Coeliac Disease

Some Still Controversial Aspects*

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When Dicke (1950) discovered the harmful effects of dietary wheat and rye flour in children with coeliac disease he opened the way for an effective empirical form of dietary treatment which has been widely accepted. But in spite of the apparently specific nature of the intolerance to wheat and rye flour or, to be more precise, the gluten contained in these flours, and the numerous studies directed towards elucidating this relation, the precise pathogenesis of the disorder remains unclear. This has allowed the persistence of a non-uniform approach to its definition, diagnosis, and management, and a number of points of controversy regarding these three aspects still remain.

Definition

We believe that coeliac disease should be considered a permanent inability to tolerate dietary wheat and rye gluten characterized by:

- (i) Histological abnormalities of the duodenal and jejunal mucosa.
- (ii) Clinical and investigational evidence of impaired intestinal absorption, whether of fat, vitamins, or minerals, when the diet includes gluten.
- (iii) Clinical and histological remission after removal of gluten from the diet.
- (iv) Clinical and histological relapse after reintroduction of dietary gluten.

This definition satisfies the essential criteria laid down recently by Rubin, Eidelman, and Weinstein (1970) and also agreed by members of the European Society for Paediatric Gastroenterology (Meeuwisse, 1970). Controversy has surrounded the terminology of this disorder (Rubin and

Dobbins, 1965), partly because of confusion with other malabsorptive disorders loosely termed, for example, 'coeliac syndrome' (May, McCreary, and Blackfan, 1942) or 'malabsorption syndrome' (Mudge, 1953), and more recently, 'primary malabsorption syndrome in infancy' (Visakorpi and Immonen, 1967). These syndromes have intestinal malabsorption in common, but may contain examples of many other underlying causes apart from coeliac disease. Confusion also results from the use of numerous synonyms, but by accepting the definition outlined above coeliac disease implies a specific disease entity, the same in children and adults (Rubin *et al.*, 1960) and is identical to 'gluten-induced enteropathy' (Frazer *et al.*, 1959) and coeliac sprue (Rubin *et al.*, 1970). 'Adult coeliac disease' (Cooke, 1958) and 'idiopathic steatorrhoea' (Stewart *et al.*, 1967), terms used by physicians dealing with adults, probably comprise predominantly patients with coeliac disease who fit the above definition. However, still included in these groups are patients who do not respond histologically and clinically to a gluten-free diet. Whether these are patients who have become resistant to recovery after removal of gluten from the diet, or whether their intestinal pathology results from other diseases is not at present clear.

Because of the widespread imprecision of the definition of coeliac disease, the European Society for Paediatric Gastroenterology recently convened a round table discussion to try to lay down guidelines about this and other controversial aspects of the disease. It was decided (Meeuwisse, 1970) that the diagnosis of coeliac disease should be restricted to patients with *permanent* intolerance to gluten and conforming to the general terms of the definition outlined above. Particular attention was given to the possibility that intolerance to gluten might, in some cases, be temporary. Though this has been

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claimed by several authors and termed variously 'acquired gluten intolerance' or 'temporary gluten intolerance' (Frazer, 1968; Sheldon and Simpkins, 1961; Visakorpi and Immonen, 1967; Walker-Smith, 1970), it was decided by the panel that if this state does exist, it must be uncommon and that more relevant facts are needed about patients so diagnosed. For the present, to minimize confusion, particularly in case reports and other scientific papers, it was decided that patients with characteristic histological lesions and clinical and histological improvement on a gluten-free diet can be definitely said to have or not to have coeliac disease (i.e. a permanent intolerance to gluten) only on their clinical and histological relapse after the reintroduction of dietary gluten. In research studies, particularly those directed towards the aetiology of gluten toxicity, it was agreed that these guidelines should be adhered to strictly. However, in clinical practice reintroduction of gluten and rebiopsy was not universally considered desirable if all the preliminary criteria were unequivocally fulfilled.

