Coeliac Disease

Reappraisal of Clinical Diagnosis

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Cook, D. M., Evans, N., Lloyd, A., and Stewart, J. S. (1971). *Archives of Disease in Childhood*, **46**, 705. **Coeliac disease: reappraisal of clinical diagnosis.** Twelve children previously diagnosed as having coeliac disease on criteria now regarded as incomplete have been reinvestigated. Six were found to have an intestinal mucosal lesion characteristic of coeliac disease. All but one had been asymptomatic on a normal diet for more than 18 months. Response to diet fails to distinguish between coeliacs and non-coeliacs. Establishing the diagnosis of coeliac disease by intestinal biopsy is essential, since even apparently symptomless individuals are at considerable risk.

It is now evident from follow-up studies of childhood coeliac disease that the mucosal abnormality persists if gluten remains in the diet and that relapse is common in early adult life (Mortimer *et al.*, 1968). This paper presents the results of reinvestigating a group of children previously suspected of having coeliac disease.

Material and Methods

Twelve children at the West Middlesex and Ashford Hospitals, diagnosed between 1959 and 1969 as having coeliac disease, were studied haematologically, radiologically, and by intestinal biopsy. The original diagnosis had been made on clinical grounds in most instances, though fat excretion had been investigated in some patients. Intestinal biopsies had not been performed. All the children had been treated with gluten restriction for at least 6 months. At the time of the present study they had all been on normal diets for over a year with the exception of one (Case 6) who had had a normal diet for only one month.

Haematological methods were those of Dacie and Lewis (1970). Serum folate concentrations were measured by the method of Waters and Mollin (1961). The unequivocally normal range is from 6 to 21 ng/ml; patients with megaloblastic anaemia due to folate deficiency have levels of less than 3 ng/ml. Red cell folate concentrations were obtained by the method of Hoffbrand, Newcombe, and Mollin (1966). The range in control subjects is from 160 to 640 ng/ml packed red cells.

Barium meals were interpreted using the criteria of Haworth *et al.* (1967; 1968) which these authors

modified for use in children from the methods described for adults by Laws *et al.* (1963).

Mucosal biopsies of the proximal small bowel were performed with a Crosby intestinal biopsy capsule (Crosby and Kugler, 1957) modified for use in children and guided through the pylorus with the help of an outer cuff which simplified and shortened the procedure (Evans *et al.*, 1970). All specimens were first examined using a dissecting microscope (Holmes, Hourihane, and Booth, 1961) and subsequently studied histologically (Stewart *et al.*, 1967). The measurements of epithelial surface cell height were made by one of us without knowledge of the clinical history. The normal range of proximal surface cell height is from 29.3 μ to 36.8 μ .

The diagnosis of coeliac disease was considered confirmed if a flat, flat with mosaic, or convoluted proximal intestinal mucosa was found, which showed reduced surface cell height histologically.

Results

The Table summarizes the results. Only 6 of the 12 patients were found to have coeliac disease.

Clinical features. Symptoms had begun before the end of the second year of life in all but 2 of the coeliac children. These 2 (Cases 4 and 6) presented in their third year. Weight loss and diarrhoea were the most common presenting features, and were more marked in the children subsequently shown to have coeliac disease. With the exception of one child (Case 2) all had a good initial response to gluten withdrawal. Subsequently a normal diet had been introduced without

TABLE
Results

Case No.	Sex	Age at Biopsy (yr)	Age at Clinical Diagnosis (yr)	Duration of Normal Diet Before Biopsy (mth)	Weight Centile	Height Centile	Hb (g/100 ml)	Folate		Biopsy		Final Diagnosis
								Red Cell (ng/ml)	Serum (ng/ml)	Dissecting Microscope Appearance	Surface Cell Height (μ)	
1	F	4	1	18	55	50	10.2	126	4.2	Flat	15.9	Coeliac
2	F	12	1	108	50	<3	11.6	535	7.6	Flat	19.0	Coeliac
3	F	4	1	18	60	30	12.2	178	4.8	Flat with mosaic	19.3	Coeliac
4	F	10	2½	21	10	15	10.8	—	2.0	Flat	21.8	Coeliac
5	M	6	1	24	50	55	11.0	139	2.0	Flat	22.4	Coeliac
6	M	10	3	1	75	35	13.1	362	14.9	Convulsed	26.1	Coeliac
7	M	7	2	9	50	40	11.8	290	10.6	Normal	31.2	Normal
8	F	4	1	24	60	65	12.2	769	7.2	Normal	32.3	Normal
9	M	9	1½	12	25	40	12.0	434	8.6	Normal	34.5	Normal
10	F	11	1½	16	20	25	12.0	241	14.0	Normal	34.6	Normal
11	M	4	2½	18	10	50	10.8	664	12.8	Normal	36.0	Normal
12	F	6	1	14	10	8	11.4	172	7.4	Normal	36.4	Normal

clinical relapse in 11 of the 12 cases, only one (Case 6) having been unable to tolerate gluten.

