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Dietary protein intolerance

Clinical food ‘intolerance’ has many causes and many manifestations, including psychological aversion to the sight, smell or taste of food as well as psychological intolerance to one or more of the many constituents of food.

Intolerance to various food proteins especially the protein of cows’ milk, has been recognized in children for many years. Such food intolerance may be a result of a variety of causes; for example, congenital digestive enzyme defect such as sucrase–isomaltase deficiency, or acquired lactase deficiency secondary to small intestinal mucosal damage, which in turn can be the result of a food allergy.

Bleumink (1974) has classified adverse reactions after food ingestion as follows:

- Toxic effects, including those due to bacterial contamination and food additives.
- Intolerance phenomena due to enzyme deficiencies, e.g. lactose intolerance as a sequel to lactase deficiency.
- Allergic reactions.
- Symptoms resembling allergic reactions but not elicited by immunological phenomena. To this category belong symptoms caused by histamine releasers, e.g. strawberries, where histamine release is not the consequence of an immunological reaction.

In recent publications the term ‘food idiosyncrasy’ has been used in the sense of a non-immunological abnormal response to food. There is, however, increasing evidence that dietary protein intolerance may be mediated via an allergic reaction. In this chapter, the varieties of food protein intolerance in which there is some evidence for such an allergic reaction or reactions affecting the small intestine will be discussed.

Allergy

Von Pirquet of Vienna in 1906 introduced the term allergy. He used it to describe a deviation from the original state or normal behaviour of the individual. His contribution and its relevance to current concepts of immunity and allergy have been very clearly reviewed by Turk (1987).

Today, when the term allergy is used, it implies a heterogeneous group of conditions which have in common a state of altered reactivity to foreign proteins (antigens) (Gell and Coombs, 1968). These antigens are called allergens when they produce symptoms in an allergic person. A child who has an allergy is distinguished
from other children by an abnormal response on contact with an allergen or allergens, a response that does not occur when a non-allergenic child is exposed to the same allergen. The typical features of an allergic reaction are: first, the lack of any untoward reaction on the child's first exposure to the allergen; and second, that subsequent exposure to the allergen produces a hypersensitivity reaction. Indeed, Ferguson (1976) regards the term 'hypersensitivity' as preferable to the term 'allergy' when used to describe tissue damage resulting from the immune reaction to a further dose of antigen occurring in a previously immunized host.

Gell and Coombs (1968) have classified the allergic or hypersensitivity reactions that may produce tissue damage of some kind into four types, as follows.

**Type I anaphylactic or immediate hypersensitivity**

This is initiated by an allergen reacting with mast cells that have been passively sensitized by IgE (reaginic) antibody with release of vasoactive agents such as histamine. The reaction occurs within minutes of exposure.

In the modern usage of the term atopy, this is the state where an individual is prone to develop antibodies of the IgE class. The presence of such antibodies, however, does not necessarily mean that the child is intolerant to the antigen producing the antibody, in a clinical sense.

**Type II cytotoxic hypersensitivity**

This reaction is initiated by antibody reacting with an antigenic component of a cell or tissue element or one that is intimately associated with these. Complement is usually necessary to affect cellular damage.

**Type III immune complex (Arthus-type) hypersensitivity**

In this type of reaction, antigen and antibody (IgG or IgM) react in the presence of antigen excess with the subsequent fixation of complement and consequent local inflammatory response. This reaction is maximal a few hours after exposure to antigen.

**Type IV delayed hypersensitivity (cell-mediated immunity)**

This reaction is mediated by T-lymphocytes and macrophages and manifests by infiltration of lymphocytes and macrophages at the site where antigen is present, due to release of lymphokines. These are soluble factors secreted by lymphocytes on contact with antigen. This reaction takes 1–2 days after antigen exposure.

Evidence of such an allergic reaction, with tissue damage, in children who show clinical intolerance to dietary protein is not always available. Therefore, in clinical practice, the descriptive term 'food protein intolerance' is often used rather than the more precise term 'food allergy'. Until more is known about the pathogenesis of food allergy terminological difficulties will continue to arise (Walker-Smith et al., 1984).
History

The first case report of food allergy (cows' milk allergy) was made by Hamburger in 1901. Then Finkelstein in 1905 described cows' milk as a cause of acute death in an infant.

Schloss, in 1911, related gastrointestinal symptoms to food allergy. He made the diagnosis of egg allergy on the basis of a positive skin test with a protein fractionated from ovomucoid. Gastrointestinal food allergy has since come to be recognized as an important cause of gastrointestinal symptoms in infancy.

Many paediatricians in the past, however, have been sceptical about this diagnosis because of the absence of precise and objective diagnostic criteria, nevertheless most paediatricians now accept the existence of the condition. On the other hand, there are those who undoubtedly have exaggerated its true importance. There is still debate, however, concerning its frequency and importance in different parts of the world.

Gastrointestinal symptoms may be the only manifestation of clinical intolerance to food protein but there may also be respiratory symptoms, skin reactions and other clinical features. Only gastrointestinal effects will be discussed in any detail here.

Definitions

Dietary protein intolerance is the clinical syndrome resulting from the sensitization of an individual to one or more dietary proteins that have been absorbed via a permeable small intestinal mucosa. Clinically, it appears to be a transient phenomenon of variable duration in children.

Gastrointestinal food allergies may be defined as clinical syndromes which are characterized by the onset of gastrointestinal symptoms following food ingestion where the underlying mechanism is an immunologically mediated reaction within the gastrointestinal tract.

A food-sensitive enteropathy is a disorder characterized by an abnormal small intestinal mucosa whilst having the offending food in the diet; the abnormality is reversed by an elimination diet only to recur once more on challenge with the relevant food.

Clinical spectrum

Clinical intolerance to a variety of food proteins has been described. The most common are cows' milk, eggs and fish; but intolerance to tomatoes, oranges, bananas, meat, nuts, chocolates and cereals, including soy protein, have been described (Bleumink, 1974). There is no consistent association between a particular food and specific syndromes. In fact the clinical manifestations that may occur in cows' milk protein intolerance are large in number and diverse in nature (Table 5.1) (Bahna and Heiner, 1980; Hill et al., 1986; Hutchins and Walker-Smith, 1982). Chemically, allergens are usually glycoproteins with a molecular weight of between 20 000 and 40 000.

Broadly, gastrointestinal reactions to food in children with gastrointestinal food allergy may be divided into those that manifest quickly, i.e. within minutes to an
Table 5.1 Clinical manifestations attributed to cows’ milk protein intolerance

| I | Gastrointestinal Symptoms | Syndromes |
|---|---------------------------|----------|
| Vomiting | Quick onset syndromes |
| Diarrhoea | Late onset syndromes |
| Abdominal pain | Cows’ milk sensitive enteropathy |
| Rectal bleeding | Protein losing enteropathy |
| Gross | Cows’ milk-induced colitis |
| Occult | |

| II | Respiratory Symptoms | Syndromes |
| Nasal stuffiness and sneezing | Allergic rhinitis |
| Chronic cough | Asthma |

| III | Skin Symptoms | Syndromes |
| Rash | Atopic eczema |
| Local swellings | Urticaria |

| IV | Secondary general effects |
| Iron deficiency anaemia |
| Hypoproteinaemia |
| Thrombocytopenia |
| Eosinophilia |

hour of food ingestion, and those in which the onset is slow, taking hours or days after food ingestion. Both types of reaction may occur individually or together in different children. Yet there are clear immunological differences between these groups. For example, it has been shown by Fallstrom et al. (1986) that children with slow onset reactions to cows’ milk feedings have significantly elevated titres of IgG antibodies against both native and digested beta-lactoglobulin, when compared with both controls and those children who develop symptoms quickly after milk ingestion. These children also tended to have higher levels of antibody of IgA class to both native and processed milk.

Seven out of nine children with quick onset cows’ milk allergy had IgE antibodies to cows’ milk but these did not occur at all in the slow onset group.

Age of onset and duration of syndromes

The incidence of gastrointestinal food allergic diseases is greatest in the first months and years of life and decreases with age. This is especially true for late onset reactions to food with food induced small intestinal mucosal damage (Dannaeus and Johansson, 1979). It remains uncertain as to whether gastrointestinal syndromes of allergic origin causing small intestinal mucosal damage exist in adult life. These gastrointestinal food syndromes of early childhood appear to be temporary in duration, although it does seem possible—as in the case of cows’ milk protein intolerance—that gastrointestinal syndromes may be replaced with the passage of time by syndromes involving other systems.

Quick onset syndromes

These syndromes are usually easy to diagnose on historical grounds. Levels of food-specific IgE antibodies are typically elevated and skin prick tests are also often
positive. Children with such problems often present to allergy clinics rather than to gastroenterology clinics. Thus diagnosis is usually simple and specific diagnostic tests are available. A good example of this is egg hypersensitivity. The most dramatic deleterious response is acute possibly life threatening anaphylaxis to food.

The peculiar attribute some proteins possess, when injected, to diminish instead of to increase the defences of the body against their harmful action is described as anaphylaxis (the reverse of a guard or protection). Anaphylaxis was first observed at the beginning of this century. Charles Richet and Paul Portier in 1901 on the yacht of Prince Albert of Monaco discovered anaphylaxis by injecting dogs with an extract of the sea anemone La Physalie without their becoming ill after the first injection. A second injection lead to acute vomiting and diarrhoea with their rapid death.

