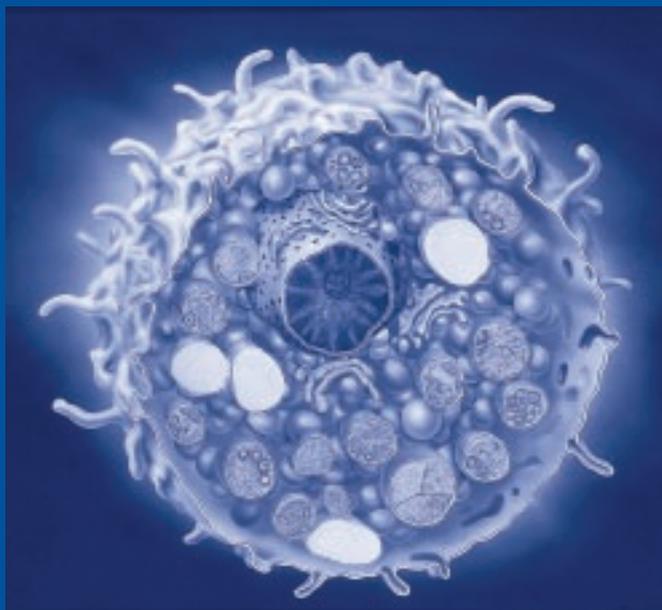


ILSI EUROPE CONCISE MONOGRAPH SERIES



# FOOD ALLERGY

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# FOOD ALLERGY

by William F. Jackson



**ILSI Europe**

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*Cover picture*

An artist's representation of a mast cell. Produced by Bo Viesland, The Medical Image Bank, Malmö, Sweden, and used here by kind permission of AstraZeneca AB, Lund, Sweden.

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## FOREWORD

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Adverse reactions to food are of concern and interest to consumers, industry and science. In recognition of this a European Symposium was held on “Food Allergy and Food Intolerance: Nutritional Aspects and Developments”. This provided the basis for the ILSI Europe Concise Monograph *“Food Allergy and other adverse reactions to food”*, published in 1994.

Food allergy is increasing in prevalence across Europe, particularly in children. After nearly ten years, it was felt that an update to describe and clarify the differences between true food allergy and other adverse reactions was required. It is of particular importance to provide an overview on this issue for the broader audience given the growing public trend to ascribe any adverse reaction to food as an “allergy”.

This concise monograph clarifies the differences between allergic hypersensitivity reactions and other

adverse reactions to food. It describes the symptoms and syndromes associated with food allergy, and the currently available analytical and clinical tools used to discriminate between allergy and other adverse reactions to food. The monograph also explains the biological mechanisms involved in food allergy. The impact of food processing, cross-reactivity between allergens, and allergen thresholds in the elicitation of allergic reactions to food are discussed, along with dietary exclusion and food labelling practices as aspects in food allergy risk management.

This monograph is intended as a resource for regulatory authorities, health professionals and the many individuals actively involved in the debate on food allergy and other adverse reactions to food.

Rachel Ward  
Frito Lay Europe

## INTRODUCTION

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The variety of natural and manufactured foods available in most developed countries in Europe and the rest of the world has never been as wide as it is today. Public interest in the preparation and enjoyment of good food is demonstrated by the proliferation of television programmes about food and cookery in many countries, and by the emergence of “celebrity chefs,” who can attract as much media interest as pop stars and fashion models.

In parallel with this interest in “good food” there has been a great increase in the level of public awareness of the links between diet and health. In general, this is likely to benefit the population, but it has been accompanied by periodic “health scares” in which possible but often unsubstantiated hazards of particular foods or food groups (including, for example, those derived from genetically modified crops) have been highlighted in the media. Although many foods have the potential to produce adverse reactions in some individuals by a number of different mechanisms, such intense media interest can cause considerable and often unwarranted alarm to consumers.

Against this background, it is perhaps not surprising that many people have become convinced that adverse reactions to foods, drinks, and food additives are common, and that such reactions may be responsible for a range of distressing physical and psychological symptoms, and even for some chronic and disabling diseases. These beliefs have been reinforced by the involvement of many alternative practitioners at or beyond the fringes of conventional medicine and by the widespread availability of a number of supposed tests for “food allergy” that have no scientific validity.

One study [1 – see References page 39] showed, for example, that 20% of the British population now believe that they have some form of food allergy or food

intolerance, and that many believe this to be the underlying cause of skin problems, abdominal pain, bowel irregularity, weight gain or headaches. Most commonly, these symptoms are blamed on wheat or dairy products, and many sufferers attempt to adhere to complex elimination diets, which may sometimes be nutritionally inadequate – especially in infants and young children. However, only 19% of those who believed they were food intolerant and were willing to undergo further testing had an allergic or hypersensitive reaction on double-blind challenge with the suspected food. Thus the real prevalence of food allergy and non-allergic hypersensitivity was much lower than their perceived prevalence. Some individuals prefer to think of an aversion to a particular food as a medical problem – it is often easier socially to say, “I’m allergic to carrots” rather than “I don’t like carrots,” for example.

The aim of this monograph is to place food allergy in perspective. Around 1% of adults and 2%–2.5% of children worldwide have true food allergy, although the prevalence is higher in some populations and age groups and lower in others. Allergic reactions to food are thus less common than many believe, although 1%–2.5% of the population does represent a very large number of people. The symptoms resulting from food allergy are often predictable and mild. However, some forms of food allergy are life threatening, occasionally in an unpredictable manner.

Although individuals may become allergic to proteins in almost any type of food, the most common and severe reactions usually result from exposure to one of a relatively small number of food types. Much can be achieved by identifying the individuals who are at risk and controlling their exposure to the problem foods. To do this requires the combined efforts of the medical profession, nutritionists, food manufacturers, caterers, and individuals who are affected by food hypersensitivity.

## **CLASSIFICATION OF ADVERSE REACTIONS TO FOOD**

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Adverse reactions to food can be divided into those which can occur in any individual who consumes the food and those which occur only in susceptible individuals (Figure 1).

Reactions due to food that contains toxins, micro-biological contaminants, or pharmacologically active ingredients do not involve allergic mechanisms, and although there is some variation in individual susceptibility, symptoms can potentially develop in all individuals who eat these foods if the amount consumed is large enough. The possibility of such reactions has major implications for public health and for the food industry, but their relative predictability means that appropriate preventive measures can greatly lessen or eliminate the risks.

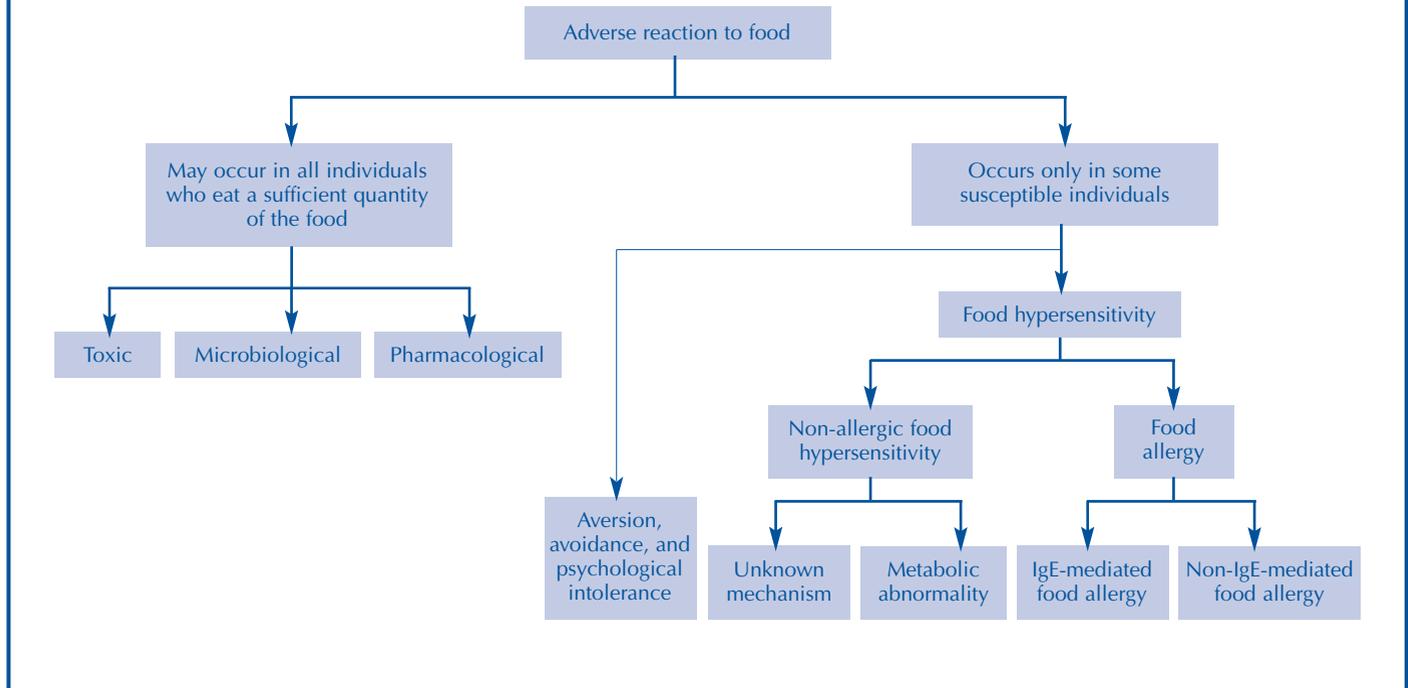
Such reactions are often unpredictable in practice, because food is not known to be contaminated before it is consumed. Some of these reactions may also closely mimic an acute allergic reaction. For example, the high levels of histidine that normally occur in the flesh of scombroid and some other fish may be converted to histamine and other bioactive products as the result of microbiological activity during a period of inadequate refrigeration or preservation. When consumed, such fish have been associated with “scombroid fish poisoning,” in which the affected individual develops a severe and apparently “allergic” reaction. Such a reaction, however, is not dependent on allergic mechanisms and will affect anyone who eats a sufficient quantity of the fish.