Physical examination showed no significant abnormalities and measurements of height and weight were not found helpful in separating the coeliac children from those with normal intestinal mucosa.

Haematological and radiological investigations. 2 of the 6 patients with coeliac disease (Cases 1 and 4) had a low Hb (> 11 g/100 ml), though only one of these (Case 1) showed hypochromia.

The red cell folate and the serum folate were normal in all 6 non-coeliac patients. The red cell folate was also normal in 2 of the patients with coeliac disease. One of these (Case 2) has been previously reported (Cook *et al.*, 1970). The other (Case 6) had been on a gluten-containing diet for only one month. The serum folate was unequivocally abnormal in only 2 patients with coeliac disease (Cases 4 and 5) but was in the borderline range in 2 others (Cases 1 and 3).

Barium follow-through examination of the small intestine showed that 4 of the 6 coeliac children had dilatation of the small gut and thick mucosal folds.

Intestinal biopsies. Dissecting microscope examination showed a completely flat mucosa in 4 of the 6 coeliac children and in 1 (Case 4) the mucosa was flat with a mosaic pattern. The one biopsy to show a convoluted mucosa, corresponding to moderately severe 'partial villous atrophy', was obtained from the child (Case 6) who was unable

to tolerate a normal diet for more than one month. Similarly, this child's epithelial surface cell height (26.1μ) was the only one from the coeliac children that approached the normal range (29.3 to 36.8μ).

Discussion

Our results show that coeliac disease cannot be diagnosed on clinical grounds, nor by a response to gluten restriction. 6 children who had previously been diagnosed as having coeliac disease showed no histological evidence of the disease; haematological, biochemical, and radiological findings were also normal. Gluten restriction in these children had therefore been unnecessary. McNeish (1968) reviewed 23 children diagnosed as having coeliac disease on inadequate criteria, of whom 6 proved to have normal mucosa. However, all his patients had continued with a gluten-free diet until just before the biopsy. 5 of the 6 coeliac children in our study had been free of symptoms on a normal diet for periods between 18 months and 9 years. These children had been considered normal, since they had not relapsed on reintroduction of gluten to the diet.

As it has been shown that the mucosal changes in coeliac disease persist into adult life (Mortimer *et al.*, 1968), children with this disease should continue with their gluten-free diet indefinitely. Complications resulting from inadequately treated coeliac disease are widely recognized. Iron and folate malabsorption in untreated coeliac disease may cause hypochromic and macrocytic anaemias (Dormandy, Waters, and Mollin, 1963; Stewart, 1968; Kilpatrick and Katz, 1969). Folate deficiency secondary to unrecognized coeliac disease

may be responsible for megaloblastic anaemia of pregnancy (Giles, 1966; Whitfield and Love, 1968). Folate deficiency in pregnancy may be associated with an increased incidence of fetal abnormality (Hibbard and Smithells, 1965); it may also be responsible for some cases of abruptio placentae (Hibbard and Hibbard, 1963) and for recurrent abortions (Martin, Harper, and Kelso, 1965). Morris, Adjukiewicz, and Read (1970) described 3 women with untreated coeliac disease who were infertile until treated with gluten restriction. The aetiology of the infertility in these cases remains obscure, though it may be related to folate deficiency.

Lack of growth is a further potential hazard of untreated coeliac disease. Hamilton, Lynch, and Reilly (1969) showed that 36% of newly diagnosed children with coeliac disease lay below the 3rd centile for height and 62% below the 3rd centile for weight. Sheldon (1969), however, found only 6 of his 57 follow-up patients treated during childhood were dwarfed in adult life.

An increased incidence of malignant lymphoma and carcinoma of the gastrointestinal tract has been reported in adults with untreated coeliac disease (Gough, Read, and Naish, 1962; Harris *et al.*, 1967; Wright and Richardson, 1967). There is suggestive evidence that a gluten-free diet may decrease the risk of developing malignancy (Harris *et al.*, 1967). McNeish and Willoughby (1969) have claimed that a normal whole blood folate may be used with confidence to exclude the diagnosis of coeliac disease, but we have not been able to confirm this. In our view no single haematological, biochemical, or radiological test can take the place of an intestinal biopsy. Nevertheless, in an ill, emaciated baby, it may be wiser to postpone the biopsy and to make a provisional diagnosis from indirect investigations. Sufficient evidence may be obtained from the clinical features, red cell folate, faecal fat excretion, and radiological abnormalities to justify treatment with nutritional supplements such as iron, folic acid, or calcium and vitamin D, and even with a gluten-free diet until the child's nutrition has improved. A biopsy examination must be carried out at a later date, and as little as one month on a gluten-containing diet may be sufficient to cause diagnostic abnormalities of the mucosa as in our Case 6.

The absence of symptoms in a child previously suspected of having coeliac disease, but now on a normal diet, does not exclude the diagnosis. We suggest that these children require further investigation and, if the biopsy shows a coeliac mucosal lesion, treatment with a gluten-free diet.

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