Only 4 years later Schlossman in 1905 documented similar symptoms of acute shock not after injection but after ingestion of a foreign protein namely cows’ milk in infants. In the same year Finkelstein described a death due to cows’ milk ingestion in infancy. It is now known that anaphylaxis usually results from a generalized immediate IgE mediated reaction following the introduction of sufficient antigen into a previously sensitized individual, releasing histamine and other biologically active mediators from sensitized mast cells. Reactions with the clinical features of anaphylaxis have also been described without evidence of IgE mediation. Thus their precise causation is not clear. The term anaphylaxis in clinical practice remains a term used to describe a severe collapse-like reaction, not necessarily IgE mediated.

This phenomenon of an acute anaphylactic reaction to an ingested food represents the most severe example or one extreme of the clinical spectrum of gastrointestinal food allergy, but fortunately does not usually result in death.

**Acute cows’ milk allergy**

The acute syndrome is usually characterized by the sudden onset of vomiting, after cows’ milk ingestion, occasionally followed by pallor and a shock-like state, but acute anaphylaxis is rare. When it occurs, acute anaphylaxis is a dramatic syndrome (Figure 5.1) (de Peyer and Walker-Smith, 1977) and can be fatal.

A breast-fed infant given cows’ milk feeding may react in this dramatic way. In these circumstances, acute vomiting with or without diarrhoea can be clearly related to the ingestion of cows’ milk by taking a careful history. Other clinical features usually accompany these gastrointestinal symptoms, such as swelling of the lips and tongue, oedema, and urticaria. All these symptoms disappear in a few hours if cows’ milk is stopped. The amount of cows’ milk responsible for this can be extremely small. It has been proven that infants can be sensitized to cows’ milk via its presence in maternal breast milk when mother is herself drinking cows’ milk (Walker-Smith et al., 1981; Lake, Whitington and Hamilton, 1982).

Investigations show a high serum IgE level and elevated milk specific RASTS. The milk antibodies of the other immunoglobulin classes (IgG, IgA and IgM) are present but usually at a low titre (Firer, Hosking and Hill, 1981). Skin prick tests are also positive (Ford et al., 1983). In a series of 100 children with cows’ milk allergy (Hill et al., 1986) 27 children fell into the quick onset group.

The role of cows’ milk hypersensitivity in the genesis of sudden unexpected death or ‘cot death’ was raised by Parish et al. (1960). The postulated mode of death was
An acute anaphylactic reaction to cows' milk. Devey et al. (1976), in Cambridge, went on to report that guinea-pigs given cows' milk to drink, instead of water, soon became anaphylactically sensitized to the proteins of cows' milk. Coombs, Devey and Anderson (1978) then found that when the drinking of cows' milk was continued by the guinea-pigs for more than 70 days they became refractory to the effect. Anderson et al. (1979) then showed that there were differences in the anaphylactic sensitizing capacities of different milks in their animal model. Evaporated whole cows' milk was practically without sensitizing capacity to beta lactoglobulin, and a formula in a liquid concentrate form had extremely low sensitizing capacity to both casein and beta lactoglobulin. In both cases this only occurred when given to the guinea-pigs by mouth, sensitizing capacity being retained when given parenterally. This suggests that these formula are handled differently in the small intestine from other milk feeds. These observations have far-reaching implications if they are true for human infants, because they suggest that modification of artificial feeding formulae may profoundly influence their allergenic or sensitizing capacity. This aspect is discussed further on page 154.
Acute wheat allergy

Rudd, Manuel and Walker-Smith (1981) have described an acute anaphylactic reaction after feeding an infant with a wheat rusk. This infant did not have RAST antibody to wheat and his IgE was only marginally elevated to 17 iu ml⁻¹.

Acute egg allergy

Egg hypersensitivity was first described by Schloss in 1911. Vomiting within a few minutes to an hour of egg ingestion is characteristic of egg hypersensitivity. Diarrhoea, abdominal pain and nausea may also occur. Typically, skin and respiratory manifestations also occur and may be a more important part of the clinical presentation than gastrointestinal symptoms (Ford and Taylor, 1982).

Ovomucoid is the most important egg protein capable of producing this syndrome (Bleumink and Young, 1969). RAST and skin prick responses to egg are usually positive and helpful diagnostically. They provide a useful guide to resolution or persistence of egg allergy (Figure 5.2).

Other foods

Acute abdominal pain seems to be a particular feature of fish hypersensitivity (Niziami, Lewin and Baloo, 1977), whilst peanuts often produce immediate reactions of the oral mucosa (Wraith et al., 1979) as well as abdominal pain.

Where one or a number of foods produces quick onset symptoms skin prick and RASTS responses are usually positive and give helpful information. The total serum IgE is usually elevated (Dannaeus and Johansson, 1979).

One unfortunate aspect of recent times has been the appearance of a number of commercial laboratories offering diagnostic tests for allergy directly to the public. The ability of such laboratories to accurately diagnose nine fish-allergic patients and nine controls who provided specimens of blood and hair for testing was assessed by Sethi et al. (1986). All five laboratories were not only unable to diagnose fish allergy but reported many allergies in apparently non-allergic subjects and also provided inconsistent results on duplicate samples from the same subject. Thus laboratory investigations appear to be most helpful when they are clinically least necessary, as history should give a clear indication of the diagnosis in most cases of quick onset syndromes. Sodium cromoglycate as an oral preparation (Nalcrom, Fisons Ltd.) has been reported to be an effective treatment for some cases of immediate food allergic disease. Symptoms provoked by ingestion of one or more foods may be prevented by sodium cromoglycate if it is taken before taking the food. The literature contains many anecdotal reports of the beneficial effect of this treatment of small numbers of patients at various ages (Freier and Berger, 1973; Watson and Timmins, 1979), but larger studies are still awaited. Scepticism about the value of this drug has been based upon its failure to act on mucosal mast cells in the animal model (Pearce et al., 1982). However, recent evidence that it has an effect on improving abnormal gastrointestinal sugar permeability in patients suggests its mode of action may be other than on the mast cell (Scotto et al., 1987).

In England and Wales there has been a sharp decline in the number of childhood deaths reported to be due to choking on food. The number of deaths from this cause fell from 144 in 1974 to 46 in 1984. This was especially due to a fall in mortality for those under 3 months of age. Roper and David (1987), drawing
attention to this, relate the fall to the change in infant feeding practice, namely that early introduction of solid food should be avoided. This appears to be yet another beneficial consequence of the DHSS Present Day Practice in infant feeding publication which recommended that solids should not be given before the age of 3 months.

Multiple food allergy

Some individuals have gastrointestinal and other symptoms related to a wide variety of foods. Such patients characteristically have a number of immediate
symptoms such as vomiting, urticaria or wheezing upon exposure to multiple foods. They often have an individual and family history of atopy, peripheral eosinophilia, elevated total serum IgE and positive RAST and skin tests to specific foods. Diets involving the elimination of a number of foods may be impractical or ineffective on their own. However, the addition of disodium cromoglycate may be highly effective as in the group of children described by Syme (1979).

The therapeutic dose is empiric at present (Kocoshis and Gryboski, 1979). It is usually 100 mg twice daily. Curiously if oral disodium cromoglycate alleviates symptoms these may not relapse when the drug is discontinued.

These patients need to be distinguished from cases of eosinophilic gastroenteritis.

**Slow onset syndromes**

Whereas quick onset syndromes often present to allergy clinics, by contrast the slow onset syndromes usually present as a gastroenterological problem to paediatric or paediatric gastroenterology clinics. Such children may often have failure to thrive. In these cases there is often no clear history of food being related to the onset of symptoms.

Diagnosis may be difficult. Accurate diagnosis centres upon the following three groups of tests:

- Investigation of gastrointestinal structure, e.g. proximal small intestinal mucosal biopsy.
- Investigation of gastrointestinal function, e.g. intestinal sugar permeability.
- Investigation of immunological function:
  - Systemic, e.g. specific antibody production.
  - Gut associated, e.g. studies of local antibody producing cells.

Once these initial investigations have been performed, dietary elimination and challenge continue to have an important diagnostic role. This approach is of best value when such elimination and challenge is related to gastrointestinal structure and function, i.e. serial observations. At present there are no simple laboratory tests available for diagnostic screening of children with these slow onset gastrointestinal symptoms. In individual patients cows' milk antibody estimation is not diagnostically useful (see Figure 1.1).

In children such problems often overlap with gastrointestinal infection which may coexist thus making diagnosis difficult. Unless full microbiological study of the stools is done, i.e. stool electron microscopy for viruses as well as stool bacterial culture, infection of the gastrointestinal tract can be easily overlooked. Food allergy and infection often coexist.

**Transient food sensitive enteropathies**

Changes in the structure of the small intestinal mucosa in response to the ingestion of particular foods provide clear objective evidence for the existence of food sensitive disorders affecting the small intestinal mucosa. This approach of using serial small intestinal mucosal biopsies related to dietary elimination and challenge was first used for the diagnosis of coeliac disease in the Interlaken or ESPGAN
Diagnostic Criteria (see Chapter 5). Coeliac disease is a state of permanent food sensitivity, but there also exists a group of temporary food sensitive enteropathies, presenting in infancy. Indeed ingestion of a number of foods apart from gluten have now been shown to produce food sensitive enteropathies in infancy.