Reactions that occur only in susceptible individuals may result from true physical hypersensitivity to components of foods or from psychological factors. Such reactions affect only relatively small numbers of people; the majority may eat the same foods without experiencing any adverse effects.

Aversion to individual foods is a relatively common phenomenon that usually becomes a problem only if it is associated with symptoms. Some individuals who believe they have food allergies actually have aversion to the food with the accompanying physical features of anxiety or panic (including hyperventilation and its physical consequences). Such “aversion with symptoms” or psychological intolerance is difficult to recognise, but is best dealt with by recognising and treating the underlying anxiety. In such cases, if double-blind challenge testing with the suspected foods (see Diagnosis of Food Allergy) is carried out, no consistent response can be demonstrated. Aversion may also accompany true food allergy, and it may persist even after food allergy has remitted.

The recent nomenclature task force of the European Academy of Allergology and Clinical Immunology (EAACI) proposed that the term food hypersensitivity should be used in preference to food intolerance to describe any reproducible, abnormal, non-psychologically mediated reaction to food [2]. This suggestion is likely to be widely adopted, but food intolerance has a similar meaning. Food hypersensitivity may also sometimes be used less broadly to describe only reactions not thought to be caused by allergy; or in contrast, in North America, to describe any immunologically mediated reaction. This monograph follows the EAACI recommendations.

**FIGURE 1**  
**A classification of adverse reactions to food**



Non-allergic food hypersensitivity may be due to a metabolic defect in the affected individual. In some cases the mechanism is known, involving an enzyme deficiency (e.g. lactose intolerance) or a hyper-reactivity to substances such as vasoactive amines normally present in food. In many cases, however, the mechanism of such hypersensitivity is completely unknown.

The term *food allergy* is appropriate only where an allergic or immune mechanism is involved. As the EAACI task force has suggested, food allergy can be

further subdivided into IgE-mediated food allergy and non-IgE-mediated food allergy, depending on the underlying allergic mechanism (see Mechanisms of Food Allergy).

The detailed roles of controlled food challenges and immunological investigations in the diagnosis of food hypersensitivity are discussed later, under Diagnosis of Food Allergy.

## **THE PREVALENCE OF FOOD ALLERGY**

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Studies suggest that around 2% of the world's adult population have food hypersensitivity, and around 1% have true food allergy. The figures are generally higher in children: 5%–8% may have some form of food hypersensitivity, and 1%–2.5% have food allergy. These figures are based on studies using valid diagnostic techniques (see Diagnosis of Food Allergy), but they are subject to the difficulty of establishing a firm diagnosis in some types of food allergy and hypersensitivity. The true prevalence of food allergy and food hypersensitivity is likely to be higher in some populations and age groups. For example, up to 70% of infants with atopic eczema may have demonstrable food allergy or non-allergic food hypersensitivity. Given the increasing prevalence of eczema, this association alone could mean that at least 10% of infants in some countries have some form of food hypersensitivity.

The higher prevalence of confirmed food hypersensitivity in infants and young children suggests that much food allergy and hypersensitivity is a relatively transient phenomenon of early life. Clinical experience confirms that perhaps 80% of infants with milk allergy and 50% of infants with egg allergy will “grow out of it,” for example. However, peanut allergy usually persists into adult life, and its manifestations sometimes become more severe with age. Much less frequently, food allergy becomes evident for the first time in an adult.

The prevalence of allergic diseases, including asthma, rhinitis, and eczema, has been increasing over the past 20–30 years in Western Europe and the rest of the developed world. There is no specific evidence of a similar increase in food allergy, but it is likely that this

has also occurred. Food allergy contributes to the problem of eczema, and there also is evidence of an increase in acute severe allergy to peanut in populations in developed countries where peanut is widely present in foods (as shown by peanut allergy becoming more common in successive generations of atopic families).

A number of food allergies have appeared in increasing numbers in parallel with the introduction or spread of “new” foods in the European diet. Allergies to kiwi fruit and sesame seed have rapidly become frequent and significant in the UK and some other European countries. It is possible that exposure to new food allergens may contribute to the increasing prevalence of food allergy in some countries, as potentially susceptible individuals will be exposed to a greater number of potential allergens than previously. However, this is unlikely to be the major reason for any increase in food allergy. As with other allergies, it is likely that the principal factor is an increased risk of sensitisation at a time when the individual is exposed to the relevant allergen. The reasons for this increased risk are unknown, but this is the focus of much current research.

## MECHANISMS OF FOOD ALLERGY

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*Allergy* is best defined as “a hypersensitivity reaction initiated by immunologic mechanisms.” Allergic reactions may occur both at the point of contact between allergen and immune cells (locally) and throughout the body (systemically).

Most cases of confirmed food allergy involve the production of antibodies known as immunoglobulin E (IgE) and a network of interactions between various cell types and chemical mediators. This type of allergic reaction is known as an *IgE-mediated allergy* (or a type I hypersensitivity reaction), and it produces immediate symptoms. The most severe form of IgE-mediated allergy is anaphylaxis; immediate symptoms in the mouth, gut, skin, and respiratory tract may precede anaphylaxis or occur alone as less severe manifestations.

Another recognised mechanism in food allergy is delayed cell-mediated allergy (type IV hypersensitivity), developing hours or even days after exposure, which is not mediated by IgE. Interactions between cells and chemical mediators, rather than antibodies, are the key mechanisms here. Type IV reactions can probably occur in response to a range of ingested foods, in addition to or instead of immediate reactions, and may lead to a range of symptoms in various parts of the body, including the skin, the gut and other organs. Such delayed reactions are much more difficult to investigate and diagnose than immediate reactions, but they probably play an important role when food allergy is a factor in chronic conditions.

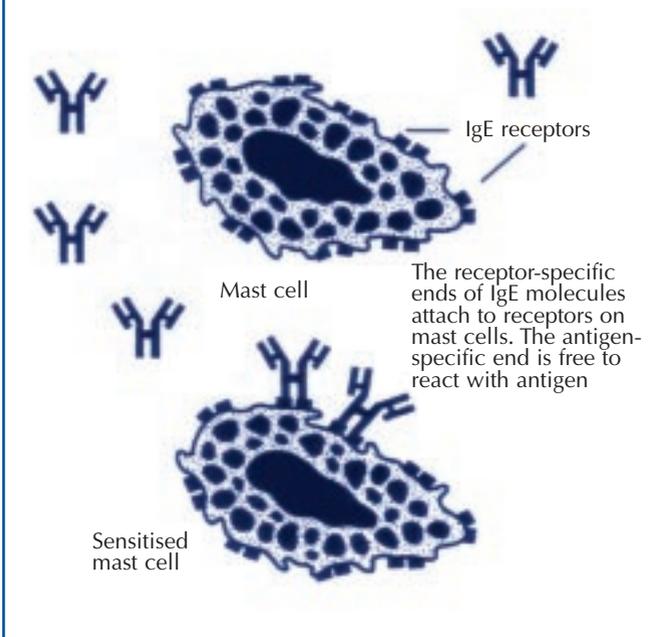
### *Immediate IgE-mediated reactions*

*Antibodies* (also known as *immunoglobulins*) are proteins manufactured by B lymphocytes (a type of white blood cell) in response to the presence of proteins or glycoproteins foreign to the body (*antigens or allergens*). The biological function of antibodies is to counteract infection with bacteria, viruses, protozoa and other microorganisms, and infestation of the gut, blood or tissues with worms. The body retains the ability to produce antibodies against an individual antigen for many years and sometimes for life, although the extent of this response can vary with time, between different antigens and following different levels of exposure.