Pathogenesis

Before 1950 exclusion of all starch-containing foodstuffs (except bananas) from the diet was generally advocated (Haas, 1924; Andersen, 1947; Sheldon, 1949). The Dutch workers (Dicke, 1950; Dicke, Weijers, and van de Kamer, 1953) clearly explained the observed response to diets low in starch by showing the harmful effect of a component of flour which they termed 'wheat factor'. Their findings were confirmed by others who helped establish the beneficial clinical response and improvement in steatorrhoea after exclusion of the gluten portion of wheat and rye (Anderson *et al.*, 1952; French, Hawkins, and Smith, 1957).

Our understanding of the symptomatology of coeliac disease assumed a new dimension with Paulley's (1954) demonstration of morphological abnormalities of the small intestine in specimens taken at operation from patients with idiopathic steatorrhoea. With the introduction of satisfactory methods for peroral small intestinal biopsy shortly afterwards, these findings were confirmed (Shiner, 1956; Sakula and Shiner, 1957; Rubin *et al.*, 1960) and the histological features of the mucosal lesion were carefully documented. The mucosal lesion is most severe in the proximal small intestine, where the villi are usually absent and the mucosa quite flat. The changes are less marked distally (Rubin *et al.*, 1960). The pathogenic importance of gluten to these structural changes received strong support from Anderson's (1960)

finding that complete removal of gluten from the diet of coeliac children was followed by histological recovery. Rubin *et al.* (1962) gave more direct evidence of the deleterious effect of gluten on the small intestinal mucosa by instilling it into the distal small intestine of an adult patient with coeliac disease and inducing local histological changes in a previously normal area of small intestine. This important finding is supported by recent studies in children where similar structural changes have been caused by instilling gluten directly into the upper small intestine during a period of histological remission after strict dietary gluten restriction (Jos, Rey, and Frézal, 1969; Shmerling and Shiner, 1970).

The mechanism of evolution of the characteristic histological changes in coeliac patients after exposure to dietary gluten is not clear and has allowed speculation about their pathogenesis. The two major theories are the 'toxic' and the 'immunological'. The apparently direct toxic action of gluten on the small intestinal mucosa at least superficially supports the former, and originally Frazer (1956) postulated a primary enzyme defect which allowed a toxic substance produced by incomplete digestion of gluten to damage the epithelial surface of the gut. However, as yet no abnormality of the proteolytic digestive processes of the coeliac patient has been conclusively demonstrated, and though mucosal enzyme deficiencies, notably of disaccharidases (Plotkin and Isselbacher, 1964) and peptic hydrolases (Douglas and Peters, 1970) have been found, these are secondary to the mucosal damage and return towards normal after successful dietary treatment.

Various immunological abnormalities have been shown in patients, predominantly adults, with coeliac disease. Among them are an increase of antigluten antibodies in small intestinal cells shown by immunofluorescence (Malik *et al.*, 1964), an increased number of immunoglobulin-M and immunoglobulin-G containing cells in the small bowel mucosa of treated or untreated coeliacs (Søltøft, 1970), and alteration of the levels of circulating immunoglobulins. The significance of these findings has recently been succinctly summarized by Hobbs *et al.* (1969). There is more evidence to suggest disturbed lymphoreticular function in coeliac disease, i.e. defective lymphocyte transformation in response to phytohaemagglutinin in some patients, or high incidence of lymphomata in adults with the disease (Harris *et al.*, 1967), and the clinical and histological response to steroid therapy in spite of the continued ingestion of gluten (Wall *et al.*, 1970). All favour the 'immunological'

theory. Furthermore, Shmerling and Shiner (1970) have carefully studied the dissecting, light, and electron microscopical changes in coeliac children in remission after intraduodenal instillation of gluten and showed the first discernible changes to be of infiltration by lymphocytes, plasma cells, and mast cells in the lamina propria, with thickening, widening, and coarsening of the subepithelial and vascular basement membranes occurring after 48 to 96 hours, and before degeneration and shedding of the villous epithelial cells. These changes suggest that the effect of gluten is not directly on the epithelium. It could be via a cellular-mediated immune mechanism, but further studies are certainly needed, particularly in young newly diagnosed cases, before these controversial theories can be finally settled.