Pathogenesis

From studies in the experimental animal (MacDonald and Ferguson, 1977; Ferguson, 1980) it seems likely that such enteropathies may result from a type IV or T-cell mediated reaction within the mucosa. In such animal studies a type I reaction in the small gut mucosa is associated with only minimal morphological changes (mast cell degranulation and some oedema), while mucosal type III reactions which are associated with polymorph infiltration do not cause crypt hyperplasia. Of course more than one type of allergic response may coexist within the mucosa at any one time and it is possible, for example, that a type I reaction may precede a type IV reaction.

Abnormalities of the small intestinal mucosa have been reported in children suffering temporary intolerances to cows’ milk protein, soy protein, gluten, eggs, chicken, ground rice and fish. The evidence that the enteropathy is directly related to ingestion of a particular food is based upon serial small intestinal biopsy studies related to dietary elimination and challenge, as in coeliac disease. The enteropathy is not usually as severe as that seen in coeliac disease, although a flat mucosa may occasionally be seen. These disorders usually resolve by the age of 18 months to 2 years.

In some cases the children appear to develop food intolerance after an acute episode of gastroenteritis. The underlying causes of these temporary food intolerances of infancy probably relate to a transient sensitization of the child to dietary antigens, which may be a result of a breach of the mucosal barrier. The precise mechanisms which cause the enteropathy are unclear although the application of the Gell and Coombs classification of hypersensitivity reaction provides a basis for investigation. For the reactions to occur the offending food antigen must enter the mucosa in appropriate amounts to cause sensitization. There are two hypotheses regarding this process: one suggests sensitization caused from an overstimulation of the immune system by excess antigen entry, the other proposes a minimal entry of antigen sufficient to stimulate a reaginic response, which in turn leads to increased antigen entry leading to mucosal damage. In the experimental animal it has been shown that intestinal anaphylaxis can lead to increased uptake of intestinal luminal antigens (Walker et al., 1975). Both hypotheses may be correct. Post-enteritis food sensitive enteropathies may result from excess local food antigen entry in susceptible individuals following gut damage induced by viral or bacterial pathogens. An hypothesis relating acute gastroenteritis and cows’ milk sensitive enteropathy is illustrated in Figure 5.3.

It is known from the observations of Gruskay and Cook (1955) that excess antigen absorption (in their studies egg albumin) occurs in infants with acute gastroenteritis. This has been well documented in animal studies of viral enteritis (Keljo, Butter and Hamilton, 1985). Clinical studies have also shown increased entry of both small molecular weight sugars in acute gastroenteritis (Figure 5.4) (Ford et al., 1985), and a larger molecular weight protein, horse radish peroxidase, in post-enteritis food sensitive enteropathies as observed using organ culture (Jackson, Walker-Smith and Phillips, 1983). Thus direct and indirect evidence
Figure 5.3 Hypothesis: relationship between gastroenteritis and lactose intolerance with cows' milk sensitive enteropathy.

exists that damage to the small intestinal mucosa may result in a local increase in antigen entry. However, most children in whom this happens are not sensitized to food. Thus for this excessive antigen entry to be of pathogenic importance it must occur in susceptible individuals. The nature of such susceptibility remains to be established but clearly relates in part to impaired immunoregulation by the local defence mechanisms in the small intestinal mucosa. The local effect of excess antigen absorption may be also determined by the allergenicity of the antigen entering the mucosa, as suggested by the guinea-pig studies of Coombs and colleagues in Cambridge referred to earlier and supported by the clinical studies of Manuel, Walker-Smith and France (1979). The role of cows' milk sensitive enteropathy as a cause of the post-enteritis syndrome is discussed further in Chapter 6.

It remains yet to be established whether small intestinal mucosal damage due to food ingestion occurs in adults, other than with gluten ingestion in patients with coeliac disease.

Specific syndromes

Cows' milk sensitive enteropathy

Cows' milk proteins
Cows' milk and human breast milk have different protein compositions, as Table 5.2 illustrates. Human milk does not contain beta-lactoglobulin, which represents the major protein in cows' milk whey proteins. Most observers, including Visakorpi and Immonen (1967) and Freier and his colleagues (1969), have noticed that this protein is often the factor responsible for cows' milk allergy, although the other proteins may also be allergenic in children. Cows' milk contains three times more protein than human milk (due to its higher content of casein), but has the same
content of soluble proteins (Table 5.2). It is perhaps unfortunate that proteins in breast milk and cows’ milk such as casein are not distinguished by special names to describe human casein and cows’ casein respectively. Both these proteins, despite the same name, are biologically and chemically (e.g. their amino acid composition) quite distinct.

In modern adapted milks, the so-called ‘humanized’ milks, the total protein content is reduced to about the level of human milk and the proportion of soluble proteins to casein is corrected by the addition of whey proteins (i.e. all the soluble proteins in milk after precipitation of casein either by the action of rennin or by
Table 5.2 Protein content in g 100 ml$^{-1}$ mature milk

| Protein content | Cows' milk | Human milk |
|-----------------|------------|------------|
| Total proteins  | 3.5        | 1.1        |
| Casein          | 2.8        | 0.4        |
| Proteins in lactosérum (when protein) | 0.6–0.8 | 0.7 |
| Beta-lactoglobulin | 0.37 | - |
| Alpha-lactalbumin | 0.18 | 0.35 |
| Immunoglobulins, total* | 0.05 | 0.1–0.15 |
| Other proteins  | 0.13       | 0.1        |

*Pahud, J.J. Thesis, University of Lausanne (1971). Reproduced from Montreuil (1971), by kind permission of author and publishers.

acidification to pH 4.6). Thus these milks contain more beta-lactoglobulin. Despite this there is both clinical and experimental evidence that they are less sensitizing (Walker-Smith, 1986).

The immunoglobulins present in breast milk are chiefly of the IgA class. Table 5.3 indicates the difference in the immunoglobulin composition of breast and cows' milk.

Pathogenesis

There are probably two syndromes, a primary disorder of immunological origin and a secondary disorder, a sequel of mucosal damage. Abnormal handling of dietary antigens across the intestinal mucosa probably occurs in infants with this disorder. This may be related to a temporary immunodeficiency state such as transient IgA deficiency (Taylor et al., 1973), or to non-specific small intestinal mucosal damage from any cause permitting excess antigen entry as referred to above. There is indeed clinical evidence that acute enteritis may be followed by not only lactose intolerance but by more persistent and longer lasting cows' milk sensitive enteropathy (Harrison, Wood and Walker-Smith, 1976; Harrison et al., 1976; Walker-Smith, 1982) (see Chapter 6).

In the experimental animal increased protein antigen uptake occurs when the mucosa is damaged by parasitic infection (Bloch et al., 1979). The pathogenetic role of circulating antibodies to cows' milk remains to be established. Lippard et al. (1936) showed that at whatever age a child first begins to drink cows' milk, cows' milk antigen and then cows' milk antibody can be detected in his blood. Delire, Cambiaso and Masson (1978) have found that neonates fed on cows' milk have in their blood immune complexes containing cows' milk protein antigens, and IgG antibodies of maternal origin. Despite these findings, only a few children go on to develop cows' milk protein intolerance. How such a state of clinical intolerance develops is unknown. Even the presence of a high level of serum anti-milk antibodies is not necessarily associated with damage, e.g. there is a high incidence

Table 5.3 Immunoglobulin content in mg 100 ml$^{-1}$

| Immunoglobulin | Cows' milk | Breast milk |
|----------------|------------|------------|
| IgA            | 100        | 1,735      |
| IgG            | 4          | 150        |
| IgM            | -          | 43         |

Reproduced from Silverman, Roy and Cozzeto (1971), by kind permission of authors and publishers.
Specific syndromes

of elevated titres of cows' milk antibodies in children with both coeliac disease and kwashiorkor (Chandra, 1976) yet, as a rule, these children improve clinically on cows' milk diet.

As stated earlier the local reaction in the small intestine may be mediated via one of the allergic reactions as classified by Gell and Coombs (1968), namely type I, type III, and type IV. Evidence that these three types of reaction may occur in children with cows' milk protein intolerance include the following observations.

First, in relation to type I reaction, elevated titres of IgE antibodies to cows' milk protein, have been observed in some children with enteropathy but are more typical of quick reactors. However, such elevated titres can also be found in milk tolerant children. Positive skin prick tests may be found in milk intolerant children but, again, correlation with symptoms is variable. The involvement of IgE in the immunological response of the lamina propria to milk challenge in children with cows’ milk protein intolerance has been described by Shiner and her colleagues (1975), also by Kilby, Walker-Smith and Wood (1976), who showed an increase in IgE cell numbers in the small intestinal mucosa after a milk challenge in a child with cows’ milk sensitive enteropathy. However, whether IgE mediated small intestinal disease due to sensitized mast cells releasing mediators at the site of reaction between cows’ milk protein, and reaginic IgE antibody fixing to mast cells really occurs, has not yet been proved. If this does happen, disodium cromoglycate may help.