Although many types of antibodies are protective, the inappropriate or excessive formation of antibodies may lead to illness. Potential antigens are present in many substances that may be inhaled or ingested or come into contact with the body. These include pollens, house-dust mites, moulds and foods, all of which may lead to the unwanted production of antibodies in susceptible individuals.

Antibodies fall into five structural immunoglobulin (Ig) classes: IgA, IgD, IgE, IgG, and IgM; only IgE is an integral part of the immediate allergic response in man.

The IgE produced by B lymphocytes on exposure to an allergen circulates throughout the body. The antigen-specific ends of the IgE molecule have an affinity for a specific part of the antigen molecule (known as an epitope – many allergens have several epitopes). The other (fixed or receptor-specific) end of the IgE molecule has an affinity for the surface of immune cells including mast cells. When IgE molecules bind to receptors on the surface of mast cells (Figure 2), the mast cells are said to have become sensitised to the specific allergen that provoked production of the IgE molecule.

**FIGURE 2****Sensitisation of mast cells**

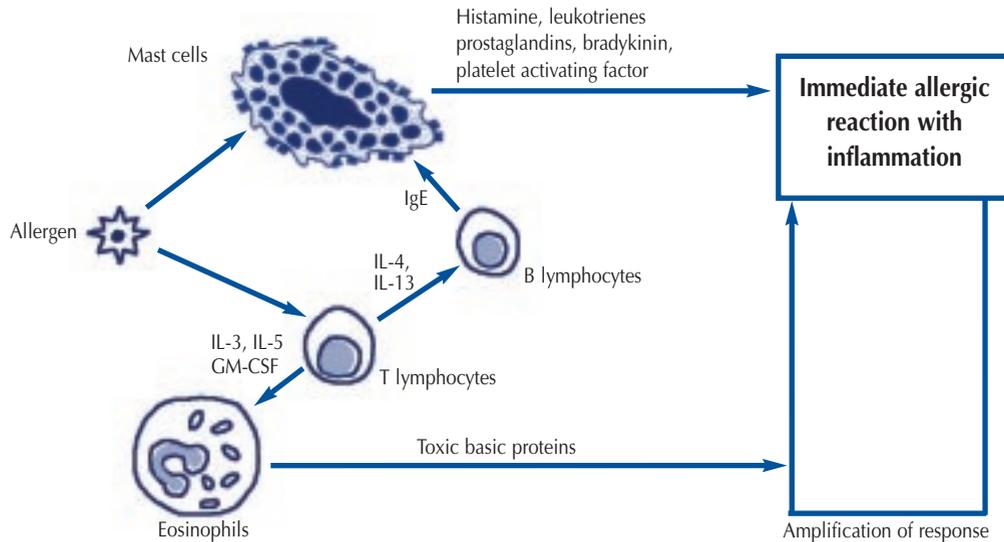
Subsequent re-exposure of sensitised mast cells to the same allergen (or even to the same epitope in a different allergen) results in an immediate IgE-mediated allergic reaction. The allergen forms a bridge between two adjacent IgE molecules on the cell surface. This acts as a trigger for the cell to release ready-made chemical mediators, including histamine and other biologically active substances, and to produce and release other pro-inflammatory substances, including various leukotrienes and prostaglandins (Figure 3). The release of these substances causes an immediate inflammatory response, in which the blood supply to the area is increased and other white blood cells and components of the immune system are attracted to the area. Local

swelling, itching, redness and heat all result from the release of these mediators.

Several other cell types also have very important roles in the immediate response (Figure 3). Mast cells and T lymphocytes release mediators that stimulate B lymphocytes to produce more IgE. The T lymphocytes also produce mediators that stimulate eosinophils (another type of circulating white blood cell) to migrate to the affected area and become activated. The activated eosinophils then release a variety of potent chemicals from their storage granules, including a range of toxic basic proteins, which damage local tissues and thus intensify and prolong the inflammatory response. Other chemical processes also contribute to the severity of the immediate allergic response.

Mast cells are scattered below the skin surface, and below the mucous surfaces in the mouth, gut, eyes, nose and lower respiratory tract. Closely related cells (basophils) circulate throughout the body in the blood and can be sensitised in exactly the same way as mast cells. An individual with immediate food allergy can therefore have both a local and a widespread reaction when mast cells and basophils coated with specific IgE are triggered into activity after encountering the food allergen. The reaction can become generalised as the result of the absorption and spread of the allergen and/or as the result of the circulation of the mediators and cells stimulated by the local reaction.

Non-allergic processes may closely mimic an IgE-mediated allergic reaction. Some foods can contain substances that trigger mast cells to release histamine and other mediators (strawberries, pineapple, various other foods and some food additives may do this in a rare and unpredictable manner), and others (e.g., spoiled scombroid fish) may also produce systemic effects similar to those of mast cell activation.

**FIGURE 3****A simplified view of the cells and mediators involved in an IgE-mediated allergic reaction**

Each case of apparent IgE-mediated allergy must be carefully assessed before food or other allergy is confirmed as the cause, because mast cell activation and mediator release can also be triggered by other non-allergic factors in some individuals.

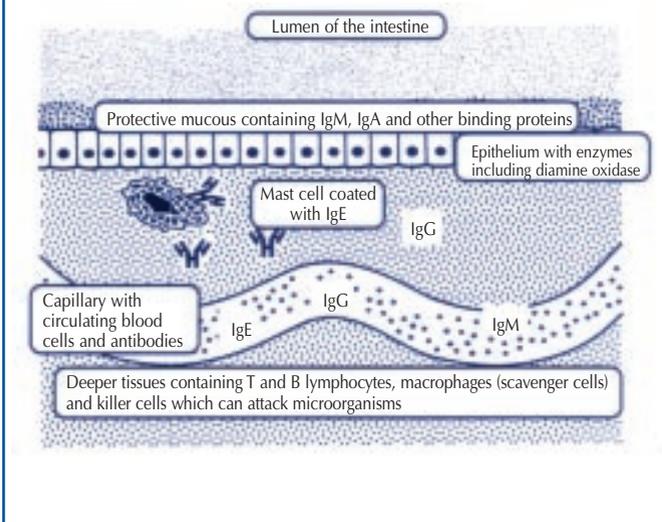
### ***Defensive barriers in the intestine***

Food is full of potentially allergenic substances, yet food allergy seems to be less common than allergy to inhaled substances. One reason for this is that the intestine has a series of defensive barriers, which largely prevent food and other intestinal contents from entering further into the body or making contact with mast cells in the gut wall. These barriers also prevent other potentially

harmful substances and microorganisms from penetrating the tissues.

The gut wall (Figure 4) is normally coated with viscous mucus, which is produced by specialised lining cells of the gut. This mucus contains various protective substances, including special “secretory” forms of IgA and IgM (s-IgA and s-IgM) which are modified to allow their secretion across the gut wall. The mucus acts as an antiseptic “paint,” and the secretory antibodies also help to counteract the entry of soluble food allergens – a process known as immune exclusion.

**FIGURE 4**  
The defensive barriers of the intestinal wall

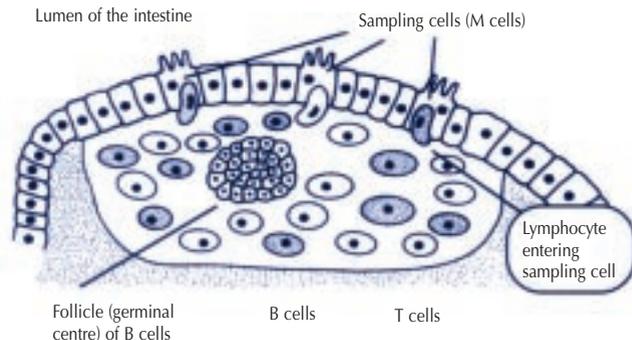


Beneath the mucous membrane of the gut is a layer of epithelial cells, which produce enzymes capable of inactivating histamine and many other active substances from the gut and preventing their access to other tissues and the circulation. Any substances that penetrate beyond the epithelial cell layer may be inactivated by combination with specific IgG antibodies (without generating an inflammatory response). Only if they escape all these mechanisms can food allergens trigger mast cells primed with specific IgE.

