

## Current topics

# The diagnosis of coeliac disease

A commentary on the current practices of members of the European Society for Paediatric Gastroenterology and Nutrition (ESPGAN)

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**SUMMARY** In 1977, 53 members of ESPGAN completed a questionnaire on their current practice in diagnosing coeliac disease. The usefulness of the 'Interlaken' criteria enumerated 9 years previously was reassessed. Details were obtained about the initial diagnostic approach, the acceptable histological criteria of the initial jejunal biopsy, and the timing, technique, response, and interpretation of early and late rechallenges with gluten.

Answers indicated that, although the initial mucosal lesion is usually 'flat' at the time of diagnosis, a few infants may present at a time when the mucosal lesion is less completely damaged. Furthermore, the degree of histological change after gluten challenge that is acceptable as a positive response may vary according to the state of the mucosa before challenge.

It was noted that there are still no generally agreed criteria by which the histological lesions may be described, so that (after further discussions at the Third International Coeliac Conference in Galway) a European panel has been set up to make recommendations.

In the experience of ESPGAN members, most coeliac children will have a histological relapse within 2 years of reintroduction of gluten. But a small number of unorthodox cases were reported that suggest that (a) histological relapse may take longer than 2 years to appear, or (b) the degree of sensitivity to gluten may vary at different ages.

Very long-term follow-up will be needed to explain these anomalies. Meanwhile the search continues for 'the basic defect'.

In 1969, members of the (then) European Society of Paediatric Gastroenterology discussed in Interlaken the criteria for diagnosing coeliac disease. Their conclusions were published (Meeuwisse, 1970) and contained the following points: (1) Coeliac disease is

a permanent condition of gluten intolerance. (2) The initial mucosal lesion is 'flat', and recovers on a gluten-free diet. (3) Reintroduction of gluten will produce a histological relapse within 2 years.

These points were subsequently described as criteria for the definitive diagnosis of coeliac disease in childhood (Visakorpi, 1974).

It was also noted in Interlaken that transient gluten intolerance, if it exists, is rare, and that more facts are needed.

Nine years after the original discussion, 53 members of the (now) European Society for Paediatric Gastroenterology and Nutrition (ESPGAN) completed a questionnaire on their current practice in diagnosing coeliac disease. The questions were designed to find out how often and in what manner 'the Interlaken criteria' were used.

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Details were obtained about the initial diagnostic approach to a child with suspected coeliac disease; the most commonly used laboratory tests; the acceptable histological criteria of the initial biopsy; and the timing, technique, response, and interpretation of early and late rechallenges with gluten. The results were discussed at the annual meeting in Utrecht in 1977, and some of the basic data have been presented elsewhere (Shmerling, 1978).

We believe that this questionnaire and the ESPGAN discussion that followed have given important information to test the validity and usefulness of 'the Interlaken criteria' and have raised new problems in the diagnosis of coeliac disease. We met in Zurich in September 1978 to examine further the results of the questionnaire and the discussion that took place in Utrecht. The following paragraphs are our commentary, based on the current thinking and practice of the members of ESPGAN.

#### **Initial mucosal lesion**

A 'flat' mucosa with absent or nearly absent villi has been widely accepted as an essential diagnostic feature of coeliac disease in childhood (Visakorpi, 1974). The discussions in Utrecht showed that this continues to be the usual finding in untreated childhood coeliac disease. However, it now appears certain that, in a few cases (which have been confirmed later by positive gluten challenge), the initial mucosal lesion is not 'flat' but is 'severely damaged' (Walker-Smith *et al.*, 1978). This less extreme lesion has been found in young infants and is likely to be the result of a relatively low gluten intake, ingested over a relatively short period. Great caution must be shown before diagnosing coeliac disease in such infants with less severe mucosal lesions, because there are other conditions that can cause similar histological changes. If the condition of the child permits, it may be possible to continue a diet containing a known (adequate) amount of gluten for a few weeks before repeating the biopsy. Whether or not this practice is adopted in individual cases, all must be rechallenged later (see below) for final proof of the diagnosis.