Second, in relation to type III reaction, elevated titres of IgG and IgM milk antibodies have been described in cows’ milk protein intolerance but again with a poor clinical correlation. Increased numbers of IgA cells, but not in general IgM plasma cells after a positive milk challenge, may occur. Matthews and Soothill (1970) have observed the effect of milk feeding on complement activation, and reports of circulating immune complexes in children fed with cows’ milk has already been referred to. Whether such complexes are implicated in the genesis of the mucosal lesion of cows’ milk protein intolerance is unclear.

Third, abnormalities of cell mediated immunity leading to abnormal lymphocyte transformation tests (Fontaine and Navarro, 1975) have been reported. Studies by Macdonald and Ferguson (1977) and Ferguson (1980) in the animal show that type IV hypersensitivity produce an appearance similar to cows’ milk sensitive enteropathy.

The importance of the type I reaction in the gut would be in allowing increased amounts of antigen to cross a damaged mucosa, and by causing capillary dilatation and increased permeability, allowing large amounts of antigen into the systemic circulation to initiate secondary immunization. If this antigen meets tissue fixed IgE on mast cells then type I reaction would occur, e.g. in the skin (rash), in the gut (mucosal damage) and in bronchial mucosa (wheeze). Thus the very variable clinical reactions encountered can be accounted for by differences in antigen reaching IgE on mast cells in different sites in the body.

Involvement of systemic immunity, and the local immune system, could explain the transient nature of the illness. The illness could disappear after a period on a milk-free diet when the small intestinal mucosa local immune system was mature enough to prevent much antigen getting through. The exact role of cell-mediated immunity in this hypothesis is not certain but it is clearly important.

The allergenicity or antigenicity of the cows’ milk formula may be of critical importance in pathogenesis, as clearly most individuals who have acute gastroenteritis associated with increased gut permeability do not become sensitized to food.

Manuel et al. (1981) showed a remarkable difference in the incidence of delayed
recovery between infants fed with different formulae immediately after an acute attack of gastroenteritis. Old formula Pregestimil (high osmolality and based on a casein hydrolysate) and Al 110 (based on casein) and standard SMA (a conventional adapted formula) were compared for infants aged under 6 months. It is likely that delayed recovery in these circumstances is related to cows' milk sensitive enteropathy; 26% of infants fed with the casein formula Al 110 developed delayed recovery compared with only 5% with Pregestimil and the very low figure of 2.5% with SMA. This later figure may have been by chance unusually low. Nevertheless, when these milks are tested in an animal model (guinea-pigs) then similar results are found: Al 110 is sensitizing, Pregestimil not sensitizing at all and SMA sensitizing significantly less often (McLaughlan and Coombs, 1983; Manuel et al., 1979).

Thus adapted feeding formulae appear to be much less sensitizing than the older infant feeding formula still routinely used in much of the developing world. This is consistent with the decline in the severity of cows' milk sensitive enteropathy in societies where such milks are now universally used. Thus the allergenicity of the milk formula fed at the time of an acute attack of gastroenteritis may be a central factor in the development of cows' milk sensitive enteropathy.

**Genetic factors**

Boys and girls appear to be equally affected (Table 5.4). Although an atopic family history is very common, no definite genetic factor has been identified. Kuitunen et al. (1975) have shown an HLA status identical to that of the community. However, Swarbrick, Stokes and Soothill (1979) have shown, in animals, a genetic variation in the control of antigen absorption by the gut, which suggests certain individuals may be predisposed to develop dietary protein intolerance.

**Table 5.4 Mode of presentation of cows' milk sensitive enteropathy**

| Mode of presentation                                      | Number |
|-----------------------------------------------------------|--------|
| Chronic diarrhoea and failure to thrive                    | 10     |
| Failure to thrive without obvious gastrointestinal symptoms| 4      |
| Chronic vomiting and failure to thrive                     | 2      |
| Abdominal distension, constipation and failure to thrive   | 1      |
| Acute vomiting and abdominal distension in infant failing to thrive | 1      |
| **Total**                                                 | **18** |

**Pathology**

In the vast majority of patients with slow onset of symptoms related to cows' milk ingestion the architecture of the proximal small intestinal mucosa is abnormal but the severity of the enteropathy is variable (Kuitunen et al., 1975; Fontaine and Navarro, 1975; Harrison et al., 1976). However, in some early reports the mucosa was flat and indistinguishable from that seen in coeliac disease (Kuitunen et al., 1975). More recently from the same centre in Finland less severe mucosal damage has been characteristic and now very few children are seen in Finland with severe cows' milk sensitive enteropathy (Verkasalo et al., 1981). However, in some early reports the mucosa was flat and indistinguishable from that seen in coeliac disease (Kuitunen et al., 1975). More recently from the same centre in Finland less severe mucosal damage has been characteristic and now very few children are seen in Finland with severe cows' milk sensitive enteropathy (Verkasalo et al., 1981). When present, the enteropathy can be shown to be cows' milk sensitive by serial biopsies related to withdrawal and challenge with cows' milk (Figure 5.5). Unlike the gluten sensitive enteropathy of untreated coeliac disease, this cows' milk sensitive enteropathy is of variable severity on proximal mucosal biopsy, and is patchy in distribution, while a
flat mucosa, indistinguishable from the mucosal appearances found in coeliac disease, may occasionally occur (Figure 5.5).

Typically the mucosa in untreated cows' milk sensitive enteropathy is thin (Maluenda et al., 1984) (Figure 5.6). The pathological changes are often patchy (Manuel et al., 1979). The intra-epithelial lymphocytes count is increased although not to the level found in untreated coeliac disease (Phillips et al., 1979) (Figure 5.7). There is also often a dense accumulation of fat in the epithelium which is a particular feature of this disorder and the post-enteritis syndrome (Variend et al., 1984) (Figure 5.8). The mucosa rapidly returns towards normal or near normal on withdrawal of milk, only to relapse following challenge with cows' milk albeit to a variable and inconsistent degree (Walker-Smith, 1975). However, unlike coeliac disease the mucosa remains thin throughout (Maluenda et al., 1984) (see Figure 5.6) and the intra-epithelial lymphocytes fall to levels below normal on a milk-free diet rising to levels within normal limits after cows' milk challenge (Phillips et al., 1979) (see Figure 5.7).

Cows' milk sensitive enteropathy only affects children less than 3 years of age as a general rule. One remarkable exception is the case report of Watt, Pincott and Harries in 1983 of a child with coeliac disease whose small intestinal mucosa was responsive to cows' milk until at least the age of 7 years.

After a positive milk challenge, alteration in microvilli of the enterocyte may be seen (Figure 5.9) with a reduction in microvillous surface area (Phillips et al., 1980)
Figure 5.6 Diagrammatic representation of thickness of mucosa in cows' milk-sensitive enteropathy.

Figure 5.7 Intra-epithelial lymphocyte counts in relation to a cows' milk challenge, pre- and post-challenge levels indicated.
Figure 5.8 Fat in the mucosa.
Figure 5.9 Electron micrograph of brush border of enterocytes of small intestinal mucosa of child with cows' milk protein intolerance. (1) and (2) on a cows'-milk-free diet: (1) mid-villus region, (2) villus-tip region. (3) and (4) after a positive cows' milk challenge: (3) mid-villus region, (4) villus-tip.
(Reproduced by kind permission of Phillips.)
in parallel with a fall in disaccharidase activity (Figure 5.10). Figure 5.11 shows the relationship between milk challenge and lactose tolerance.

**Clinical features**
The onset of symptoms may be acute with the sudden onset of vomiting and diarrhoea; the diarrhoea persisting and becoming chronic. Alternatively in some infants the onset is insidious and the presentation is very similar to coeliac disease. In fact in most cases in the early reports the onset with acute symptoms commenced before the age of 6 months. In those earlier reports the majority of infants were less than 3 months of age at the onset of symptoms (Harrison *et al.*, 1976; Walker-Smith, Kilby and France, 1978). In the more recent study of Digeon *et al.* (1986) the mean age of onset was 7 months and some patients were over 1 year at the age of presentation. This change may relate to the fact that for the first 6 months of life

![Figure 5.10](image.png)

**Figure 5.10** Mean disaccharidase activity related to cows' milk intake in five infants with cows'-milk-sensitive enteropathy.

![Figure 5.11](image.png)

**Figure 5.11** Relationship between milk challenge and lactose tolerance. (Reproduced from McNeish (1974), by kind permission of author and publishers.)
most infants were fed modern adapted formulae, whereas in the previous reports infants were fed old-fashioned partly modified milks. The onset of symptoms usually occurred at a time when infants were having ordinary pasteurized (door-step) milk. As referred to earlier, it seems likely that modern adapted milks are less sensitizing, and there is both animal model (Coombs and McLaughlin, 1985) and clinical evidence (Manuel and Walker-Smith, 1981) to support this view.

There is usually a latent interval between the introduction of cows' milk and the onset of symptoms. Such an onset may be clinically indistinguishable from acute gastroenteritis. Indeed the illness may begin with acute gastroenteritis and then after return to a cows’ milk feeding the diarrhoea becomes persistent. Lactose intolerance may also be present. Whatever the mode of onset of symptoms most often at the time of diagnosis these infants have chronic diarrhoea and failure to thrive. Cows’ milk sensitive enteropathy is a most important cause of the syndrome of chronic diarrhoea and failure to thrive in infancy. The mode of presentation of 18 infants at time of diagnosis seen at Queen Elizabeth Hospital for Children is illustrated in Table 5.4.

