Archives of Disease in Childhood, 1973, **48**, 692.

Cystic fibrosis and coeliac disease

Report of two cases

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Taylor, B., and Sokol, G. (1973). *Archives of Disease in Childhood*, **48**, 692.
Cystic fibrosis and coeliac disease: report of two cases. Two cases of coeliac disease occurring in children with cystic fibrosis are presented. Both cases had low disaccharidase levels in intestinal biopsies even after 1 year on a gluten-free diet.

Neither coeliac disease nor cystic fibrosis (CF) are common diseases. The incidence of CF is slightly under 1:2000 live births (Honeyman and Siker, 1965; Hall and Simpkiss, 1968). The incidence of coeliac disease seems to vary from place to place, even within the British Isles. Black (1964) found an incidence of 1:1778 in Glasgow, McCrae (1970) found 1:1850 in the general population of Edinburgh, and Carter, Sheldon, and Walker (1959) reported 1:3000 in the London area. The condition is more common within families; McCrae found an incidence of 1:465, and Mylotte *et al.* (1973), by biopsying asymptomatic relatives, found an incidence in Galway, Eire, of 1:448.

Taking the incidences at 1:2000 and 1:1000, the chances of the 2 conditions occurring together would be 1:2,000,000.

Hide and Burman (1969) described an infant with both CF and coeliac disease. We present 2 similar cases, from a CF clinic of 175 children, with histological appearance and disaccharidase levels in intestinal biopsies before and after treatment with a gluten-free diet.

Case reports

Case 1. A male child was born, weighing 3·60 kg after a normal term pregnancy, to an unmarried half-Negro mother. On the second day of life he became distended, vomiting bile-stained material. An operation for meconium ileus was performed. 45 cm of grossly dilated midileum were resected; he was left with an ileostomy. A sweat sodium of 92 mEq/l. confirmed the presumptive diagnosis of CF.

At home on pancreatic supplements, vitamins, and cloxacillin, first with his mother, then with foster parents, he failed to gain weight and had recurrent chest infections. When next seen at this hospital aged 11 months, he weighed only 6·4 kg (A, Fig. 1). His stools were noted to be extremely loose but no sugar was demonstrated in them. After treatment of his chest condition the ileostomy was closed. Over the next year he failed to thrive. His foster parents at outpatient visits always gave a history of very loose, foul smelling, bulky stools, 4 to 8 per day. His abdomen was always distended. Progressive wasting and failure to thrive (7·5 kg at 3 years) led to further investigation. Serum

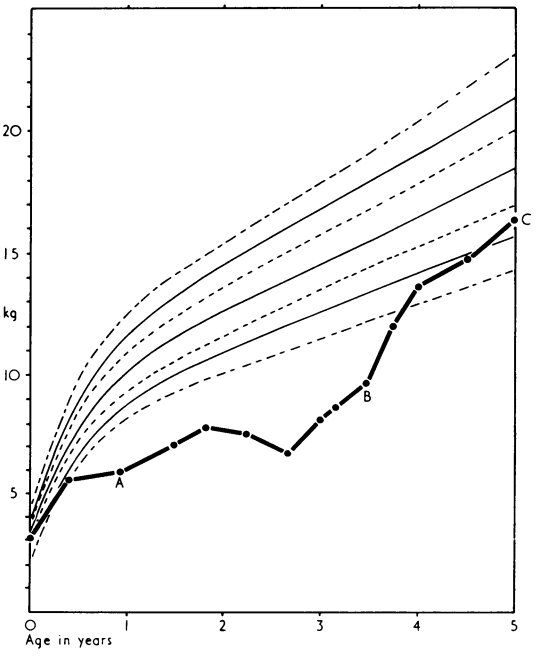


FIG. 1.—*Case 1. Weight chart (Tanner, Whitehouse, and Takaishi, 1966). Gluten-free diet begun at point B.*