During these and subsequent discussions (at the Third International Coeliac Conference in Galway) it became clear that there are still no generally agreed criteria by which the histological lesions may be described. A European panel has been set up to make recommendations.

#### **Gluten challenge**

It is a central part of the definition of coeliac disease that the disease is permanent. The implication that

follows is that reintroduction of gluten into the diet (a gluten 'challenge') will produce a relapse.

In the original Interlaken paper, it was stated that 'the only decisive criteria are the abnormal morphology of the small intestinal mucosa, its normalisation on gluten withdrawal, and the reaction on reintroduction of gluten.' It was also stated that the mucosa should be normal before rechallenge.

In 1977, the only significant change in these views related to the state of the mucosa before attempting rechallenge, and to the degree of mucosal change that is induced by the challenge. About 14% of members now consider that it is not necessary for the mucosa to be completely normal before attempting challenge; in such cases the reappearance of severe lesions would be necessary before deciding that the challenge was 'positive'. About the same proportion of members felt that, if the mucosa before challenge was normal, then a 'deterioration' of mucosal histology could be considered evidence of a positive response.

There is obvious need for caution in this approach, otherwise coeliac disease will be wrongly diagnosed and its frequency will be overestimated. A further difficulty at present is our inability to define precisely the degree of mucosal change. This is another area where it is hoped that the European panel will be able to introduce more satisfactory criteria.

#### **Transient (temporary) gluten intolerance and 'the 2-year rule'**

At Interlaken, the panel and most of the audience agreed that transient gluten intolerance (if it exists) is relatively rare. It was further stated that 'before a patient is classified as having been suffering from transient gluten intolerance the intestinal biopsy should still be normal 2 years after the reintroduction of gluten'.

In Utrecht, there was general agreement that the condition does exist, that it usually occurs in young infants, and lasts 'for a short period'—generally a few weeks or months. The pathogenesis may be similar to that in cows' milk protein intolerance. There are no firm data on the upper age limit or maximum duration of transient gluten intolerance. Stricter criteria, including a positive early challenge and a negative late challenge have been described elsewhere (McNeish *et al.*, 1976), but they are difficult to apply routinely. It should be noted that a positive early challenge will be found in both transient intolerance and coeliac disease, and that a late challenge will be required to confirm either diagnosis.

The '2-year rule' was originally developed in the context of temporary gluten intolerance (see above), but it carried the implication that, in cases of

permanent gluten intolerance (that is, coeliac disease), there would be a recurrence of the mucosal lesion within 2 years of gluten reintroduction. Discussions at Utrecht confirmed that this concept had proved useful, and that most coeliac children who have been challenged have obeyed it. ESPGAN members have performed challenges on 652 children, and 619 (95%) have shown mucosal relapse within 2 years. Those who did not relapse within 2 years may represent a heterogeneous population, since the cases were studied in different centres at different ages, and with no uniformity of approach to the method of gluten challenge. They comprise at least two groups. In the first, there was no relapse after gluten reintroduction, and these children may have had transient gluten intolerance that had recovered spontaneously. In the second group, 7 members reported 20 patients in whom there was a histological relapse after 2½ to 7 years. Precise information is available on only 7 of these children, and still more thorough analysis of their data is needed and is being sought. If these claims are substantiated, they may alter recommended clinical practice.

#### Permanence of coeliac disease and gluten challenge

This key concept appears to have been accepted in principle. The implication that follows is that gluten challenge will always produce a relapse. While the answers to the questionnaire indicated virtual unanimity of belief on this point, there remains a considerable discrepancy in clinical practice. Some members thought that the place for gluten challenges was in research clinics only, and did not challenge their patients; others did not routinely challenge patients in whom early diagnostic features and responses to a gluten-free diet were 'classical'; still others challenged only those infants in whom the initial diagnoses were made at less than one year, in the belief that it is in this age group that there might be confusion between coeliac disease and transient gluten intolerance.

The gap that exists between theory and practice is illustrated by the fact that only 652 gluten challenges have been performed in clinics that must contain several thousand 'coeliac' children.