Cows’ milk protein intolerance may also be associated with protein losing enteropathy and with iron deficiency anaemia due to intestinal blood loss (either occult or overt). This is related to an endoscopic colitis, which is not discussed here (Gryboski, 1967; Jenkins et al., 1984). Usually cows’ milk sensitive enteropathy and cows’ milk induced colitis do not coexist in the same patient.

Cows’ milk protein intolerance has also been described as producing severe gastritis with antral erosions accompanied in some cases by duodenitis, diagnosis being made by upper endoscopy. These infants presented between 2 and 4 months with vomiting and failure to thrive as the principal symptoms. All had hypochromic anaemia and occult faecal blood, responded favourably to cows'-milk-free diet, and relapsed on milk challenge. Neither small intestinal biopsy nor colonoscopy was performed so the state of the rest of the gastrointestinal tract in these infants remains unknown (Coello-Ramirez and Larrosa-Haro, 1984).

**Diagnostic criteria**

Until recently, the only satisfactory way to make the diagnosis of cows’ milk protein intolerance has been based purely on clinical observations of repeated withdrawal of milk and challenge with milk, associated with clinical remission and relapse as formulated by Goldman and colleagues in 1963, and since spoken of as the Goldman criteria (Table 5.5).

These criteria have obvious drawbacks. Most mothers are reluctant to submit their infants to three potentially hazardous challenges, especially after one positive challenge. Diagnosis of clinical relapse can be misleading, e.g. intercurrent illness may cause vomiting and diarrhoea and lead to error in interpretation. It is also now clear that children may take longer than 48 hours to relapse after a milk challenge. Finally, positive challenges do not always have a similar onset, duration and clinical features

| Table 5.5 Goldman criteria |
|-----------------------------|
| 1. Symptoms subside following dietary elimination of milk |
| 2. Symptoms recur within 48 hours after milk challenge |
| 3. Reactions to three such challenges must be positive and have similar onset, duration and clinical features |
features. The use of these rigorous criteria has probably led to under-diagnosis of this syndrome.

Serial small intestinal biopsies taken first at the time of initial presentation, and second after the return of symptoms following a milk challenge, now permit a firm diagnosis to be made on the basis of one diagnostic milk challenge.

Because of its transient nature it may be difficult to fulfil all the diagnostic criteria for cows' milk sensitive enteropathy. Nevertheless, accurate diagnosis is important. It is important to exclude an infective cause of the enteropathy in any infant with chronic diarrhoea. As with all dietary protein intolerances, diagnosis is based upon the response to withdrawal and subsequent reintroduction of the offending protein. There is no specific laboratory test apart from serial biopsy related to elimination and challenge. The first stage in making the diagnosis is the suspicion that the child's symptoms relate to milk ingestion. If the small intestinal mucosa is shown to be abnormal on biopsy the finding of a patchy enteropathy with a thin mucosa in a cows' milk fed infant, when the infant responds rapidly to a cows' milk elimination diet provides firm presumptive evidence for this diagnosis. Such children may then be described as having a milk elimination responsive enteropathy. The transient nature of this disorder as well as the desire to avoid early milk challenge (because of the potential risk of acute anaphylaxis) (de Peyer and Walker-Smith, 1979) leads in practice to a late milk challenge at the age of 9 months to 1 year or even later. These children may then no longer be milk intolerant at the time of milk challenge (i.e. at the age of 9–12 months). Milk provocation in such circumstances merely establishes the safe return of cows' milk into the diet. It does not confirm the diagnosis of a cows' milk sensitive enteropathy which must remain forever unproven, at least on present-day diagnostic criteria.

Technique of cows' milk challenge

It is important that a challenge with cows' milk should be carried out in hospital so that it may be critically evaluated and because of the occasional risk of an acute anaphylactic reaction. The infant who is having a milk-free diet (almost the same as a lactose-free diet) is admitted to hospital. First, he has a control pre-challenge small intestinal biopsy to show that his mucosa has returned to normal or near normal. If it has not improved, challenge should be deferred and the diagnosis reconsidered, the diet being carefully checked. In these circumstances if the child is truly on a milk-free diet but continues to have gluten in his diet coeliac disease must be considered.

When the mucosa has been shown on biopsy to have healed, the following day an oral lactose load of 2 g lactose/kg is given. This is followed by a lactose mixture containing 7% lactose for 24 hours. During this period the infant should be observed carefully and any loose stools tested for reducing substances. If watery diarrhoea with excess reducing substances occurs, the infant is clearly lactose intolerant and goes back to his milk-free diet, and milk challenge is deferred. If there is no diarrhoea the milk challenge takes place the next day. The amount given in the challenge will depend upon the previous severity of symptoms. If the history suggests the possibility of a previous anaphylactic reaction an intravenous infusion should be set up before the challenge and the initial amount of milk given should be small; for example 0.2 ml. If there has been a previous anaphylactic reaction before challenge, resuscitation equipment should be ready, and 1:10 000 adrenaline 0.1 ml kg⁻¹ for injection, hydrocortisone 100 mg for intravenous use, intramuscular chlorpheniramine (Piriton) 2.5 mg for intravenous use, plasma infusion,
oxygen and equipment for intubation. All children who have had a previous anaphylactic reaction should be admitted to hospital. It is suggested that at least a year should elapse before reintroduction is attempted.

In clinical practice an anaphylactic reaction may be defined as collapse, hypotension, impairment of consciousness or significant upper airway obstruction (swelling of structures in mouth or throat). When this has occurred previously the following method is used to determine if the child is still allergic. A drop of full-strength cows' milk is placed on the skin of the forearm. If no skin reaction occurs, cautiously administer 1 ml of a 1 in 20 dilution of milk or 15 ml teaspoon on the tongue. If a reaction such as swelling, itching, redness or pain occurs, no further milk is given. If no reaction occurs within 20 minutes, 1 ml full-strength milk may be given.

In most children who have no history of previous reaction, 5 ml of milk should be given, followed after an hour by a further 10 ml if no symptoms occur. If this is tolerated the child is then regraded in quarters back onto cows' milk or his normal milk feeding. Should symptoms recur, such as vomiting and diarrhoea, evidence of an intercurrent infection, e.g. hospital acquired rotavirus gastroenteritis, should be sought, i.e. stools should be sent for rapid viral diagnosis. If viral gastroenteritis is excluded, it is only a biopsy that can establish whether a relapse has occurred and should be done as soon as possible. If the previously normal mucosa is now abnormal, then this is regarded as a positive challenge, i.e. a cows' milk sensitive enteropathy has been shown and a firm diagnosis of cows' milk protein intolerance is made. If the mucosa is still normal, he continues on milk, and other causes for the symptoms are sought, such as an intercurrent illness, e.g. urinary tract infection or other infection. An occasional child may clinically relapse after a milk challenge despite a normal biopsy in the absence of any other explanation. This poses a difficult problem in diagnosis and may be due to patchiness of the cows' milk sensitive enteropathy. The symptoms that occur after challenge vary considerably and range from an alarming anaphylactic reaction that comes on rapidly after the child has ingested cows' milk, to the development of diarrhoea, with stools obviously blood-stained 24 or more hours after exposure to milk protein (Table 5.6). Vomiting is usually a striking symptom and is often the first to appear.

However, there is still no unanimity concerning the diagnostic criteria for cows' milk protein intolerance; for example, there is no consensus as to how a milk challenge should be performed; some use whole milk for the challenge and others use milk protein fractions such as lactoglobulin.

### Table 5.6 Clinical features of a positive milk challenge in 30 children at the Queen Elizabeth Hospital for Children

| Feature                          | No. tested | No. positive |
|---------------------------------|------------|-------------|
| Diarrhoea                       | 30         | 30          |
| Vomiting                        | 30         | 30          |
| Occult blood in stools          | 25         | 24          |
| Weight loss > 300 g in 24 hours | 30         | 27          |
| Rise in T° to 38°C.             | 29         | 21          |
| Rise in eosinophilis > 450 × 10/dl | 30     | 28          |
| Rash/urticaria                  | 30         | 9           |
| Wheezing                        | 30         | 3           |
| Anaphylaxis                     | 30         | 3           |

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Goldman and his colleagues in 1963 reported investigations of 89 children with cows’ milk protein intolerance and found the following frequencies of reactions to challenge with various milk protein fractions: beta-lactoglobulin, 66%; casein, 57%; alpha-lactalbumin, 54%; bovine serum albumin, 51%. In addition to the above challenge procedure, related to small intestinal biopsy, various laboratory tests have been studied to help to diagnose cows’ milk protein intolerance. Anderson and Schloss in the USA in 1923 found antibodies to cows’ milk protein in the serum of infants exposed to cows’ milk. Since then the occurrence of circulating milk precipitins in the serum of children has been reported in a wide variety of disorders, including chronic respiratory disease and IgA deficiency. However, most authorities believe that the presence of circulating milk antibodies cannot be correlated with clinical intolerance to this protein. A good example of this is provided by some children with coeliac disease who still have cows’ milk antibodies in their sera whilst in remission on a gluten-free diet with no symptoms related to milk ingestion.