### **Sensitisation**

The intestinal wall is a very important component of the body's immune system, containing huge numbers of lymphocytes. Most of these lymphocytes are found in specialised areas of the gut wall known as Peyer's

**FIGURE 5**  
A Peyer's patch in the wall of the small intestine



Both food antigens and microorganisms can penetrate into the M cells and are brought into contact with migrating lymphocytes. The Peyer's patch can induce either immune tolerance or an immune reaction, depending on the solubility, concentration, and other features of the antigen it encounters.

patches (Figure 5). Each patch contains 30–40 groups (follicles) of cells, mostly T and B lymphocytes. Other lymphocytes occur individually and in smaller clusters throughout the lining layers of the intestine.

Scattered over the surface of the Peyer's patches are specialised "antigen presenting cells", known as M cells, through which samples of the antigens present in the intestinal lumen penetrate into the lymphoid tissue of Peyer's patches. This presentation of antigens by the M cells can lead to priming of the lymphocytes to produce specific antibodies. The lymphocyte population of Peyer's patches is not static, and the migration of T and B lymphocytes can potentially spread any local immune response in the gut to other parts of the body.

An immune response is not the invariable outcome of antigen presentation to the immune system. The response engendered on first exposure to an antigen, via the gut or elsewhere, may take one of three main forms.

- The individual may become “tolerant” to the antigen, not producing any immune response to it on subsequent exposure. This response is still not fully understood, but it is probably the usual and desirable situation for most food proteins and glycoproteins.
- The individual may develop an immune response, involving cell-mediated immunity and immunoglobulins such as IgG, which may recur on subsequent exposure, but does not necessarily lead to symptoms.
- The individual may become sensitised, developing an IgE-mediated response that may lead to unwanted symptoms on subsequent exposure to the same antigen.

Some individuals have a personal or familial tendency to produce IgE antibodies in response to exposure to low doses of antigens via the gut or elsewhere, and to develop typical symptoms on re-exposure, such as asthma, rhinitis, urticaria, or other immediate responses, including anaphylaxis. This tendency is present from birth. It is known as *atopy*, and the affected individuals are said to be atopic.

Many sufferers from immediate-type food allergy are atopic, but this is not a full explanation for susceptibility, as a non-atopic individual can produce IgE antibodies to food allergens and react in the same way, especially during infancy. Also, most atopic individuals do not have food allergy.

The factors controlling the nature of the response in an individual on a particular occasion are still not fully understood, but age is probably important. The induction of tolerance to oral food proteins is probably the usual outcome in children and adults, although sensitisation can occur at any age if severe infection or other factors transiently disturb normal immune mechanisms. Only in infancy, and probably also before birth, is there a period during which sensitisation is likely to occur.

Oral tolerance is poorly developed in early infancy, and most infants are potentially vulnerable to the development of food allergy during this period. The concept of a “window of sensitisation” in early life is supported by studies of the effect of introducing cow’s milk into the diet at different times during infancy, which show that sensitisation to milk protein is more likely if cow’s milk is introduced early.

A current theory suggests that the hygiene of modern life could help explain why allergies (including food allergy) appear to be becoming more common. The reduced incidence of previously common infections and possibly also an increased rate of exposure to antimicrobial drugs during infancy may shift the immune system towards the sensitisation process necessary for immediate-type allergic reactions.

Some newborns are already sensitised to some allergens, such as peanut, milk and eggs, and it seems likely that they were sensitised by exposure to allergens *in utero*. Thus the mother’s diet during pregnancy may be relevant to subsequent food allergy. However, it is also possible that tolerance to allergens could develop *in utero*, so exclusion of allergenic foods from the maternal diet may not be beneficial. Food antigens can also pass from mother to child via breast milk, and this may be an important route for sensitisation in early life.

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Sensitisation *in utero* or from breast-feeding may explain why around 80% of peanut-allergic children have a reaction on what is apparently their first exposure to peanuts. Exposure to peanut oil in breast creams used by the mother or eczema treatments used on the infant is another possible explanation.

The amount of allergen required for sensitisation is unknown. It is possible that different doses of allergen may have different effects – a large dose might lead to tolerance, while a smaller dose leads to sensitisation, or vice versa.

The sensitising exposure in food allergy may not be with the food to which the individual subsequently reacts: cross-reactivity between allergens from different sources can occur. For example, sensitisation to birch pollen may lead to oral allergy to various fruits. Many other examples of cross-reactivity have been described (see below).

Clearly sensitisation results from a complex interaction between the individual and the timing and nature of his or her first exposure to relevant allergens. A greater understanding of this process would be very helpful in suggesting appropriate preventive measures against food allergy.

### ***Cross-reactivity in food allergy***

The match of an antibody to its antigen is specific, but it involves only the epitope, not the entire antigen molecule. If another antigen has a very similar epitope, it may also be bound by the same antibody, leading to cross-reactivity or cross-allergenicity – reaction in an individual on exposure to a second antigen after sensitisation to a first. The more resemblance there is between molecules, the more likely such a cross-reaction

becomes. Of course, an individual may also be independently sensitised to more than one unrelated allergen. It is important to distinguish such co-sensitisation from true cross-allergenicity.

Animals or plants that are descended from a relatively close common ancestor share many similar molecules. This explains the commonly seen cross-allergenicity between different kinds of crustaceans, including prawns, shrimps, crab and lobster, between the eggs of different birds and between cow's milk protein and sheep and goat's milk.

Some cross-reactions unite diverse animal or plant groups that have a particular shared protein. For example, antibodies to house-dust mite muscle protein (tropomyosin) may cross-react with the similar tropomyosin found in crustaceans and molluscs. This explains why some shellfish-allergic patients react to all kinds of shellfish, both molluscs and crustaceans. The cross-allergenicity between latex and various fruits and vegetables (e.g. chestnut and avocado) is due to a shared enzyme called chitinase, which protects plants against insect pests and is present in various unrelated trees.

Cross-reactivity to different nuts is a common clinical problem, although nuts come from a variety of unrelated plant families. The reason for such cross-reactivity is still unclear, but it may reflect some chemical similarity related to the need for nuts to resist rotting in the soil. Cross-reacting allergens in wheat, rye, hazelnut, sesame and poppy probably have a similar explanation related to biological survival of the allergenic plant.

Many patients who are allergic to inhaled birch pollen also develop symptoms when they eat various nuts, fruits and vegetables, including hazelnuts, apples, cherries, pears, carrots and others. This cross-reactivity

may also be related to a conserved functional protein. There are similar lists of potentially cross-reacting plant foods for grass pollen, mugwort pollen and ragweed pollen.

Peanuts are legumes, but while peanut-allergic individuals may have positive skin prick reactions to other legumes, such as peas, beans and soy, they rarely develop symptoms when they eat them. Rarely, peanut-allergic patients have had anaphylactic reactions when exposed to soy protein uncontaminated by peanut, and others have reacted to lupin (lupin flour is now widely used in bakery products in some countries, such as the Netherlands, often as an alternative to flour of genetically-modified soy beans). Co-sensitisation to peanuts and biologically unrelated tree nuts is common and can be severe.

A few cross-reactions defy biological classification, such as that between allergy to the house-dust mite and to kiwi fruit.

Some of the cross-reactions discussed above are between inhaled or contact allergens and foods. Thus, a patient may react to a food even though the original sensitisation was via inhalation. The origin of an individual's food allergy may not always be sensitisation via the gut. Conversely, a patient with respiratory or contact allergy could have been sensitised originally via the gut.

## **SYMPTOMS AND SYNDROMES CAUSED BY ADVERSE REACTIONS TO FOODS**

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An immediate reaction to an individual food is easily identified, but the diagnosis of adverse reactions to foods is complicated by the possible involvement of many different foods and by the possibility of delayed reactions.

- A single food may give rise to different symptoms in different individuals, or even in the same individual at different times or in different doses, and the mechanisms of these reactions may also vary.
- The same symptoms may also be caused by different foods – in the same individual or in different individuals.

As a consequence, it can sometimes be very difficult to establish a cause-and-effect relationship between food and symptoms.

True food allergy often produces a variety of symptoms, including life-threatening anaphylaxis, urticaria, angioedema, asthma, rhinitis, abdominal pain and vomiting. Acute allergic reactions usually occur within minutes of ingestion of the food, so the dietary history of the individual makes diagnosis relatively simple. Skin prick tests and IgE antibody tests to the food are usually positive (see Diagnosis of Food Allergy).