Diagnosis. The corner-stones for the diagnosis of coeliac disease are: (i) demonstration of impaired intestinal absorption; (ii) finding characteristic histological changes in the duodenojejunal mucosa; and (iii) definite clinical response to withdrawal of dietary gluten. Using these criteria the diagnosis will be reached without undue difficulty in most cases, but difficulties of interpretation of the different features may arise.

Most paediatricians use the faecal fat excretion method (van de Kamer, ten Bokkel Huinink, and Weyjers, 1949) to assess intestinal absorption in suspected coeliac disease, but the patients sometimes do not have diarrhoea, and steatorrhoea may be absent (Cameron *et al.*, 1962; Hamilton, Lynch, and Reilly, 1969; Egan-Mitchell and McNicholl, 1972). The use of more prolonged balance studies (e.g. for 8 days) and more rigid criteria for fat excretion values may help overcome some of these problems and the use of another test of small intestinal absorptive function, such as the xylose absorption test, may increase the sensitivity of this assessment. Standard values for this test in childhood have been established (Hubble and Littlejohn, 1963; Jones and di Sant'Agnese, 1963) and the estimation of 2- and 5-hour urinary excretion values adds to its diagnostic usefulness (Sammons *et al.*, 1967).

Even so, no abnormality of fat or carbohydrate absorption may be demonstrable, and as this type of patient is almost invariably asymptomatic, the decision to proceed with intestinal biopsy may be difficult. However, the presence of iron or folate deficiency or impaired calcium absorption will often indicate appropriate investigation in this group of patients. We do not recall a child with coeliac disease who had no evidence of impaired intestinal absorption, though this might have been no more than the indirect evidence of low red cell folate

levels, but, if there is any doubt as to the possibility of coeliac disease causing, for instance, short stature in a child, intestinal biopsy is, at present, the only means of resolving the question. Intestinal biopsy should certainly be performed in any patient with poor growth or anaemia, even in the absence of laboratory evidence of malabsorption, if there is a family history of coeliac disease.

Rubin and his colleagues have clearly shown the importance of meticulous handling, preparation, and sectioning of small intestinal biopsy specimens (Rubin and Dobbins, 1965), and in a recent Editorial commenting about the diagnosis of coeliac disease, Rubin *et al.* (1970) reiterated that the most frequent source of misinterpretation was the use of tangentially cut sections in which normal intestine may apparently have an abnormal or absent villous pattern. They also caution against placing too much reliance on the dissecting microscope appearance of the intestinal mucosa. Anderson (1966) believes that in children this can be relied upon only to differentiate between the gross absence or presence of villi. A completely flat mucosa is usual in children with newly presenting coeliac disease, and lesser degrees of abnormality such as those commonly accepted in adults, e.g. leaves, ridges, and convolutions, must be very cautiously interpreted. In clinical practice we feel that the only use that examination under the dissecting microscope serves is to be able to identify those with a flat, honeycomb mucosa immediately, so that in an ill child or for other reasons the initiation of treatment can be speeded rather than wait for the histological sections. Leaves, ridges, and convolutions may yet show a normal histological picture. As well as the villous pattern, particular attention must be paid to the quality of the surface epithelial cells and to the degree of cellularity of the lamina propria and its type.

It was originally thought that the characteristic mucosal lesion described in coeliac disease was specific for this disorder, but during the 1960's it became clear from a number of observations that this was not so, but rather that the appearance was the end result of a reaction by the mucosa to a number of noxious influences, either irritants, infections, or possibly immunological reactions.