Some observers, e.g. Matthews and Soothill (1970), have studied complement activation after milk challenge. Five children with gastrointestinal symptoms due to milk protein intolerance had evidence of complement activation after milk challenge with 5 ml of milk. However, assay of complement activity after milk challenge has not been adopted as a useful laboratory confirmation of the diagnosis of cows’ milk allergy.

However, the above authors were not considering cows’ milk sensitive enteropathy specifically but were looking at cows’ milk allergy as a whole.

**Relationship to lactose intolerance**

It may not be possible to distinguish cows’ milk sensitivity from lactose malabsorption at the time of initial presentation as both cows’ milk sensitive enteropathy and lactose intolerance may coexist. However, when a child is on a cows’ milk-free diet it is possible by cows’ milk challenge to make the distinction. In a classic paper, Liu, Tsao and Moore, in 1967, showed that challenge with cows’ milk protein could induce intestinal malabsorption of lactose in children who were intolerant to cows’ milk protein. It is now clear that lactase deficiency with secondary lactose intolerance may be produced by cows’ milk challenge in children who have cows’ milk sensitive enteropathy, particularly when this has occurred as a sequel to acute gastroenteritis. This secondary lactase deficiency is a consequence of mucosal damage produced by cows’ milk protein *per se* (see Figure 5.1) (Harrison, 1974; Harrison et al., 1976).

While it may be impossible at the time of initial presentation to make the differential diagnosis, at the time of milk challenge it is practicable and important that the distinction should be made.

**Management**

The therapy for this disorder is to eliminate cows’ milk from the child’s diet and also all foods based upon cows’ milk. This latter point is most important as dietetic failure may sometimes relate to neglect of restriction of foods such as ice-cream, which are based on cows’ milk, despite strict adherence to avoidance of cows’ milk *per se*.

Treatment involves substituting cows’ milk feeds with the commercially available
cows’ milk protein-free formulae (Francis, 1987). In practice five categories of cows’ milk substitutes have been used, namely those based on:

- **Casein hydrolysate**, Pregestimil, and for infants over 6 months, Nutramigen.
- **Lactalbumin hydrolysate**, Alfare.
- **Soya protein** (Cow and Gate formula S, Prosobee, Wysoy).
- A formula based upon comminuted chicken which requires supplements with the complete range of vitamins and minerals.
- **Boiled goats’ milk** for children over 6 months plus vitamins A, D, C, B₁₂ and folic acid tablets (these contain lactose).

As children may become sensitized both to soy and goats’ milk feeds, the author prefers a hydrolysate formulation in most circumstances, with the occasional use of comminuted chicken formulae. This is used when the child is intolerant to one of the hydrolysates. A casein hydrolysate has most often been used but there are some children who are intolerant to it. This sometimes is due to glucose polymer intolerance (see Chapter 7). In a study comparing a casein hydrolysate and a whey hydrolysate, whilst both were effective, weight gain and healing of the mucosa was better in some cases fed a whey hydrolysate. However, the latter formula was more unpalatable (Walker-Smith, 1985; Walker-Smith, Digeon and Phillips, 1987).

Only those formulae that are nutritionally complete (if necessary with vitamin supplementation) are to be recommended. Those with a low osmolality should be chosen for young infants or infants with small intestinal disease. It is important to ensure that both liquid and solid feeds are free of cows’ milk proteins. Lactose intolerance may accompany the protein intolerance, and in such circumstances lactose should also be withdrawn from the diet. The necessity for dietary treatment is always temporary, and reintroduction of a normal diet is normally nearly always possible between the age of 1 and 2 years. This may be done in the home, but a history of previous severe reactions, such as urticaria or anaphylactoid shock, is an absolute indication for reintroduction of a normal diet under very close medical supervision usually in hospital. When a repeat biopsy is done to assess mucosal healing before challenge, clearly this will be done in hospital, which the author recommends on most occasions. Usually this shows significant improvement. Because of the risk of anaphylaxis milk challenge is usually delayed to the age of 9–12 months.

**Soy protein intolerance (soy sensitive enteropathy)**

Soy bean was first proposed as a substitute for cows’ milk in infants by Ruhrah in 1909. However, it was not until the recommendation by Hill and Stuart in 1929 that a soy bean food prepared to resemble milk began to be used in many countries for infants with milk allergy. Glaser and Johnstone went on in 1953 to suggest that soy bean milk when used as a substitute for cows’ milk could play an important role in the prevention of allergy to cows' milk in those who were at risk. Soy bean is rich both in protein (40%) and fat (20%). It belongs to the leguminaceae family as does the pea. It is principally produced in the USA.

**Soy bean formulae**

There were some difficulties with the first-generation soy formulae. These included carbohydrate intolerance because of indigestible carbohydrates and vitamin deficiencies. From the mid-1960s second-generation soy bean formulae have been
used, based on a soy-protein isolate. The commercial formulae available in Britain—Formula S, Isomil, Prosobee and Wysoy—are based on soy protein isolate. Soy beans contain trypsin inhibitors, and in the experimental animal soy bean diets may cause growth retardation, pancreatic hypertrophy and even adeno-carcinoma (McGuiness et al., 1980). None of these serious effects has been described in infants probably because heat-labile trypsins inhibitors are inactivated in the manufacture of the formulae. However, the Kunitz soy bean trypsin inhibitor has been reported to be the antigenic stimulant for an acute anaphylactic reaction in an adult woman (Moroz and Yang, 1980).

Some problems with the second-generation formulae do remain. Amongst these are mineral bioavailability. This is probably due to its 1% phytate content and there is a report of its use exacerbating acrodermatitis enteropathica (Glasgow and Elmes, 1975).

One other immunological concern about the use of soy formulae is the report from Verona that healthy non-atopic infants fed soy formulae have lower immunoglobulin levels and more infections than do similar infants fed cows’ milk (Zoppi et al., 1979, 1983).

Soy protein
The globulin fraction of soy beans is the major protein component. It consists of four main components (Shibaski et al., 1980). The 2S globulin has the highest allergenic potency. Heat treatment increases this potency. Haemagglutinating titres to heat treated soy were higher when injected into rabbits than crude soy powder extract (Eastham et al., 1982). This is in contrast to cows’ milk formulae which became less antigenic after heat treatment (McLaughlin et al., 1981).

Antigenicity of soy protein
Soy-based formulae have been shown to be at least as antigenic as milk-based formulae in a study by Eastham et al. (1978, 1982). Circulating antibodies developed rapidly for up to 3 months with little further rise in normal infants fed these formulae. High levels of haemagglutinating antibody have been shown in amniotic fluid, suggesting in-utero sensitization (Kuruome et al., 1976).

Although it has been shown that soy bean has low antigenicity in guinea-pig studies (Ratner and Crawford, 1955), over recent years there has been an increasing number of clinical reports of intolerance to soy protein. Such reactions have varied from a dramatic anaphylactic response, the onset of respiratory symptoms and the appearance of gastrointestinal symptoms. These observations are in accord with the concept that soy protein is in fact not a weak antigen in man.

The first report of soy allergy was as long ago as 1934 (Duke). Acute anaphylaxis has been described in infancy (David, 1984). It has been shown that soy protein can produce a small intestinal enteropathy which resolves with soy elimination and which reappears when soy protein is reintroduced into the diet, i.e. a soy-sensitive enteropathy (Ament and Rubin, 1972). These workers described a flat mucosal lesion indistinguishable to that found in coeliac disease. This observation has been confirmed by others, but more usually the small intestinal damage is less severe and is similar to cows’ milk sensitive enteropathy (Perkkio et al., 1981).

As with cows’ milk protein intolerance the colon may also be affected and there are reports both of enterocolitis (McDonald et al., 1984) and colitis (Halpin et al., 1977).
**Pathogenesis**

Soy formulae have been recommended in three situations:

- When the small intestinal mucosa is normal as a prophylaxis against cows’ milk allergy.
- In those already who are cows’ milk protein intolerant, some of whom may have small intestinal mucosal damage.
- For the management of gastroenteritis by virtue of the formulae being lactose free. Here too the small intestinal mucosa is likely to be abnormal.

It is particularly in these last two situations when the mucosa is already damaged that the use of soy formulae may lead to intolerance by sensitizing the mucosa to this protein. There is clear evidence that the incidence of soy protein intolerance is lower when used for prophylaxis than as treatment for cows’ milk allergy (0.5% versus 15–50% or even higher). The very high figure of 80% reported by Wong in 1965 (Wong, 1985) for children with severe cows’ milk protein intolerance contrasts to the figure of 11% reported by Kuitunen et al. referred to earlier. However, the former report concerned first-generation isolate. In between is the figure of 15% reported by Perkkio, Savilahti and Kuitunen (1981) who described 16 cases of soy intolerance from 108 children with cows’ milk sensitive enteropathy treated with soy formula. It is because of such data that the author recommends a protein hydrolysate rather than a soy formula for the management of children with cows’ milk sensitive enteropathy.

The pathogenesis of soy protein intolerance is probably very similar to that of cows’ milk sensitive enteropathy. It frequently appears to occur as its sequel. Butler et al. (1981) studied neutrophil chemotaxis and neutrophil random migration in infants with milk and/or soy protein intolerance. Chemotaxis is the ability of certain cells to move or to turn towards other cells or substances that exert a chemical influence (positive chemotaxis) or away from them (negative chemotaxis). All infants showed a significant decrease in chemotaxis at a time when the disease was active. However, this depression did not relate to the severity of the protein intolerance as judged by symptoms or the nutritional status. Random migration of neutrophils was increased in patients with active protein intolerance as compared with controls. The relationship of this observation to pathogenesis is unclear at present.

