Archives of Disease in Childhood, 1970, **45**, 523.

Transient Gluten Intolerance

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Walker-Smith, J. (1970). *Archives of Disease in Childhood*, **45**, 523. **Transient gluten intolerance.** An infant presented with hypoproteinaemic oedema two months after an episode of salmonella enteritis. His oedema subsided spontaneously, but he failed to thrive and small bowel biopsy revealed partial villous atrophy of a severe degree. He was started on a gluten-free diet with a dramatic clinical response and this diet was continued for one year. He was then reinvestigated and small intestinal biopsy was then normal. He was then given a normal diet and a third biopsy performed 16 months later showed that the mucosa was still normal.

It is suggested that a transient intolerance to gluten occurred in this patient as a sequel to enteritis, and that a clinical response to a gluten-free diet is not necessarily diagnostic of coeliac disease.

It is now apparent that children with coeliac disease have a permanent intolerance to gluten, though the clinical manifestations of this may vary widely (Mortimer *et al.*, 1968; Shmerling, 1968; Sheldon, 1969). Transient gluten intolerance has been described in adults by Frazer (1968) and in children by Dicke (1952) and Visakorpi and Immonen (1967). These reports were based on clinical and biochemical assessment, and they were not supported by serial biopsy studies. It is important to distinguish such patients from those with coeliac disease. Children with coeliac disease will require a gluten-free diet for life, whereas children with transient gluten intolerance will need such dietary restriction for a briefer period. The purpose of this paper is to present the clinical findings in a child who appeared to have transient gluten intolerance, to describe the serial biopsies of the small intestine, and to discuss the differentiation of this syndrome from coeliac disease.

Case History

The patient, a male, was born at full term after a normal delivery, weighing 2·9 kg. He progressed satisfactorily till the age of 1 year 3 months, when he developed acute gastro-enteritis. Salmonella was cultured from his stools on 3 occasions. He was treated without antibiotics. Though the diarrhoea diminished after 3 days, loose stools persisted for 4 weeks. Thereafter, the child was listless and anorexic. At the age of 1 year 5 months he developed generalized oedema, and was referred to hospital with the provisional diagnosis of the nephrotic syndrome. On examination, he had periorbital oedema, pitting oedema of his legs, hands and prepuce, but urine contained only a trace of protein.

Serum protein 3·8 g./100 ml.; albumin 1·6 g./100 ml., and cholesterol 60 mg./100 ml.; Hb 14·8 g./100 ml.; blood urea 21 mg./100 ml.; stool culture for pathogens was repeatedly negative.

The child was given a high protein diet. His oedema gradually disappeared over 3 weeks, with loss of weight (10 kg. to 8·7 kg.) and rise in serum albumin (1·6 to 2·9 g./100 ml.). One month after admission he had a return of diarrhoea which became severe, leading to dehydration, and he needed intravenous feeding for 3 days. On rehydration his serum albumin level was 2·1 g./100 ml. and weight 8·5 kg. The reintroduction of full strength cow's milk to his diet over 4 days was accompanied by a slight fall in weight to 8·4 kg. He was then given a normal toddler's diet which included gluten-containing foods such as bread and porridge, but over a 2-week period, his weight gain was minimal (8·4 to 8·7 kg.) (Fig. 1) and he was anorexic, miserable, and irritable, but his serum albumin rose from 2·1 to 3·3 g./100 ml.

Further investigations at this time showed daily faecal fat 2·4 g./day (3-day collection); prothrombin index 74% rising to 100% after 1 mg. vitamin K_1 intramuscularly; maximal rise 22 mg./100 ml. in blood glucose after oral glucose (2·2 g./kg.) and 19 mg./100 ml. after lactose (2·2 g./kg.). There was no diarrhoea after the oral load of lactose and there were no reducing substances in the stools. Xylose excretion was abnormal (0·4 g. excreted

Received 5 February 1970.

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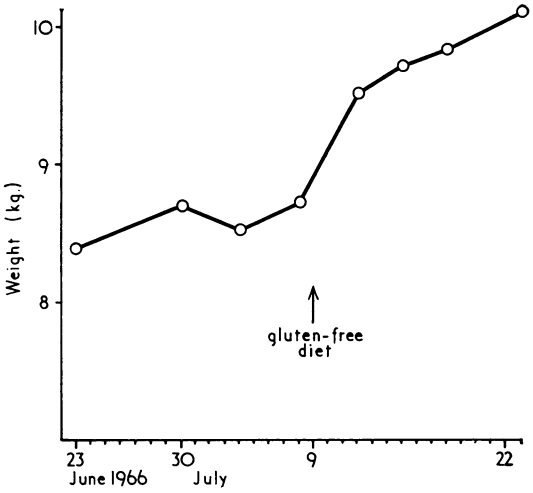

FIG. 1.—*Weight gain before and after gluten-free diet.*

in urine 5 hours after 5 g. dose). Serum calcium 9·4 mg./100 ml., phosphorus 5·3 mg./100 ml.