However, in children as distinct from adults, there are fewer causes of this appearance and those particularly worthy of consideration in association with the type of clinical story one is usually investigating are post-bacterial or virus enteritis associated with secondary disaccharidase deficiency (Burke, Kerry, and Anderson, 1965), *Giardia lamblia* infestation (Cameron *et al.*, 1962) and, in less

affluent communities, severe malnutrition or kwashiorkor (Brunser *et al.*, 1968).

The differentiation between post-gastroenteritis, secondary disaccharide intolerance, and true coeliac disease has in recent years been rendered more difficult by the increasingly common practice in our community of introducing solid foods, which may be derived from wheat cereal, into the diet in early infancy, often even in the first month of life. This means that those with coeliac disease are presenting much earlier and are often more acutely ill than formerly. It is also in these early months of life that secondary disaccharide intolerance is more common as the baby who develops viral or bacterial enteritis at this time seems more susceptible to the persistence of mucosal abnormality and consequent disaccharidase deficiency.

We have been impressed with the marked differences in the presenting features of children with coeliac disease attending the same clinic in Birmingham in the early 1950's and on the return of one of us (C.M.A.) to the clinic in the late 1960's. Though this change is mentioned elsewhere (Gerrard and Lubos, 1967), it has not been very adequately documented. During an 18-month period from October 1968 compared with an 18-month period 1950-52 there was a dramatic reduction in the mean age at presentation, i.e. 43.6 months to 9.3 months in 10 consecutive patients in the first group and 9 in the second, and a corresponding drop in the mean age of introduction of gluten-containing cereals into the diet, i.e. 9.4 months to 3.4 months. The number of patients in each group is small and factors other than early feeding of solids may be partly responsible for earlier presentation. However, the differences are striking and confirm clinical impressions mentioned to us by others.

Since it may be difficult to differentiate coeliac disease and post-gastroenteritis sugar intolerance at presentation in the early months of life, even from the biopsy appearances, it may occasionally be justifiable to treat the patients for some months with both sugar and gluten restriction and review the diagnosis of coeliac disease on clinical and histological criteria after the age of say, 18 months to 2 years, after reintroduction of gluten into the diet for at least several weeks (McNeish, 1968). More often, however, one is able to make the differentiation of sugar or gluten intolerance on clinical grounds. In sugar intolerance watery stools containing excessive sugar follow a few hours after ingestion of the offending disaccharide, and, with an appropriate disaccharide-free diet, stools become less frequent and more formed

within 24 hours (Burke *et al.*, 1965). If diarrhoea is related only to sugar intolerance rapid weight gain follows. However, in coeliac disease, where sugar intolerance may occur secondary to mucosal damage, abnormal stools and inadequate weight gain persist. This approach avoids the unsatisfactory nature of assessing a response to simultaneous removal of two suspected harmful materials, sugar and gluten, and may avoid the need for dietary changes and rebiopsy at a later date.

Recently a questionnaire was circulated by the European Society for Paediatric Gastroenterology to its members in Europe and Great Britain and to other paediatric gastroenterologists in North America and Australia, with the aim of ascertaining information on current practice in the diagnosis of the disease in different paediatric centres (Visakorpi, 1970). Though complete unanimity was not reached in the replies, there was a large majority who found that the diagnostic tests of most importance in their experience were faecal fat excretion, D-xylose excretion, and intestinal biopsy. The question of testing tolerance to gluten was also raised. All respondents agreed that appropriate clinical response to dietary gluten withdrawal was essential to the diagnosis, most confirmed this effect by laboratory investigation, and many by biopsy. Though rebiopsy after gluten withdrawal may never gain universal acceptance, it has an undoubted place where clinical response has been suboptimal. It also has an important place when the initial diagnosis of coeliac disease has been made on slender grounds and reintroduction of gluten has not produced clinical relapse (McNeish, 1968). In this case it will avoid unnecessary, indefinite dietary restriction. However, reassessment may have to be continued for no less than 2 years of normal dietary intake before coeliac disease is positively excluded.