**Clinical features**

Kuitunen et al. (1975) who described the clinical findings in 54 children with cows’ milk intolerance reported that 35 of these children were given soya protein as a cows’ milk substitute. Four of these developed soya protein intolerance. The symptoms were vomiting, diarrhoea and weight loss. Three had partial villous atrophy on biopsy and the fourth had a flat mucosa. It is clear that soy sensitive enteropathy may occur as a sequel to cows’ milk sensitive enteropathy.

**Management**

Treatment is with a protein hydrolysate formula such as Pregestimil. Strict avoidance of soy may be difficult as so many modern prepared foods contain some soy. Like cows’ milk protein intolerance, the need for dietary avoidance is temporary.
Transient gluten intolerance (transient gluten sensitive enteropathy)

Definition
Transient gluten intolerance may be defined as the syndrome seen when a child with gastrointestinal symptoms and an abnormal small intestinal mucosa who responds clinically and histologically to a gluten-free diet, subsequently thrives and continues to have a normal mucosa despite returning to a normal gluten-containing diet.

Dicke in Holland, in 1952, described a transient wheat sensitivity in pre-school children following gastroenteritis. Visakorpi and Immonen in Finland, in 1967, described a state of transient gluten intolerance in 28 children associated in some cases with temporary cows' milk protein intolerance. These reports did not include serial small intestinal biopsies. In 1970, a child with transient gluten intolerance was described in Australia, and this report included such biopsies (Walker-Smith, 1970). This child had an abnormal small intestinal mucosa (a severe degree of partial villous atrophy) and he responded clinically to a gluten-free diet. After 1 year, while he was still on a gluten-free diet, a further biopsy revealed a normal mucosa. He was put back onto a normal gluten-containing diet, and 16 months later a further biopsy demonstrated a persistently normal mucosa. He has subsequently remained in excellent health.

Diagnostic criteria
Despite these case reports there has been considerable scepticism expressed that transient gluten intolerance does actually exist. In particular scepticism has been expressed as to whether those children reported to have had transient gluten intolerance had really been gluten intolerant ab initio.

Hence stricter criteria were laid down for diagnosis. These were first, the need to provide evidence that gluten toxicity was in fact present and that the apparent clinical response to gluten restriction was not fortuitous and second, the need to demonstrate the presence of a normal small intestinal mucosa 2 years or more after the return to a normal diet (i.e. the 2 years rule) as laid down by the European Society for Paediatric Gastroenterology in Interlaken in 1970 to exclude coeliac disease (see Chapter 4) (Meeuwisse, 1970). The precise criteria necessary to establish the existence of any form of transient intolerance to a dietary substance are indicated in diagrammatic form in Figure 5.12. McNeish et al. (1976), in fact, have demonstrated such early evidence of gluten toxicity by serial xylose absorption studies at the time of an early gluten challenge in an infant with an enteropathy who had previously responded to a gluten-free diet. Serial biopsies were not used to establish gluten toxicity at that time in their infant, but the mucosa has been shown to be normal 2 years after return to a normal gluten-containing diet. At the Queen Elizabeth Hospital, a child has been observed who completely fulfils both the ESPGAN and McNeish criteria for the diagnosis of transient gluten intolerance (see Table 5.8) (Walker-Smith and Phillips, 1979). This child had an early gluten challenge at age of 1 year 2 months, having previously had a flat mucosa and a clinical response to a gluten-free diet. She relapsed clinically and histologically with gluten. Subsequently, after a second challenge with gluten, she has remained clinically well and her mucosa 2 years 3 months after return to a normal gluten-containing diet has remained normal. She has now left the paediatric age group symptom free. It thus seems clear that this child had transient gluten intolerance from which she has now recovered (see Table 5.7).
Figure 5.12 Diagrammatic representation of diagnostic criteria for transient gluten intolerance. (Reproduced from McNeish (1974), by kind permission of author and publishers.)

Thus application of these very strict criteria has established evidence that transient gluten intolerance does in fact exist in this very small number of patients.

In routine clinical practice these criteria are impossible to fulfil as early gluten challenge is no longer performed. Thus the diagnosis of transient gluten intolerance is usually retrospective and presumptive, i.e. a child provisionally diagnosed as coeliac disease fails to relapse clinically and histologically after 2 years or more back on a gluten-containing diet. Thus the child fails to fulfil the ESPGAN criteria for the diagnosis of coeliac disease (see Chapter 4). Thus in current clinical practice the term transient gluten intolerance is reserved for the small group of children provisionally diagnosed as coeliac disease who fail to relapse after 2 years or more back on a gluten-containing diet. This retrospective diagnosis is then based upon the following diagnostic criteria.

- Initial illness associated with a severe small intestinal enteropathy.
- Complete clinical remission on a gluten-free diet.
Specific syndromes

Table 5.7 Features of child with transient gluten intolerance

| Age          | Small intestinal biopsy grading | Diet                              | Intra-epithelial lymphocyte count | Symptoms                      |
|--------------|--------------------------------|----------------------------------|----------------------------------|-------------------------------|
| 6 months     | +++                             | Gluten started 2½ months of age   | 51.8                             | Severe diarrhoea and vomiting |
| 1 yr 2 months| N                               | Gluten-free                      | 16.8                             | Symptom free                  |
| 1 yr 5 months| +++                             | Gluten 10 g powder daily for 3 months | 48.2                             | Anorexia, Irritability        |
| 4 yr 7 months| ±                               | Gluten-free daily for 3 months   | 21.7                             | Symptom free                  |
| 4 yr 10 months| ±                             | Gluten 5 g in diet daily for 3 months | 35.0                             | Symptom free                  |
| 6 yr 9 months| N                               | Gluten 5–10 g in diet, daily for 2 years 2 months | 25.9                             | Symptom free                  |

N = Normal.

- Healing of the enteropathy on a gluten-free diet.
- Normal intestinal mucosa 2 years or more after return to a gluten-containing diet (the 'Two Years Rule').

Validity of the 'Two Years Rule'

In a review of the ESPGAN criteria, McNeish et al. in 1979 commented upon the paucity of published evidence, at that time, to endorse the concept that all coeliac children relapse within 2 years of gluten challenge and therefore that patients not relapsing after this time had transient gluten intolerance.

In fact the literature is now more extensive. Several published studies of gluten challenge in children have established that relapse most often occurs within 2 years. There are, however, a few reports to suggest that it may take more than 2 years for a relapse in some exceptional cases of coeliac disease.

McNicholl et al. (1974) described two children who took more than 2 years to relapse after return to a normal gluten-containing diet. Only one case has had the full clinical details published (Egan-Mitchell, Fottrell and McNicholl, 1978). In that case the intra-epithelial lymphocyte count rose and disaccharidase activities fell before frank mucosal relapse. A survey by the European Society of Paediatric Gastroenterology and Nutrition suggested that others had a similar experience (Shmerling, 1978).

In a study of 65 children, originally diagnosed as having coeliac disease, at the Queen Elizabeth Hospital (see Chapter 4), 15 proved on reinvestigation to have a normal mucosa 2 or more years after having gluten in their diet (Walker-Smith, Kilby and France, 1978). Nine of these had a documented abnormal initial biopsy at the time of the original presentation on a normal gluten-containing diet. They responded clinically to a gluten-free diet, but despite this they had a final biopsy which was normal or near normal after 2 or more years on a gluten-containing diet. All have now left the paediatric age group symptom free. Figure 5.13 demonstrates the histological findings in one of these children.

Seven of these children had serial disaccharidase assay after start of challenge. On two occasions, disaccharidase activity fell despite normal morphology as reported in such children by McNicholl, Egan-Mitchel and Fottrell (1974).
Their ages ranged from 8 weeks to 1 year 5 months at the time of the initial biopsy, i.e. all were less than 2 years of age at that time. A critical review of the early history in three children reveals evidence of a preceding episode of acute enteritis and evidence of other food intolerances, e.g. cows' milk protein intolerance, but in the remainder there was no such evidence (Table 5.8).

Within this group there were some children who met all the classical criteria for the initial diagnosis of coeliac disease as they had a completely flat mucosa (Figure 5.13) and evidence of malabsorption, and responded dramatically to a gluten-free diet alone without any evidence of other food intolerances. It is impossible now to convince the mothers of these children that a gluten-free diet at that time did not account for their clinical improvement. Figure 5.14 shows the weight progress over the years of one of these children.

These cases with two others making a total of 11 were further reviewed (Walker-Smith, 1987). This represents the total number of children diagnosed at Queen Elizabeth Hospital between 1972 and 1986. They have now been followed up for a period of 8–10 years in most cases but in one for 20 years. Many of these children had gluten introduced into their diet at an early age as did children with coeliac disease diagnosed at the same time. All had normal biopsies 2 years or more after a return to a normal gluten containing diet. Four had further biopsies. One was abnormal and thus this child has coeliac disease. He had in fact been symptom free, the indication for biopsy being the development of serum gliadin antibodies.

