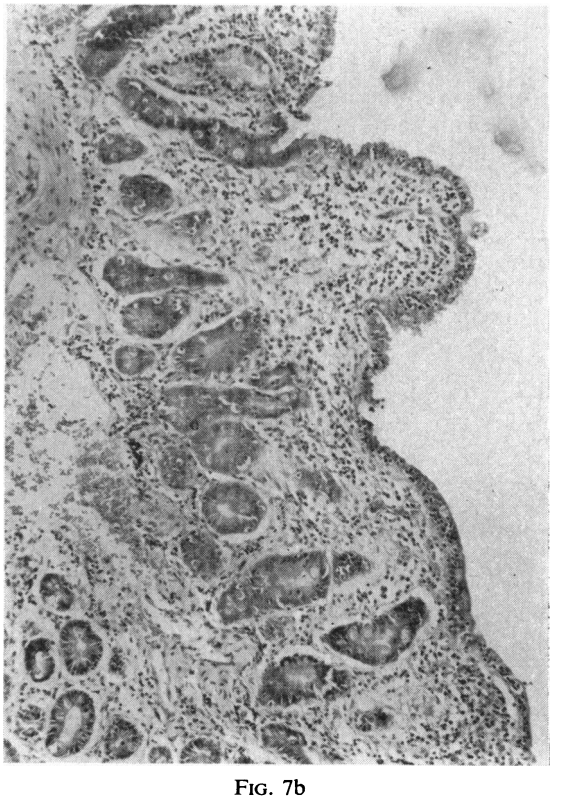

FIG. 7b

FIG. 6a.—*Repeat biopsy from same patient after 17 months on gluten-free diet. Haematoxylin and eosin × 50.*

FIG. 6b.—*High-power view of villus from same biopsy. Haematoxylin and eosin × 370.*

FIG. 7a.—*Repeat biopsy from same patient on gluten-free diet 25 months later. Haematoxylin and eosin × 100.*

FIG. 7b.—*Different area of same specimen as in Fig. 7a. Haematoxylin and eosin × 100.*

abnormalities were mainly confined to the idiopathic steatorrhoea group. These abnormalities consisted of villous atrophy, increase in mucosal thickness, and hypertrophy of the glands of Lieberkühn (Shiner and Doniach, 1959), and were possibly due to a defect in cell metabolism at the level of the gland cells which normally give rise to villous cells. Of the 34 adults with idiopathic steatorrhoea investigated, there were five patients in whom a definite history of coeliac disease in childhood was obtained. Histologically the mucosal abnormalities in the patients with or without a history of coeliac disease were identical.

In this report it has been shown that in all eight coeliac patients investigated mucosal abnormalities were found. These abnormalities were the same as in adult idiopathic steatorrhoea, but were possibly more severe. In the youngest coeliac child in this group, aged 2 years 3 months with symptoms for one year, no villi at all were found and the surface epithelium appeared grossly abnormal.

Considering the effect on the small intestinal mucosa of treatment with a gluten-free diet, no difference was found histologically between Cases 1, 4, and 6 previously treated and those almost untreated. In Case 8, repeat biopsies after a gluten-free diet showed that his rapid clinical and biochemical improvement did not correspond with any appreciable histological improvement. Although the overall impression in this patient was that of minor attempts at villous formation following treatment, this would be difficult to judge because of the slight variations normally observed from specimen to specimen obtained at a single biopsy.

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REFERENCES

Doniach, I., and Shiner, M. (1957). *Gastroenterology*, 33, 71.
Gee, S. (1888). *St Bart's Hosp. Rep.*, 24, 17.
Sakula, J., and Shiner, M. (1957). *Lancet*, 2, 876.
Shiner, M. (1956). *Ibid.*, 1, 17, 85.
——, and Doniach, I. (1959). Proceedings of the World Congress of Gastroenterology, Washington, D.C., 1958, p. 586.