The latter statement exemplifies the difficulty facing the paediatrician and patient if the initial diagnosis has been made largely on clinical grounds *without confirmation by intestinal biopsy* and the patient treated by excluding gluten. This is still apparently a common practice. In the past 20 months we have had some 22 such treated patients referred to us from a wide area for a decision as to whether they really suffer from coeliac disease and should continue on a gluten-free diet. Seven of these were found to be definite cases of coeliac disease but 15 did not show any manifestations of the disease and had a normal intestinal mucosa after they had been on a normal diet for six weeks or more. It will be necessary to follow these children carefully for at least 2 years though it

seems likely that the majority will have no abnormal finding even by that time.

It seems highly desirable therefore that no child be placed on a gluten-free diet in the absence of confirmation by intestinal biopsy if this can possibly be obtained, even if it means referral to a major centre.

Doubt has been cast by some (Partin and Schubert, 1966; Sheldon and Tempany, 1966) on the safety of peroral mucosal biopsy but perhaps this risk has been magnified. At this hospital no perforation or major haemorrhage has been caused since biopsies were first carried out in 1959 (Cameron and Astley, 1969). In our own hands, either here since 1968 or in Australia between 1958 and 1968, only one perforation of the jejunum has occurred among many hundreds. The patient was a grossly emaciated baby and it is worthy of note that those referred to by Partin and Schubert (1966) were also babies of this type. Certainly the technique is not one for the occasional performer, but with careful clinical assessment, rigid choice of those to be 'biopsied', and adequate fluoroscopic facilities with image intensifier radiation equipment, the risk is minimal. The procedure can be carried out on 'day patients' if they are carefully observed for some hours after the procedure. There is also no lower age limit for biopsy provided the baby is not grossly emaciated. Paediatric units of sufficient size to offer adequate experience in techniques and their interpretation, should contain somebody trained to perform intestinal biopsy in children, and someone trained to prepare the sections adequately and interpret the histological findings carefully. Each aspect of the latter is important, and the detailed biopsy appearances should finally be carefully considered by the clinician in association with the whole clinical details. We cannot go quite as far as Townley (1971) who performs intestinal biopsy as the first and perhaps the only investigation for coeliac disease. However, we would agree with him that biopsy is simple and safe in experienced hands, and that there is no place for a therapeutic trial of a gluten-free diet unless intestinal biopsy cannot possibly be arranged. It is also unnecessary to perform multiple tests to indicate malabsorption of one substance or another. One will do, followed promptly by biopsy, interpretation, and treatment. In this way prolonged hospitalization, still too often seen, can be minimized. In fact, with organization the diagnosis can be made in many instances as an outpatient.

Management

After the introduction of a gluten-free diet in coeliac disease the response is often dramatic, with

improvement in mood and appetite usually 3 to 5 days after withdrawal of gluten followed by weight gain after about a week. Abnormal stools may take weeks and abdominal distension months to disappear. In the absence of such a response one must seriously reconsider the diagnosis as long as one can be sure that gluten restriction is rigid (Rubin *et al.*, 1970). However, in later childhood and adolescence strict dietary control may be extremely difficult, and sometimes virtually impossible owing to lack of co-operation by the patient. Furthermore, though patients with coeliac disease have a lifelong inability to tolerate gluten normally (Gerrard *et al.*, 1955), they often undergo some degree of spontaneous remission in symptoms after childhood (Sheldon, 1959; Fone *et al.*, 1960) so that dietary relaxation allowing reintroduction of gluten-containing foods after varying periods of time did achieve widespread popularity and is still apparently advised (Visakorpi, 1970; our own recent experience from referred cases). However, Sheldon (1969) recently reviewed 57 patients almost 20 years after treatment for coeliac disease in childhood by gluten withdrawal for varying periods. He showed that 13 had relapsed clinically after dietary relaxation, subsequently resuming gluten-free diets. Of the remaining 44, 19 had low serum folate levels. Among the other 25 patients, there were 11 with serum iron figures below 80 $\mu\text{g/ml}$. The author concluded that the results of temporarily excluding gluten are unsatisfactory and disappointing and that the persistent use of a gluten-free diet throughout life is indicated. This has recently been reinforced from a 20-year study of 110 patients by Young and Pringle (1971). Our own experience and advice, particularly after following patients allowed to resume normal diets in Birmingham, are similar.