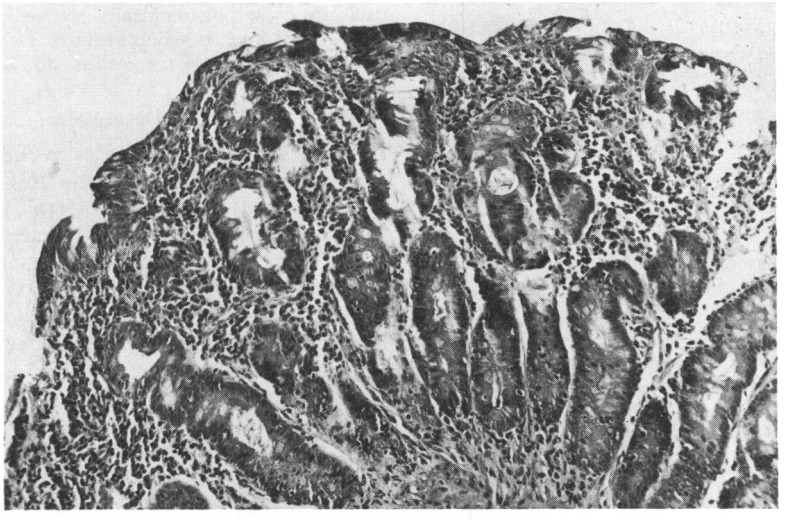
Received 26 February 1973.

folate was low at 4·4 μg/ml (normal 5·9–21 μg/ml). Peroral duodenal biopsy revealed a cobblestone appearance of the mucosa with subtotal villous atrophy (Fig. 2a). Disaccharidase activities are shown in the Table.

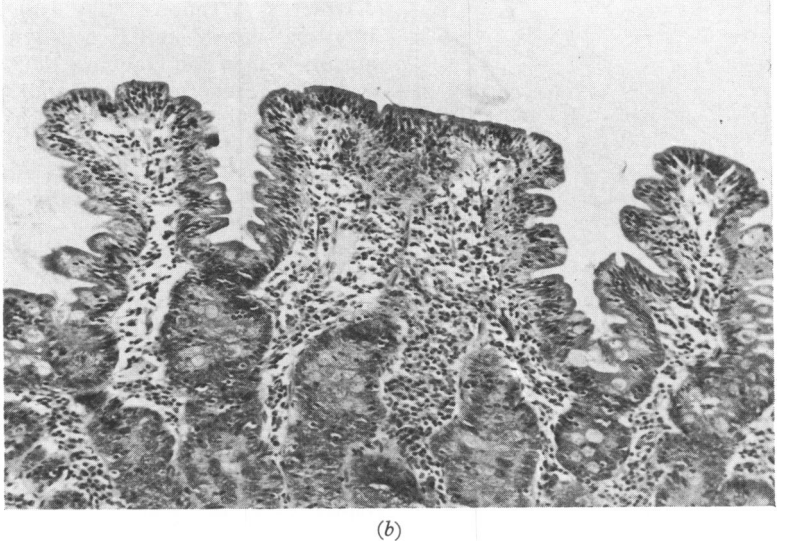
He was started on a gluten-free diet (B, Fig. 1). His stools became normal in number and consistency. He became happier and rapidly gained weight and height. At age 5 years (C, Fig. 1) his weight was 16·5 kg and height 101 cm.

After 1 year on a gluten-free and low disaccharide diet a repeat duodenal biopsy was performed. The appearance of the mucosa was improved though there was still some inflammatory cell infiltration (Fig. 2b). This improvement on a gluten-free diet, both clinically and on biopsy, was consistent with the diagnosis of coeliac disease.

At present, because of persistent chest infections, he is not at all well, though his twice-daily bowel motions remain of normal consistency.



(*a*)



(*b*)

FIG. 2.—*Case 1.* (*a*) *First biopsy, showing absent villous pattern, cuboidal epithelium at surface, increased cellularity of lamina propria.* (*b*) *Second biopsy, showing villous pattern has returned. Villi are covered by columnar epithelial cells. The villous cores are less cellular than previously.* (*H.E.* ×*106.*)

TABLE

Disaccharidase levels in duodenal biopsies

Cases	Lactase	Sucrase	Maltase
Case 1			
Before gluten-free diet	0·15	0·54	5·8
After 1 yr on gluten-free diet	0·2	1·3	4·9
Case 2			
Before gluten-free diet	0·1	0·4	
After 9 mth on gluten-free diet	0·9	2·8	
Normal values	>2·5	>3·0	>10·0

Note: All values in units/μg wet weight of mucosa.

Case 2. A male child was born at home weighing 3·35 kg after a term pregnancy. A posterior cleft palate was diagnosed at 2 days. Despite spoon feeding he failed to thrive, passing offensive, loose, greasy stools. Sweat sodium at age 6 weeks was 120 mEq/l. and he was started on pancreatic enzymes.