Other reproducible food hypersensitivity reactions occur more slowly, making their relationship to a particular food more difficult to identify. Such reactions include food-induced enteropathies, colitis and eczema.

Enteropathies cause damage to the lining of the small intestine, and thus lead to the malabsorption of nutrients from the gut. This may in turn lead to “failure to thrive” in children and weight loss in adults. There are usually no reliable objective tests to identify the allergic cause of these conditions.

Any condition caused by food allergy can also potentially be caused by other forms of allergy, so no symptoms are truly diagnostic of food allergy. In some individuals food allergy may also have a significant role in some conditions without being their root cause. For example, eczema is usually associated with allergy to non-food allergens, such as house-dust mite, and is commonly associated in infancy with allergy or hypersensitivity to foods. However, essentially identical eczema may occur in the absence of demonstrable allergies. Even when allergy to food or other allergens can be demonstrated, the severity of eczema at a given time in an individual can be influenced by many other factors, including the physical state of the skin, the presence of infection in the skin or elsewhere and the person’s psychological state. The true “cause” of eczema is still unclear.

While it is difficult to be sure about the status of all reactions to food, it is helpful to discuss the symptoms and syndromes caused by abnormal reactions to food in four groups:

- Conditions caused by food allergy
- Conditions associated with food allergy
- Conditions in which food allergy is of doubtful significance
- Conditions caused by non-allergic hypersensitivity to foods

## Conditions caused by food allergy

Food allergy may lead to a wide range of symptoms, affecting many parts of the body – especially the gastrointestinal tract (mouth and gut), the respiratory tract (lungs, nose and throat) and the skin (Table 1). Commonly, the capacity to react to foods in this way will result from initial sensitisation by food, but in some cases initial sensitisation by inhaled or other allergens may lead to subsequent food allergy by a process of

**TABLE 1**

**Symptoms that may result from food allergy.**

*(Note that many of these symptoms are much more commonly caused by other disorders.)*

**Systemic**

Anaphylaxis

**Gastrointestinal**

Swelling and itching of lips and mouth  
(oral allergy syndrome)

Nausea

Vomiting

Abdominal pain, cramp, or colic

Diarrhoea

**Respiratory**

Rhinitis (sneezing, nasal blockage)

Asthma

Swelling of larynx

**Skin**

Pruritus (itching)

Erythema (reddening of skin)

Urticaria

Angioedema

Eczema

Conjunctivitis (inflammation of surface of eyes)

cross-reactivity. All these symptoms may also be caused by reactions to non-food allergens, and most may also occur for other non-allergic reasons.

## Anaphylaxis

Anaphylaxis is the most severe consequence of food allergy, and the greatest cause for serious concern among allergy sufferers, the medical profession and the food industry. Anaphylactic reactions are fortunately rare, but they have a rapid onset and can be fatal in adults and children of all ages, unless treatment is given within minutes.

In clinical terms, anaphylaxis describes a pattern of symptoms that includes constriction of the airways in the lungs, obstruction by swelling of the upper airway and mouth (oedema of the larynx, pharynx, tongue and lips), a fall in blood pressure (hypotension) and acute swellings of the skin and deeper tissues (urticaria and angioedema). Gastrointestinal symptoms, including nausea, vomiting, diarrhoea and abdominal pain, are common accompaniments, and symptoms in the bladder and the nervous system may also occur. Without prompt treatment, the airway obstruction and low blood pressure can lead to a severe decline in oxygenation of the blood, irregularity of the pulse, damage to the heart muscle and ultimately cardiovascular collapse and death.

The manifestations of anaphylaxis are usually more severe in individuals who have pre-existing asthma, especially if it is not well controlled, because the constriction of the airways in the lungs is particularly rapid and severe. The risk of death from anaphylaxis is higher for individuals with asthma than for non-asthmatic individuals.

The most common causes of anaphylaxis are allergy to foods, to penicillins and to bee and wasp stings, but many other allergies may also occasionally lead to anaphylaxis in sensitised individuals. Among these is exposure to latex, which is a component of the cold adhesives used in some food packaging processes and may thus be ingested in trace amounts with some foods; it may also enter food from latex gloves worn by food handlers.

In developed countries, allergy to peanuts is now a very common cause of anaphylaxis. In the UK, for example, more than 1% of children are estimated to be allergic to peanut protein. In these individuals, the ingestion of – and in some cases even oral contact with – peanuts can provoke a severe reaction. Many other foods have been reported to lead to anaphylaxis in susceptible individuals, including tree nuts, soybeans, sesame and some other seeds, egg, milk, seafoods, some spices, celery and some fruits.

Some patients have exercise-induced food anaphylaxis, in which foods such as shellfish, celery or wheat lead to anaphylaxis only when the patient also exercises after ingestion.

Lesser degrees of anaphylaxis may occur in which patients have some of the oral, gut and skin symptoms without severe respiratory or cardiovascular collapse and with spontaneous resolution. Unfortunately, the severity of one attack is not a guide to the likely severity of future attacks, so all patients who have experienced any degree of anaphylactic reaction must be considered at risk of severe anaphylaxis and death in a future episode. Such patients, once identified, should make all possible efforts to avoid ingestion of the provoking food and should also be trained in the self-treatment of impending attacks (see Living with Food Allergy).

### **Oral allergy syndrome**

In the oral allergy syndrome, the affected individual experiences tingling, itching and swelling of the lips, mouth and often the upper throat within seconds or minutes of exposure to the offending food. This is usually a relatively mild and self-contained allergic response. Such oral allergy to apple and other fresh fruits is relatively common (especially in Scandinavia) in patients who are also allergic to inhaled birch pollen; this is believed to reflect a cross-reactivity in the allergic responses to birch pollen and apple. Fortunately, anaphylaxis is a rare complication of such oral allergy to fresh fruits. However, oral allergy syndrome may also be the first sign of a more generalised anaphylactic reaction. It is, for example, a common first sign of contact with peanut in patients with peanut allergy, who may progress to more severe symptoms.

### **Acute gastrointestinal symptoms**

Nausea, vomiting, abdominal pain (cramps or colic) and acute diarrhoea may all occur in a repeatable manner as part of an immediate allergic response to food, but it is relatively rare for them to be the only manifestations of food allergy. Usually there are associated symptoms suggesting allergy in the skin, respiratory tract or elsewhere.

### **Urticaria and angioedema**

Acute attacks of urticaria (hives or itchy swellings in the skin) and angioedema (swelling of tissues below the skin) may occur as an immediate allergic reaction to ingested food, usually in combination with gastrointestinal or respiratory symptoms, or as a part of an anaphylactic reaction. Sometimes the attacks are less marked, involving areas of intense itching, reddening and warmth in the skin.

In a small number of patients, urticaria may result from hypersensitivity to some food colourings or other additives, such as tartrazine or sulphites. Although the symptoms are identical to those of allergy, most food additives probably do not cause a true allergic reaction. It is likely that most reactions to food additives are the result of a pharmacological effect, which varies among individuals and induces the release of many of the same chemical mediators that are involved in a true allergic reaction. However, enzymes (e.g. papain) and a few other additives (e.g. sulphites) may occasionally provoke true allergy.

Urticaria and angioedema can have many causes other than allergy, especially in adults and when they persist for long periods. Although chronic urticaria (usually defined as urticaria persisting for more than six weeks) occasionally results from recurrent immediate reactions to hidden allergens in foods, or from multiple sensitivities to different foods or additives, it is usually unrelated to food.

### **Contact food allergy**

Contact with food, especially by chefs and food handlers, may lead to acute local urticaria by an IgE-mediated immediate allergic mechanism, as has been reported with fish, shrimp, egg, flour and other foods. In the longer term, similar contact may also lead to contact eczema or dermatitis, a delayed form of allergic reaction. Foods that are commonly implicated in contact dermatitis include garlic, paprika and other spices. Avoidance of contact or the use of protective gloves protects against such reactions.

## ***Conditions associated with food allergy***

### **Coeliac disease**

In coeliac disease (gluten-sensitive enteropathy) the small intestine is damaged by exposure to gluten. Gluten is the major protein group in wheat, and structurally similar proteins with similar effects are also present in rye, barley and possibly oats, although not in maize or rice. On a normal, gluten-containing diet, the lining of the bowel in susceptible individuals becomes flattened, which greatly reduces the area of the bowel surface through which nutrients can be absorbed. Inflammation below the surface of the bowel contributes to this damage and further impairs normal bowel function.