Nusslé et al. (1978) have described a similar group of six children, initially diagnosed as having coeliac disease, who have had a normal small intestinal mucosa 2½-4½ years after reintroduction of gluten to their diet. All had normal IEL levels, and all except one, normal disaccharidases. Thus, again, these children appear to have had transient gluten intolerance from which they have recovered. Schmitz, Jos and Rey (1978), from Paris, in a very important paper have described three children who had earlier responded to a gluten-free diet but who then developed flat mucosa on a gluten-containing diet at the ages of 10 years, 6½ years and 4 years 8 months respectively. However, they did not return to a gluten-free diet but continued on a gluten-containing diet. Further biopsies after more than 9 years, 12 years and 5 years respectively on a normal gluten containing diet, showed surprisingly normal or near normal mucosae. The third case was having a low gluten intake but had relapsed earlier on a similar low gluten diet. Thus these three children appear to have recovered spontaneously on a gluten-containing diet. A

Table 5.8 Nine children with negative gluten challenge

| Patient | Age at initial biopsy | Sex | Histology | Duration of follow-up on normal diet | Final diagnosis               |
|---------|-----------------------|-----|-----------|-------------------------------------|-------------------------------|
| D.B.    | 8 wks                 | M   | PVA       | 5 yr                                | Post-enteritis enteropathy    |
| M.M.    | 0 wks                 | M   | Flat      | 5 yr                                | Non-coeliac enteropathy       |
| S.S.    | 3 months              | M   | Flat      | 6 yr                                | Non-coeliac enteropathy       |
| T.D.    | 4 months              | F   | Flat      | 5 yr                                | Non-coeliac enteropathy       |
| L.S.    | 4 months              | M   | PVA       | 5 yr                                | Post-enteritis enteropathy    |
| T.J.    | 5 months              | M   | Flat      | 5 yr                                | Post-enteritis enteropathy    |
| A.K.    | 1 yr                  | M   | Flat      | 6 yr                                | Non-coeliac enteropathy       |
| P.M.    | 1 yr 5 months         | F   | Flat      | 6 yr                                | Non-coeliac enteropathy       |

PVA = Partial villous atrophy.
Further seven children have since been described (Schmitz et al., 1984). The author would regard this as good evidence that these children had transient gluten intolerance which was longer lasting than other children described from which they had recovered, but Schmitz, Jos and Rey have raised the possibility that the mucosal lesion of coeliac disease may disappear during adolescence only to reappear in adulthood.

Further prospective studies will establish whether this is so. It must be acknowledged that the ages of the cases described by Schmitz et al. are clearly different to those reported by Walker-Smith et al. (1975) and Nusslé et al. (1978) as they are
Figure 5.14 Serial weight measurements related to dietary gluten and small intestinal biopsies in a child with non-coeliac enteropathy and presumed transient gluten intolerance.

much older than those cases which were all under 2 years at time of initial diagnosis.

Further evidence comes from the study of Shmerling and Franckx (1986) who described three patterns of response after a gluten challenge:

- A group of 24 coeliac patients who fulfilled the ESPGAN criteria; 21 relapsed within 2 years of commencement of the gluten-challenge. Three took up to nearly 5 years to relapse.
- Six children who after a gluten challenge of 2.42–6.92 years have not relapsed. These children are being followed carefully and would appear to have had transient gluten intolerance.
- A group of 11 children whose mucosa after gluten challenge deteriorated without becoming flat. All were symptom-free and have continued on gluten. They resemble the cases described by Schmitz et al. Likewise their future is uncertain.

Thus the 2-year rule appears to be valid for the majority of children with coeliac disease who have a gluten challenge although there are occasional exceptions. Thus most children previously diagnosed on firm criteria as suffering from coeliac disease but who fail to relapse by 2 years after a return to a gluten-containing diet can be provisionally labelled as transient gluten intolerance. In each individual child, however, follow-up must be close in order to detect the occasional child who
eventually has a late relapse and thus proves in the end to have coeliac disease, i.e. permanent gluten intolerance. From all these studies it is clear that there is thus a particular need for detailed and long-term follow-up into adult life of these children retrospectively diagnosed as transient gluten intolerance.

It is therefore difficult to regard the diagnosis of transient gluten intolerance in our present state of knowledge as ever being any more than provisional and it cannot be regarded as final. It remains possible that any or all of the children referred to above ultimately may relapse after many years in adult life. Similar uncertainty must remain concerning the fate of the children described by Schmitz et al. and Shmerling and Franckx. A schematic model of the present scene is outlined in Figure 5.15.

Pathogenesis
Two explanations have been proposed to explain the development of this syndrome. Firstly, it has been suggested that there may be a temporary depression of dipeptidase activity occurring in the small intestinal mucosa, secondary to non-specific mucosal damage, such as may occur as a sequel to gastroenteritis. Such a suggestion at present is only speculative and is based on reports of this syndrome following clinical episodes of gastroenteritis where there has been the demonstration of an abnormal small intestinal mucosa on biopsy. Secondly, it is possible that a transient ‘allergy’ to gluten may occur in a similar and equally unknown
manner to that suggested earlier in this chapter in relation to cows’ milk protein. There is little evidence available so far to support either theory.

All the cases described by Walker-Smith 1985 had gluten introduced very early in to their diet (under 2 months). This may account for the fact that no new case has been diagnosed at Queen Elizabeth Hospital presenting since 1974. From 1975 mothers have been encouraged in Britain to introduce gluten at a later time and to use rice rather than wheat cereal as a weaning food. Thus the early age of introduction of gluten into the diet of these children may be an important factor in the pathogenesis of transient gluten intolerance and could account for its importance in the early 1970s.

Pathology
The small intestinal mucosa is by definition abnormal, i.e. thickened ridged mucosa characterized histologically by partial villous atrophy, or sometimes a flat mucosa. The demonstration of a flat mucosa, however, should not ordinarily suggest this diagnosis, as it is more characteristic of coeliac disease. The mucosal abnormality is therefore typically less severe than that found in coeliac disease.

In the child referred to in Table 5.9 it is notable that there was an increase in the intra-epithelial lymphocyte count in the initial diagnostic biopsy, a fall in the count after a gluten-free diet, followed by a rise on mucosal relapse following a gluten challenge and, finally, a return to normal level which has remained normal on a gluten-containing diet. Thus at the time when the child was gluten sensitive, the intra-epithelial lymphocyte count appeared to be as responsive to gluten in the diet as in children with coeliac disease (i.e. permanent gluten intolerance).

Differential diagnosis
Transient gluten intolerance should be considered as part of the differential diagnosis of the infant who develops gastrointestinal symptoms when he first encounters wheat protein, especially when he appears to be intolerant to other food proteins such as milk and egg. It should also be considered as a possibility in a child who fails to thrive following gastroenteritis, e.g. salmonellosis (Walker-Smith, 1970) in the presence of an abnormal small intestinal mucosa and the absence of other explanations, such as secondary lactose intolerance, particularly when such an infant has not responded to several other dietary measures but is having cereal in his diet.

There appear to be two clinical syndromes associated with transient gluten intolerance: first, when gluten intolerance accompanies other forms of food intolerance; and secondly, when there is gluten intolerance alone producing a clinical picture identical with coeliac disease (Walker-Smith, Kilby and France, 1978; Nussle et al., 1978). Gliadin antibodies may be detected in the serum of such children even though their mucosa is now normal.

| Age              | Diet | Histology | Lactase | IEL |
|------------------|------|-----------|---------|-----|
| 3 months         | G    | ++        | 0.5     | 81  |
| 3 yr 1 month     | GF   | N         | —       | 31  |
| 4 yr             | G    | N         | 8.1     | 32  |
| 5 yr 3 months    | G    | N         | 2.6     | 29  |
| 7 yr 4 months    | G    | +         | 3.3     | 48  |
Management
The dietary management is identical with that prescribed for children with coeliac disease but the need for such dietary restriction is, of course, by definition, a temporary one. The duration of the need for such dietary restriction will vary from child to child.

Clearly, at present this is a confusing field and in need of much clarification. It has been discussed here at some length, not because of the intrinsic importance of transient gluten intolerance itself, but rather because of the importance of distinguishing the condition from coeliac disease. If it were not for the existence of a permanent gluten intolerance this disorder would be looked upon much the same as cows' milk and soy intolerance.

Finally, it is most important that those children diagnosed as transient gluten intolerant, but who have completely recovered, should have long-term follow-up. These children could eventually relapse. It is the author's practice to follow-up such children throughout their childhood and then refer them to adult gastroenterologists for indefinite follow-up.

Other food sensitive enteropathies
It has now been established by serial biopsy and dietary elimination and challenge that egg protein (Iyngkaran, 1982), ground rice, chicken meat and fish (Vitoria et al., 1982) may all temporarily damage the small intestinal mucosa in infancy. In this latter study all infants also were cows' milk intolerant and were under the age of 6 months at the time of diagnosis. These findings are of more theoretical importance than practical as the author would not advocate in clinical practice serial biopsy and challenge if a child with an enteropathy who responds to milk elimination develops diarrhoea in the absence of infection when given one of these foods. Rather, the offending food would be removed from the diet. What is important is that there is now firm evidence that these food sensitive enteropathies do exist in infancy.

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