#### Conclusions and some questions for the future

The 1969 Interlaken statement concluded: 'these results do not solve the problem of diagnostic criteria of coeliac disease, and do not impart to us the "final truth" about the disease'. Nearly a decade later, the 'final truth' still eludes us, but we think that the original criteria have served us well, and at present do not need to be changed. The basic data

from the 1977 questionnaire (Shmerling, 1978) indicate a considerable degree of uniformity of thinking, and the Interlaken statement has clearly been influential.

Some workers have a less rigid approach than formerly to the minimum diagnostic histological criteria of the initial biopsy. There is obvious need for caution in this approach, otherwise coeliac disease will be wrongly diagnosed and overdiagnosed. It is hoped that the European panel will be able to define the histological lesions more satisfactorily.

The need for gluten challenge is widely recognised but is less widely practised. Research workers will rightly continue to say that all coeliac patients should have confirmatory gluten challenge. But first, more satisfactory criteria for a positive challenge are needed, and this itself requires more research. For the practising clinicians who at present choose not to challenge every patient, there are no definite rules about whom they should select for challenge. Some recommend for challenge all those in whom the original diagnosis of coeliac disease was made before age one year, and those in whom the original features or therapeutic response was not 'classical'. Of course this begs the question.

When the '2-year rule' is applied, some unanswered problems arise that will only be resolved by very long-term follow-up. A positive gluten challenge is used to indicate *permanence* of the intolerance, whereas it only proves *persistence* of the abnormality. Furthermore, it is possible that clinical (and possibly histological) 'expressivity' of the disease, including the degree of gluten sensitivity, may vary at different ages. Three cases (Schmitz *et al.*, 1978) have already been reported in whom a positive gluten challenge was later followed by apparent gluten tolerance, as indicated by spontaneous remission of the small intestinal mucosal lesion on a gluten-containing diet. These cases were older and the period of gluten intolerance was much longer than cases of 'transient' intolerance.

The 7 (or more) cases in whom the mucosal lesion took longer than 2 years to relapse after gluten reintroduction require more detailed documentation. If the claims are substantiated they may alter recommended clinical practice, if not basic pathophysiological concepts.

Lastly, what should be the management of the child whose original features and histology suggest coeliac disease, who apparently recovers on a gluten-free diet, but in whom no adverse response to gluten occurs after 2 years of reintroduction? Some, perhaps the majority, will rightly be considered to have had 'transient' intolerance which is now cured, and will be discharged from the clinic. The coeliac research worker will consider all the above

discussions, and may decide upon very long-term follow-up to exclude late relapses.

Meanwhile the search continues *in vitro* (Katz and Falchuk, 1978) and *in vivo* for 'the basic coeliac defect'. The answers to some of the clinical problems discussed above may have to await this dénouement.

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## Change of reference style

From January 1980, the *Archives* will change its style for citing references and will follow the number system. We are making this change in order to conform with the 'Vancouver style' of uniform requirements for manuscripts submitted to biomedical journals.

Previously the *Archives* has used the Harvard reference system. Its advantages and disadvantages compared with those of the number system have seemed evenly balanced, but the editors have been aware of the burden imposed on authors and their secretaries by the different styles which different journals require. Therefore, with the unanimous agreement of the editorial committee, we have decided to support a move whereby a large—and increasing—number of major medical journals

will accept manuscripts presented in one agreed style.

The system numbers references consecutively in the order in which they are first mentioned in the text. References are identified in the text by arabic numerals. For further details see instructions to authors inside the front cover, and the references cited.<sup>1,2</sup>

From now onwards all manuscripts submitted should accord with the new style.

<sup>1</sup> International Steering Committee of Medical Editors. Uniform requirements for manuscripts submitted to biomedical journals. *Br Med J* 1979; **1**: 533–535.

<sup>2</sup> Lancet. The Vancouver style. Uniform requirements for manuscripts submitted to biomedical journals. *Lancet* 1979; **1**: 429–430.