The clinical features of coeliac disease are mainly the result of malabsorption – especially of fat, fat-soluble vitamins and calcium. Infants and children with coeliac disease commonly have fatty diarrhoea with abdominal distension and show “failure to thrive” – they are underweight, do not grow normally, have limp, underdeveloped muscles and tend to be miserable. Less severe disease is sometimes diagnosed in older children with growth retardation and even in adults with fatty stools and signs of malnutrition. Patients with coeliac disease may also have an increased risk of malignant tumours in the bowel and elsewhere.

Patients with coeliac disease have a number of immunological abnormalities, including IgA antibodies to gliadin (a component of wheat gluten) in their blood. The symptoms and bowel changes can be reversed by adherence to a “gluten-free” diet (most such diets are in fact very low in gluten rather than truly gluten-free). However, both genetic and environmental factors are involved in susceptibility to coeliac disease, and it is possible that the gluten sensitivity is a result of bowel wall damage (which may allow gluten to come into

contact with immune cells, thus generating an antibody response), and that the initial bowel damage is not caused by sensitivity to gluten. A delayed allergic response to food is thus an important component of coeliac disease, but not necessarily its prime cause.

A long-term “gluten-free” diet is effective in reversing the symptoms and signs of coeliac disease. However, many patients find such diets to be expensive, limited and socially excluding. As a result, some patients – especially teenagers – find it difficult or unacceptable to stick to the diet.

Some patients with the blistering skin disease *dermatitis herpetiformis* also have gluten-sensitive enteropathy, which responds to a gluten-free diet.

### **Eosinophilic gastroenteritis**

Eosinophilic gastroenteritis is a rare condition, mainly affecting children and young adults, in which the wall of the gut becomes inflamed. The symptoms include vomiting, abdominal pain, diarrhoea and malabsorption. Only around 50% of those with eosinophilic gastroenteritis have evidence of associated food allergy, but this may prolong the disease, which otherwise has a tendency to spontaneous resolution.

Infants may also suffer from other distinct conditions in the gut, such as food-induced enterocolitis syndrome and food-induced colitis. The symptoms of these conditions often respond to the elimination of cow’s milk or soy from the diet, and there may be a delayed (non-IgE-mediated) allergic response to the offending foods.

### **Asthma, rhinitis and other respiratory diseases**

Allergy to ingested food is a real but rare trigger of symptoms in asthma, rhinitis and rhinoconjunctivitis (irritation of the nose and eyes – as in hay fever), although it is unclear whether food allergy can act as an

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inducer of these conditions in the first place. Some children and young adults with intermittently severe asthma are aware of specific food triggers, and hidden food triggers may be relevant in other cases. The proportion of patients with asthma and rhinitis in whom food avoidance is of benefit is very small, however, and it is not usually necessary to consider dietary investigation or treatment.

Patients with a known severe food allergy, such as allergy to peanut, who also have asthma seem to have a much greater risk of fatal anaphylaxis than those who do not have asthma. This is probably because the anaphylactic reaction in the lungs is more severe in patients with established asthma. It is therefore particularly important for patients with asthma who are also known to have food allergy to keep their asthma under the best possible control at all times.

Asthma may also occur as a result of the inhalation of various food substances in sensitised individuals. For example, the inhalation of food allergens, including those from flour, enzymes, green coffee, castor bean, soybean, other legumes, various spices, egg protein, fish and crustaceans (in dust or steam) may lead to occupational asthma or rhinitis in workers in the food industry.

### **Atopic eczema**

Many patients with atopic eczema (also known as atopic dermatitis) have high levels of IgE antibodies in the blood and positive skin prick tests to various food allergens, but the significance of these findings to the severity of the patients' eczema is doubtful. By definition, patients with atopy (see section on Sensitisation, under Mechanisms of Food Allergy) tend to produce IgE antibodies in response to low doses of many allergens, but this reactivity does not necessarily lead to disease.

Eczema can certainly be made worse by certain foods in some patients, especially young children. Cow's milk and hen's egg are the most common offending foods, particularly in infancy, although many other foods may be involved. An acute worsening of eczema may occur within minutes of ingestion, and sometimes foods also produce a reaction on skin contact, particularly around the mouth.

Specific food avoidance in some individuals with eczema can lead to improvement of eczema, but there is no evidence that it can lead to complete resolution or cure. Allergy to individual foods is rarely the only factor determining the presence or absence of eczema.

### ***Conditions in which food allergy is of doubtful significance***

A number of conditions are commonly but inappropriately attributed to "food allergy." Some conditions, such as irritable bowel syndrome, migraine and, occasionally, behavioural disorders in childhood, may be triggered by non-allergic food hypersensitivity. Inflammatory bowel diseases (ulcerative colitis and Crohn's disease) are not caused by allergy to foods, but dietary modification may sometimes be helpful in these patients, as non-food-induced damage may make the bowel unable to cope with a full diet. There are anecdotal reports of individuals with rheumatoid arthritis who appear to respond to dietary elimination, but these have not been confirmed by formal studies, and the mechanism of any such response is unknown.

Despite numerous media stories to the contrary, there is no objective evidence that food allergy or other adverse reactions to foods or food additives can cause depression, cystitis, enuresis (bed-wetting), chronic otitis media (glue ear), chronic fatigue syndromes, anorexia nervosa,

bulimia or epilepsy. There is also no consistent evidence that dietary modification can influence the progress of these disorders.

### ***Conditions caused by non-allergic food hypersensitivity***

Several conditions resulting from known enzyme deficiencies or from unknown mechanisms are commonly confused with food allergy. Foremost amongst these is lactose intolerance.

#### **Lactose intolerance**

Individuals with lactose intolerance are unable to digest significant amounts of lactose, the predominant sugar in cow's milk. This inability results from a deficiency of the enzyme lactase, which is normally produced by the cells lining the small intestine.

Lactase normally breaks down lactose into glucose and galactose, which can be absorbed into the bloodstream. When there is a deficiency of lactase, lactose remains in the intestine, where it is fermented by gut bacteria, producing gases, including carbon dioxide and methane. This fermentation also produces short-chain fatty acids in the same way as the fermentation of any soluble or insoluble fibre. These have an osmotic effect, drawing additional water into the gut.

Individuals with lactose intolerance may experience nausea, abdominal cramps, bloating, passage of wind and diarrhoea after eating or drinking foods containing lactose. The presence and severity of symptoms depends on the quantity of lactose consumed and the individual degree of lactase deficiency.

A relative deficiency of lactase can occur as a common hereditary disorder. The prevalence varies widely in

different parts of the world and various intestinal diseases may exacerbate this deficiency. However, there is no evidence that food allergy plays any role in the condition.

Thus, lactose intolerance is an example of food intolerance due to a metabolic abnormality, not a food allergy.

## ***ALLERGENIC FOODS***

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Clinical experience in the UK, Europe and North America suggests that a relatively small number of foods and food products are responsible for most cases of food allergy. In approximate order of frequency, they are as follows.

- In children: cow's milk, egg, soy, peanut, tree nuts, fish and crustaceans
- In adults: peanut, tree nuts, crustaceans, fish and egg

Many other foods are allergenic in smaller numbers of individuals, and the pattern of food allergy varies widely in other parts of the world. Interestingly, peanut allergy is rare in tropical Africa and in Korea – despite the fact that both are regions where peanuts are widely consumed from an early age. This may be partly accounted for by the fact that peanuts are commonly boiled in these regions, whereas they are usually roasted in Europe and the USA. Boiled peanuts may be less allergenic than roasted peanuts.

In 1995, an Expert Consultation of the Food and Agriculture Organisation (FAO) of the United Nations proposed a detailed list of common allergenic foods. The evidence for the inclusion of foods in this list was further reviewed by an ILSI Europe Task Force in 1998. The importance of identifying these foods lies in the need for special labelling of food and food products, even when they contain only small amounts of the allergenic substance (below the level that would otherwise require specific labelling by law). In addition, this classification established groups of foods worthy of further study, with the aim of determining threshold doses for food allergens and establishing whether food processing alters the allergenicity of foods.

The ILSI Europe Task Force [3] reached conclusions about the inclusion of specific food allergens on a list of common allergens on the basis of two main types of evidence.