He progressed reasonably until the age of 1 year, when he weighed 8·6 kg. He then lost his appetite and began to lose weight. He was first admitted to this hospital with a respiratory infection at 16 months. He was miserable and wasted, with a very large abdomen. His height was on the 3rd centile, though his weight was below that (A, Fig. 3).

Despite repair of his palate and only passing one normal stool per day, he grew slowly and his appetite was variable. Serum folate at age 22 months was low at 3·8 μg/ml. Appetite and behaviour deterioration and progressive weight loss led to duodenal biopsy at age 40 months. This showed subtotal villous atrophy (Fig. 4a). No tryptic activity was shown in the duodenal juice. Disaccharidase activities are shown in the Table.

He was started on a gluten-free diet (B, Fig. 3). Within a week his mood became friendly and outgoing, and his abdominal distension receded. His appetite improved and he thrived. Repeat duodenal biopsy at 49 months was histologically normal (Fig. 4b). Disaccharidase levels had improved. At present he is above the 75th centile for weight and the 25th for height (C, Fig. 3).

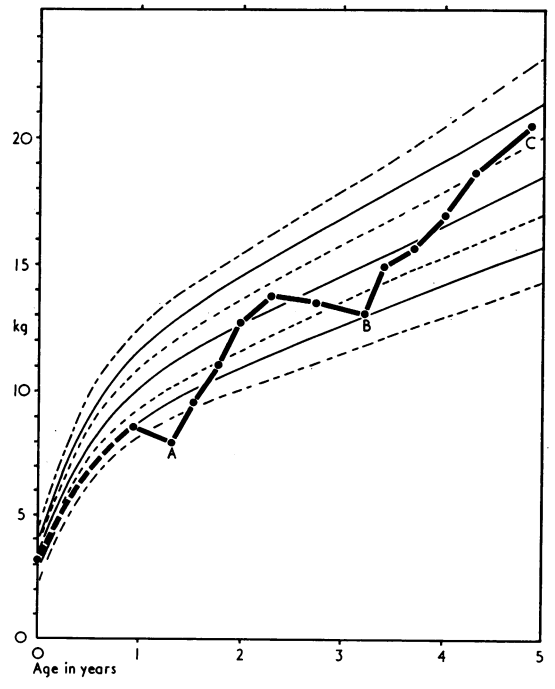


FIG. 3.—*Case 2. Weight chart. Gluten-free diet was started at point B.*

Discussion

The two main theories as to the pathogenesis of coeliac disease involve (1) the immunological status of patients affected, and (2) a postulated 'toxic' action of gluten on small intestinal mucosa associated with a congenital absence of a peptidase concerned in gluten digestion (Frazer, 1956).

Gluten intolerance might be more likely with abnormal pancreatic exocrine function. Intestinal wall enzymes may be deficient as well in cystic fibrosis.

Antonowicz *et al.* (1968) reported 7 out of 28 CF patients with 'primary' lactase deficiency. These 7 had levels in intestinal biopsy about 10% of normal. Maltase, sucrase, and palatinase levels and histological appearance were normal in all children studied. They postulated a primary genetic disorder as a cause of this association with CF. Intestinal biopsy in CF usually shows a normal mucosa (Rubin and Dobbins, 1965), though Nordio *et al.* (1966) reported a child with CF whose bowel symptoms worsened from 5 months of age; mucosal biopsy was 'rather flattened'. Lactase, maltase, and sucrase levels were all low. Another child with a normal biopsy microscopically had a low lactase and a diminished sucrase.

In coeliac disease disaccharidase levels, usually low with a flattened mucosa, return in most cases to normal or even high levels of enzyme activities after the institution of a gluten-free diet, often before the normal cell structure has been regained (Riecken, 1970).

Though we have not reinstituted a gluten-containing diet and looked for relapse, it is most likely these patients do have coeliac disease rather than some other cause of a flattened mucosa, such as transient mucosal damage after a bowel infection. This latter condition is usually accompanied by overt sugar intolerance (Burke, Kerry, and Anderson, 1965) and responds to the removal of disaccharide from the diet.