Jejunal biopsy showed a mucosa characterized by short thick ridges (Fig. 2), with partial villous atrophy of a severe degree (Fig. 3). Though the mucosa was not completely flat as is usual in coeliac disease, in view of the evidence of small bowel disease in this child a provisional diagnosis of coeliac disease was made. He was started on a gluten-free diet, appropriate for a toddler. There was a dramatic change (Fig. 4). Over the next few days his appetite increased and he became

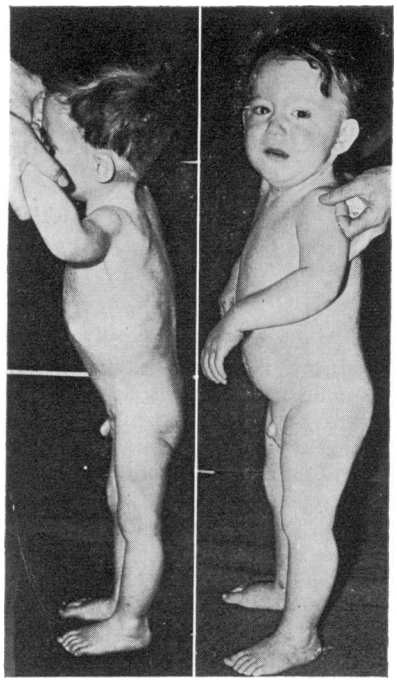

FIG. 4.—(*a*) *Appearance at time of biopsy.* (*b*) *Appearance 5 weeks later.*

livelier and less irritable and in 13 days he gained 1·4 kg. in weight (Fig. 1), and after 5½ weeks a total of 2·8 kg., while his serum albumin rose a further 1·3 g./100 ml.

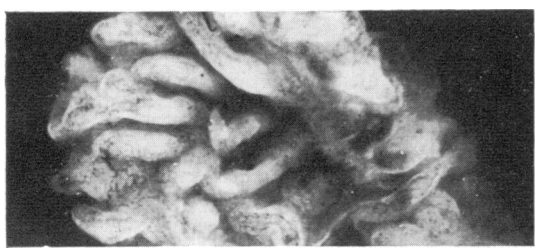

FIG. 2.—*Dissecting microscope appearance of jejunal biopsy, characterized by short thick ridges.* (×17.)

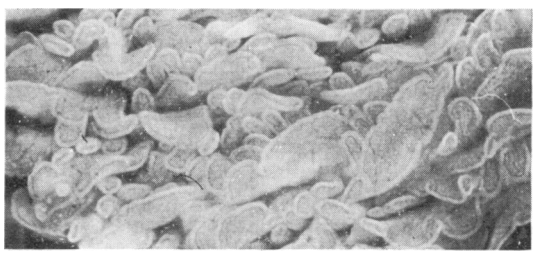

FIG. 5.—*Dissecting microscope appearance of jejunal biopsy, characterized by tongues, leaves and fingers.* (×17.)

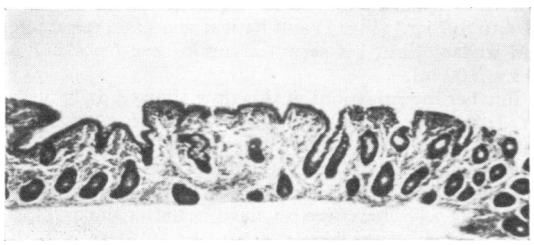

FIG. 3.—*Partial villous atrophy of severe degree.* (×4.)

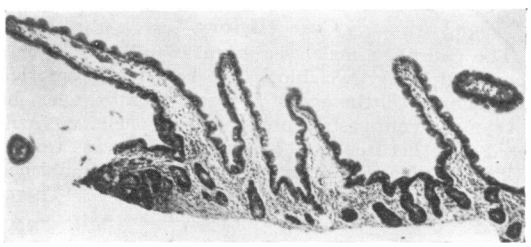

FIG. 6.—*Normal mucosa.* (×4.)

FIG. 7.—*Dissecting microscope appearance of jejunal biopsy, characterized by leaves and fingers.* (×17.)