- The double-blind, placebo-controlled food challenge (DBPCFC; see Diagnosis of Food Allergy), which is the “gold-standard” investigation
- Detailed reporting of a fatal or life-threatening anaphylactic reaction where the food is clearly implicated (and where DBPCFC would be unsafe or impracticable)

The FAO experts identified eight groups of foods (colloquially known as “the big eight”) as the major contributors to IgE-mediated food allergy, and the ILSI Europe group added sesame seeds, as well as the foods listed as group 9 in Table 2. The recent emergence of allergies to kiwi fruit, papaya, mango and pine nuts in Northern European countries suggests that the more widespread consumption of previously unusual foods may generate or reveal a new potential for allergic reactions, so any list of problem foods is subject to future revision.

The updated overall conclusions of the ILSI Europe Task Force and their suggested relevance to food labelling are summarised in Table 2.

### ***The effect of thermal processing on allergenicity***

Any protein molecule is composed of a long chain folded on itself in a complex manner, so an epitope may have molecular features that are adjacent only because of this folding (*a conformational epitope*). Changes in the shape of the molecule on cooking or processing of food may sometimes separate these features and remove

**TABLE 2****Classification of food allergens\***

Group Number	Food	DBPCFC Documented?	Fatal reaction?	Anaphylactic reaction?	Inclusion in list for positive declaration labelling?
1	Wheat	Yes	No	Yes	Yes
	Other cereals	Yes	No	No	No
2	Crustaceans	Yes	Yes	Yes	Yes
	Molluscs	No	No	Yes	No
3	Eggs	Yes	Yes	Yes	Yes
4	Fish	Yes	Yes	Yes	Yes
5	Peanut	Yes	Yes	Yes	Yes
	Soybean	Yes	Yes	Yes	Yes
	Other legumes	Unclear	No	Yes	No
6	Milk	Yes	Yes	Yes	Yes
7	Tree nuts	Yes	Yes	Yes	Yes
8	Sesame seed	Yes	Yes	Yes	Yes
	Other seeds	No	No	Yes	No
9	Prunoideae (wood-stone fruits)**	No	No	Yes	No
	Celery	No	No	Yes	No
	Rice	No	No	No	No
	Buckwheat	No	No	Yes	No

\* Adapted and updated from Bousquet *et al.* [3].

\*\* Excluding almonds which are classed as tree nuts.

allergenicity. By contrast, where an epitope is a continuous part of the protein chain (*a linear epitope*) it is more likely to be heat-stable.

The allergenicity of many fruits may be greatly reduced by cooking, and the allergenicity of eggs, milk and some fish may also be attenuated. It is also possible that the boiling, but not roasting, of peanuts may lessen their

allergenicity, but in general, cooking has little or no effect on the allergenicity of tree nuts. In general, cooked foods must be regarded as retaining the potential allergenicity of the raw food.

The thermal processing of food may also lead to the formation of allergens that are not present in the raw food. This may be because changes in the shape of a

protein molecule reveal a previously “hidden” epitope. In addition, many complex chemical changes occur during cooking, and some of these lead to a variety of potentially allergenic products, for example through the reaction of protein amino groups with sugars. A clinical example of the relevance of such allergens comes from a patient who had an anaphylactic reaction to cooked pecan nuts, but showed no sensitivity to fresh pecan nuts. An allergen was demonstrated in cooked pecan nuts. Allergens may also form as fresh foods age. The extent to which allergens are produced through the ageing or heating of foods is unknown.

### ***Allergenicity of food products***

Processing of food by other means may also affect its allergenicity. Hydrolysed milk protein formulae have a much lower allergenicity than untreated cow’s milk, and have a high safety profile in infants with cow’s milk allergy, although they are not completely non-allergenic.

Refined (neutralised, bleached and deodorised) peanut oil contains hardly any allergenic proteins, and there are few reports of reactions to this type of oil (or to mixed vegetable oils containing it) in patients with peanut allergy. Cold-pressed peanut oil contains significant amounts of peanut allergen, and some peanut-sensitive patients reacted to it in a DBPCFC. Similarly, oils produced from tree nuts, which are increasingly used in “gourmet” foods, retain their allergenicity, as they have not usually been fully refined.

Some allergenic foods, such as wheat and peanut, are used in a vast range of processed foods, and anaphylaxis following unexpected consumption of these allergens is a significant risk for sensitised individuals. In addition, the processing of foods,

especially in an industrial or a catering setting, often increases the risk of cross-contact with allergens that would not normally be expected to occur in the end product.

### ***Food additives and colourings***

The public and the media often blame food additives and colourings for an increase in the prevalence of food allergy, but there is little evidence to support this view.

True IgE-mediated food allergy may occur following exposure to enzymes and other proteins of plant or animal origin that are used in food processing (e.g. papain,  $\alpha$ -amylase and cochineal) and possibly to sulphites. There is no evidence that other additives or colourings cause either IgE-mediated or delayed non-IgE-mediated allergy. Some additives may lead to worsening of pre-existing allergic conditions such as urticaria, asthma or rhinitis, but the mechanism of this action is unclear.

Additives may produce unwanted reactions in other ways. In a few susceptible individuals, tartrazine, other azo dyes and benzoic acid may lead to the release of histamine and other mediators from mast cells by non-allergic mechanisms, and possibly to other pharmacological actions that mimic an allergic reaction in their effect. Sulphur dioxide and related compounds in food and drinks can act as an irritant to the airways and thus precipitate an asthma attack in a patient who already has hyper-reactive airways because of asthma.

### ***Threshold levels of allergen***

The sensitivity of food allergy sufferers to specific food allergens varies widely – between individuals, and probably also for the same individual at different times. Some individuals have severe reactions after exposure

to very low amounts of the offending allergen, whereas others have less severe reactions after exposure to much higher doses. This variability makes it difficult to calculate the lowest dose of a food allergen that is likely to provoke an adverse reaction.

The best estimates of the threshold doses for allergic reactions are based on the results of experimental double-blind food challenge studies, together with detailed case reports, including the results of investigations into all serious food allergic reactions in Sweden. However, such studies show a wide range of threshold doses.

- Egg corresponding to 10–190 mg ovalbumin has been responsible for severe reactions requiring medication.
- Cow's milk corresponding to 1 µg to 6 g protein (a vast dose range) caused an allergic response in one large study. In one case report 10 mg casein provoked a severe reaction, and 60 mg casein was fatal in another individual.
- Peanut protein may also show a wide range, but again some individuals are extremely sensitive. In a DBPCFC, the amounts needed to provoke allergic reactions ranged from 100 µg to 50 mg.

Such studies do not provide any information on the threshold doses for initial sensitisation to individual allergens, but other work suggests that very low doses of allergen may be sufficient for sensitisation. These doses could well be less than those required for a subsequent reaction. More research into threshold levels of allergen is required before they can be used to influence standards for food manufacturing and labelling.

## DIAGNOSIS OF FOOD ALLERGY

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The first step in the diagnosis of any food allergy or non-allergic food hypersensitivity is to assess the patient's history and dietary history in detail and to examine the patient – ideally at the time of a reaction.

If there is a clear immediate reaction to an identifiable food, the cause-and-effect relationship is relatively easy to establish, although the mechanism of the reaction may not always be clear.

If the patient believes a delayed reaction is related to food (e.g. that eczema worsens after specific food exposure), confirmation of a cause-and-effect relationship is much more difficult.

A full dietary history involves a degree of detective work for the patient and the physician. For example, if an individual consistently has oral allergy syndrome in response to strawberry yoghurt, it is important to establish whether he or she also reacts to milk, plain yoghurt, other flavours of yoghurt, fresh strawberries, preserved strawberries or any other ingredients. The food industry can often help by providing information on other products containing some of the same ingredients. A food diary kept by the patient can be very helpful.

The diagnosis of IgE-mediated food allergy is usually based on the history and confirmed by the results of one or more specific investigations, including skin tests, blood tests, response to dietary restriction and, sometimes, oral challenge tests. The confirmation of non-IgE-mediated (delayed) food allergy is more problematic, and is largely based on dietary restriction and oral challenge tests. The key features that help in distinguishing between different adverse reactions to food are listed in Table 3.

**TABLE 3****Key features of different adverse reactions to food**

	Clinical history of adverse reaction	Reaction on open food challenge	Reaction on double-blind food challenge	Evidence of IgE-mediated allergic reaction	Findings consistent with non-IgE-mediated allergic reaction
Food avoidance, aversion, and psychological intolerance	-/+	-/+	-	-	-
Non-allergic food hypersensitivity	+	+	+	-	-
IgE-mediated food allergy	+	+	+	+	-
Non-IgE-mediated food allergy	+	+	+	-	+

+ = feature present; - = feature absent

**Skin tests**

Skin prick tests (SPTs) are commonly used to demonstrate immediate hypersensitivity to a range of allergens in most types of allergic disease. A drop of allergen extract is applied to the skin of the forearm, and a lancet or needle is used to prick through this drop just under the skin. A positive reaction is shown by the rapid development of a “weal and flare” reaction, involving local redness, heat and itching. This reflects the local IgE-mediated response, with mast cell activation and the release of inflammatory mediators.