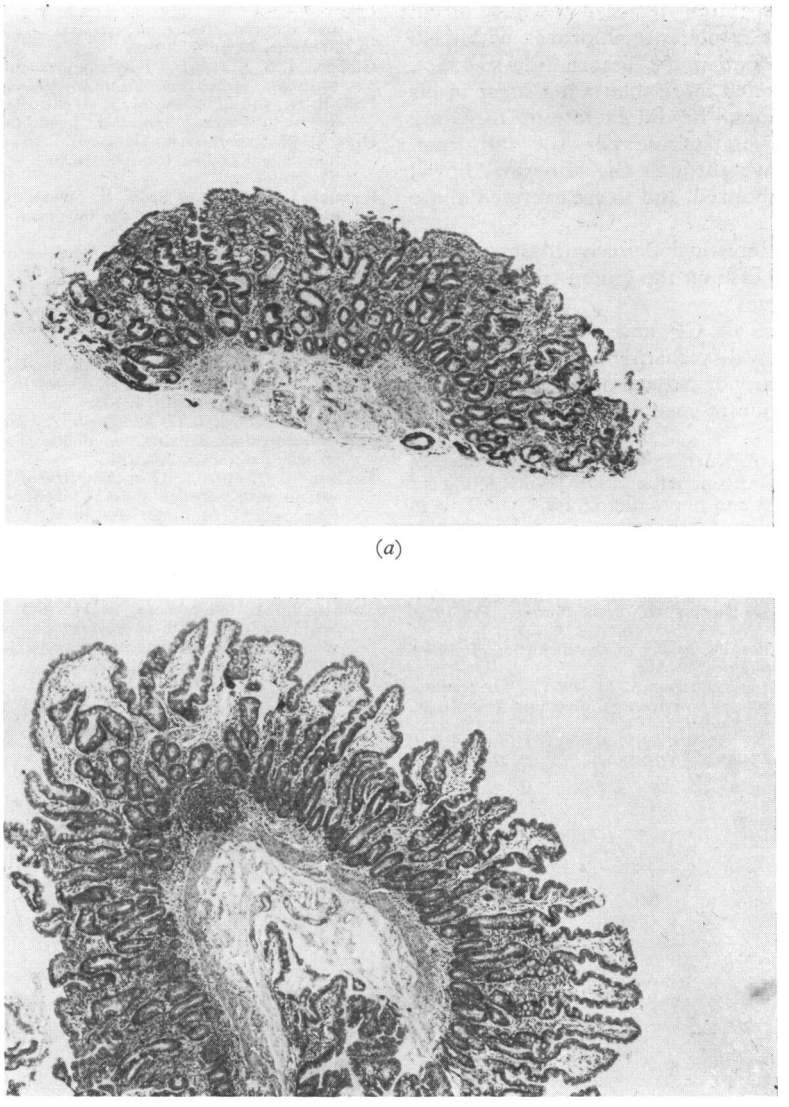


FIG. 4.—*Case 2. (a) First biopsy, showing loss of normal villous pattern, flattened surface epithelium, and marked cellularity of lamina propria. (b) Second biopsy, showing normal villous pattern, surface epithelium is columnar, and there is no increased cellularity. (H.E. × 21.)*

Sugar intolerance (an untoward reaction in bowel habit after disaccharide ingestion) is rare in both CF (Gibbons, 1969) and coeliac disease (McNeish and Sweet, 1968), though disaccharidase deficiency is apparently not uncommon in either condition on analysis of intestinal mucosa.

Case 1, before treatment with a gluten-free diet, had evidence of disaccharide intolerance. After 25 g lactose he developed abdominal cramps and passed, in 6¼ hours, a stool containing (mg/100 g) lactose >500, galactose >400, and glucose >200. (Normal stool transit time in this patient was 14–22 hours.) His urine after this load contained lactose 60 mg/100 ml. A sucrose load led to sucrosuria (400 mg/100 ml), but no bowel upset. However, he did not improve on a trial of disaccharide-free

feeding before the gluten-free diet was introduced. True disaccharide intolerance improves within 48 hours of the introduction of a disaccharide-free diet. Case 2 never excreted more than 5 mg sugar in his stool (normal), though he did excrete up to 90 mg lactose and 100 mg sucrose per 100 ml urine. Disaccharides move through the abnormal bowel wall, are not metabolized, and so are excreted in the urine.

The values of intestinal disaccharidases (Table) improved in each case on the gluten-free diets, but not to normal values.

The coexistence of CF and coeliac disease in association with low disaccharidase levels lends some support to the theory of enzyme deficiency playing a part in the causation of coeliac disease.

We thank Dr. A. P. Norman for advice and assistance in the preparation of this paper, and Dr. Jean Keeling for the histology reports and photomicrographs. B.T. is in receipt of a Cystic Fibrosis Research Trust Fellowship.

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