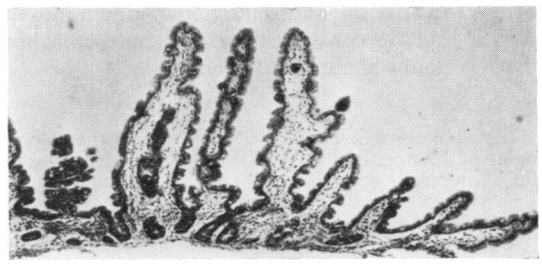

FIG. 8.—*Normal mucosa.* (×4.)

His weight at the start of the gluten-free diet was well below the 10th centile (8·7 kg.), but after 5 months it was on the 50th centile (13·2 kg.). The gluten-free diet was continued for one year and he was then reinvestigated, because of the unusual features of the original illness (absence of steatorrhoea, and absence of completely flat jejunal mucosa).

The results were as follows: total serum protein 7·2 g./100 ml., albumin 4·5 g./100 ml.; prothrombin index 100%; Hb 13·3 g./100 ml. Jejunal biopsy showed a mucosa characterized by tongues, leaves, and fingers (Fig. 5), which histologically was normal (Fig. 6). A normal gluten-containing diet was then begun.

He was investigated again 16 months later at the age of 4 years 11 months. His weight and height had remained on the 50th centile and he was symptom free. Jejunal biopsy at that time showed leaf and finger-like villi (Fig. 7) and was normal histologically (Fig. 8).

Discussion

This child had partial villous atrophy of a severe degree with significant hypoalbuminaemia, initially associated with oedema. Though a radio-isotope study was not performed, it is probable that the hypoproteinaemia was due to enteric protein loss. Such alimentary protein loss has been documented in an adult with salmonella enteritis (Jeffries, Holman, and Sleisenger, 1962) and in children with coeliac disease (Rotem and Czerniak, 1964).

The introduction of a gluten-free diet was followed by a striking clinical improvement with a rapid gain in weight and improvement in emotional state. While it is possible that this clinical response was fortuitous and the child was recovering of his own accord, it is difficult not to accept that the sudden rapidity of weight gain, improvement in appetite, and psychological state were not sequelae to the withdrawal of gluten from the child's diet.

Though there was this clinical response to a gluten-free diet and the child had an abnormal small intestinal mucosa, the fact that he did not have coeliac disease was shown by the observation that though the mucosa was normal after one year's gluten-free diet, there was no histological deterioration after 16 months on a normal gluten-containing diet. Such a deterioration has been shown by McNeish (1968), and Shmerling (1968) found it to be an invariable sequel to the reintroduction of gluten into the diet of 10 coeliac children.

The enteropathy in this patient chronologically followed salmonella enteritis, but no pathogens could be isolated at the time the child had hypoproteinaemic oedema. Infective gastro-enteritis is known to cause severe, but reversible mucosal damage (Burke, Kerry, and Anderson, 1965). Salmonella enteritis probably produced the mucosal damage observed in this child, and this may account for the transient gluten intolerance by causing a transient depression of dipeptidase activity, in an analogous manner to the transient depression of disaccharidase activity which may occur as a sequel to gastro-enteritis.

Dicke (1952) described a transient wheat sensitivity in pre-school children after severe enteritis. Grüttner (1961) described what he called an abortive form of coeliac disease in children who had a transient intolerance to gluten, and Visakorpi and Immonen (1967) also described transient gluten intolerance in 28 children based chiefly on clinical observations. The diagnosis of transient gluten intolerance in this patient is more broadly based. It rests first on the clinical evidence of small intestinal disease (viz. hypoproteinaemic oedema in the absence of proteinuria or any evidence of liver disease), diarrhoea, and abnormal xylose absorption; secondly, on the presence of a severe abnormality of the jejunal mucosa; thirdly, on a dramatic clinical improvement after the introduction of a gluten-free diet; and, fourthly, on no histological relapse after gluten reintroduction into the diet.

The experience with this patient illustrates the importance of reinvestigating children diagnosed as coeliac disease where there are some unusual features. As it now appears that patients with coeliac disease should continue a gluten-free diet for life, reinvestigation with small intestinal biopsy

before and after the reintroduction of gluten into the diet should be considered in any child in whom there is doubt about the diagnosis.

My thanks are due to Mr. C. H. Noble of the Department of Photography of the Royal Alexandra Hospital for Children.

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Addendum

Since acceptance of this paper for publication, another child with transient gluten intolerance, who has had serial biopsies, has been seen.

P.G. aged 3½ years presented with diarrhoea for 6 months and loss of weight for 3 months. Jejunal biopsy showed a flat mucosa. He responded to a gluten-free diet. He remained well thereafter, and repeat biopsy at the age of 7 years showed a normal mucosa. He was restarted on a normal diet and 6 months later a third biopsy was normal.