Even in apparently symptomless individuals the institution of gluten restriction causes a positive, subjective improvement and enhanced growth and weight gain. Sexual maturation and even frigidity and sterility may be improved (Gerrard *et al.*, 1955).

The ability to induce histological changes in patients in clinical and histological remission by introduction of gluten into the small intestine (Rubin *et al.*, 1962; Jos *et al.*, 1969) also emphasizes the persistence of the abnormality in coeliac disease.

Consideration must also be taken of the evidence that malignant lymphoma and other malignancies of the gastrointestinal tract have been reported as a late complication of coeliac disease in adults (French *et al.*, 1957; Gough, Read, and Naish, 1962; Harris *et al.*, 1967) and clinical observation

suggests a relation between this complication and prolonged exposure to dietary gluten. This possible association behoves us to undertake the dietary therapy of coeliac disease seriously and continuously.

Those familiar with the use of gluten-free diets in children and older patients are aware that the institution and maintenance of at least reasonably strict withdrawal of gluten from the diet is not nearly so demanding or restrictive as many people less familiar with this treatment seem to imagine. The minor inconveniences and self- or parental-discipline involved are worth the effort in view of the possible long-term advantages. However, parents and patients need considerable help at the outset in understanding the diet and how to make it as easy as possible. Gluten-free bread is now readily available, and in the United Kingdom by prescription on the N.H.S. Some hospitals through their dietary departments and the Coeliac Society,* a lay organization of patients and parents, have produced very comprehensive diet sheets which list all prohibited foods and indicate safe ones. They also suggest recipes and substitutions and helpful hints on 'holidays', etc. The Coeliac Society is also organizing labelling of foods by those manufacturers willing to co-operate. A symbol of a wheat ear crossed will be incorporated in the label.

There is still uncertainty as to whether oats and barley are harmful to coeliac patients. The European Society for Paediatric Gastroenterology came to the conclusion that there were insufficient data available to give a definite answer, and that more work was desirable. In the meantime it is probably wise to exclude these substances if the patients themselves find them troublesome, or if they are not making a full response to restriction of only wheat and rye. Our own experience indicates that very few patients have symptoms that could be attributed to the ingestion of oats but, as far as we know, no biopsy evidence before and after oats ingestion is available to solve this question.

Incidence

The exact incidence of this disease and the genetic pattern of inheritance remains controversial. There is no doubt that the condition has now been fully proved to be present in families—i.e. parents and children or in sibs (MacDonald, Dobbins, and Rubin, 1965). Recent experience in our own clinic suggests that more family members than is obvious may have this intolerance, indicated by confirmatory biopsy studies and response to treatment, though they may have had little in the way of overt symp-

toms initially. Some patients treated in early childhood at the Birmingham Children's Hospital, and then later followed by adult gastroenterological units in the City, are being referred back to us with offspring with suspicious symptoms which in some cases have proved to be due to coeliac disease. How should we find all those with this disease? What is a good screening test? Indiscriminate biopsy is not acceptable. By finding these patients in childhood would we not lessen the load of gastroenterology illness in adult life, lessen the number of people with suboptimal health and vigour, lessen the long-term complications and deficiencies? The determination of true incidence and complete diagnosis is one of the current problems and may well have to await an easier definitive diagnostic test.

Though there is an effective method of treatment for childhood coeliac disease, this treatment does not always seem to be completely effective when initiated in some adults. Is this because the disease has become resistant to treatment owing to its life-long presence and the development of complications, or does the adult group still include patients who have some other disease resulting in malabsorption and characteristic histological changes in the small intestine?

These controversial aspects still stimulate many of us to go on looking for the reason for the 'toxicity' of wheat gluten in some families.

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