The diagnostic accuracy of SPTs for IgE-mediated food allergy is highest for foods with well-defined allergens,

including fish, egg and milk, and lower for some other foods, such as soy. SPTs using fresh food rather than processed extracts can sometimes produce better results.

A positive reaction to SPT does not necessarily show that the allergen causes clinical problems for the patient, but a strong reaction to foods such as egg, milk, wheat, peanut, tree nuts, fish, crustaceans and molluscs makes a reaction on food challenge likely.

SPTs can be used to monitor the progress of allergy, especially in early life. A decline in the severity of the skin reaction may suggest that an individual’s allergy has lessened, and that a new food challenge is justified.

SPTs may be positive in patients with delayed allergy to foods, as many such patients are also atopic and generally reactive, but there is no correlation between such positivity and food allergy. Thus, a positive SPT to egg in a patient with eczema does not confirm that eating egg may worsen the patient's eczema. However, a negative reaction to a correctly performed SPT makes allergy to egg very unlikely.

SPTs involve the introduction of very small amounts of allergen into the body. They are usually safe, although the local reaction may be severe in extreme allergy. However, they should be avoided or applied in very low concentrations in individuals with suspected peanut allergy, as there are reports of patients who have experienced a systemic response, even to a minute dose of peanut allergen.

### **Blood tests**

It is possible to search for specific IgE antibodies in the blood, by using the radioallergosorbent test (RAST). Each RAST seeks the presence of antibodies specific for one allergen. RASTs are usually used only when there is already a high suspicion of a likely allergen, although screening panels for several allergens are available. Like the SPT, RASTs are dependent on the availability of pure allergens, and a positive reaction does not necessarily demonstrate that the patient will react to the food taken orally.

The more recently developed fluorescent enzyme immunoassay (FEIA) is an automated quantitative measure of food-specific IgE levels. It has been shown to be as useful as SPTs for several major food allergens (milk, egg, fish and peanut) in some patients. FEIAs may prove to be helpful where SPTs are not (e.g. in patients with atopic eczema) or where SPTs are unsafe (e.g. in a patient who has had a severe reaction to a suspected allergen). They may also avoid the need for oral food challenge testing in some individuals.

### **Elimination-reintroduction diets**

Elimination or exclusion diets can be used in patients with chronic symptoms when SPT or RAST is positive or when there is a high index of suspicion of a food-related cause. The content of the elimination diet can be tailored to the patient's symptoms or the suspect foods, and often the first diet can simply be dairy product free and/or egg free. If this fails to control symptoms, a standard "few foods" diet (oligoallergenic diet), containing few known food allergens, can be used. In extreme circumstances, an elemental diet (containing basic nutritional necessities without conventional food) may occasionally be needed.

If there is no improvement in symptoms over a two-week period on the diet, it is unlikely that the eliminated foods are contributing to the symptoms. A more restricted diet may be indicated if the suspicion of food hypersensitivity remains. If there is improvement, food hypersensitivity (not necessarily food allergy) is a possible cause of or contributor to those symptoms.

If symptoms have improved, foods should be reintroduced one at a time. This can take some months following "few foods" or elemental diets. Ideally, several days should pass after the introduction of each food, to reveal any delayed reaction.

Elimination diets should be supervised by a dietician, and patients may need much help, guidance and encouragement to complete the process. Sometimes diets lead to a clear diagnosis of sensitivity to a specific food, but often they suggest either multiple sensitivity or no clear result. Because this is an "open" process, it is affected by the psychological influence of an individual's aversion to particular foods, and a positive result gives no information about the mechanism of any demonstrated food hypersensitivity.

## *Oral challenge procedures*

Oral challenge with a suspect food or allergens extracted from food may be carried out in several ways. “Open” challenges, in which the patient and the investigator know the nature of the food, are relatively simple to perform, and a negative result makes further investigation of that food unnecessary. There is a significant risk of false-positive results, because psychological reactions to the known food may occur. An advantage of open challenges is that the food can be given normally by mouth, so that any oral reactions will still occur.

A double-blind placebo-controlled food challenge (DBPCFC) provides the only conclusive evidence of hypersensitivity to a food. Here the patient receives at least two challenges, without knowing which is with food or food allergen and which is with placebo (containing inactive ingredients). Often a much larger number of challenges will be needed to test different allergens or to increase the test dose.

A DBPCFC can be performed using fresh food, in which case the food can be given in normal amounts by mouth. To be “double-blind” (unidentifiable by the patient and the investigator) the food must be disguised in a carrier substance. This may be difficult, as the taste of some foods is very difficult to mask. An alternative is to pass the food by tube directly into the stomach, but this bypasses oral contact. There is no agreed standard for the preparation of the food, so fresh food tests have little value in studies of the prevalence of particular allergies. In addition these tests demand substantial resources.

Standardised DBPCFCs are usually performed using capsules or tablets containing known doses of allergen in dehydrated form (or placebo), and the allergen dose can be titrated. Preparations of many allergens and of potential causes of non-allergic hypersensitivity

(including colourings and food additives) are commercially available. The disadvantages of this technique include the lack of oral contact with allergen, the difficulty in defining an appropriate dose and the number of capsules that may need to be swallowed. However, the advantages offered by the controlled nature and the repeatability of the procedure usually outweigh these disadvantages.

In patients who have reported immediate reactions to food, food challenges must be performed in hospital, with resuscitation facilities available, because extremely low doses of allergen may lead to anaphylaxis. Food challenge is not usually carried out in those who have previously had a life-threatening reaction or with allergens that commonly provoke an anaphylactic reaction, such as peanut.

Failure to react in a DBPCFC may indicate a lack of hypersensitivity or allergy to food, but it could also indicate that the challenge dose was too low or that the relevant allergen from the food is not present in the extract used.

A positive reaction to food but not to placebo is the best objective evidence of genuine food allergy or hypersensitivity. If this is combined with a clear history and a positive SPT or RAST, it provides firm evidence that the patient’s symptoms are the result of IgE-mediated food allergy.

Although the DBPCFC is the “ideal” investigation, few centres offer the procedure as a routine investigation. In everyday practice, many patients with IgE-mediated food allergy are treated on the basis of their personal history or open challenge tests. DBPCFCs tend to be used only by specialist centres in patients in whom the diagnosis is otherwise unclear, or as part of a detailed clinical study.

## *Inappropriate investigations*

At and beyond the fringes of medicine, the investigation and treatment of possible food allergy by a large number of questionable techniques is common in some countries.

These techniques include “cytotoxic” tests on blood exposed to different foods; skin tests in which drops of suspect material are applied to the skin in different dilutions, with the aim of finding a “neutralisation point”; sublingual tests, in which drops are applied under the tongue for diagnosis and subsequently for treatment; hair analysis; applied kinesiology or “dowsing” with suspect foods (observing the patient’s muscle strength as vials containing food extracts are held near them); a variety of electrical tests; and a large number of other methods.

Many such tests are inappropriate because they have not been scientifically validated. Others have been clearly shown to have no validity. When duplicates of these invalid tests are performed in a “blinded” manner, different results are usually obtained. In one study [4], for example, nine fish-allergic and nine healthy individuals provided blood samples that were coded and sent to five commercial laboratories that utilised unproven techniques and a hospital laboratory that used a ‘conventional’ test. One commercial laboratory also received hair samples. The commercial laboratories reported widely discrepant results for identical samples from the same individual. Non-existent allergies were also diagnosed in virtually all the normal subjects. By comparison, the hospital laboratory tested for IgE antibodies, and obtained 37 correct results out of 38 samples (18 out of 19 coded pairs). Other studies have demonstrated similar inconsistencies in the results obtained from many commercial laboratories utilising purported tests for food allergies.

Commercially available ‘fringe’ investigations also often fail to distinguish between allergy and other adverse reactions to food. Their results are usually reported as confirming “allergy”, which adds to the erroneous public view of food allergy as a common problem. However, the wide availability and use of these tests undoubtedly reflects a public “need”, resulting from a perceived lack of interest in possible food allergy by many members of the medical profession.

## **LIVING WITH FOOD ALLERGY**

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True food allergy is not curable, so patients with food allergy must adjust to living with their allergies and lead their lives in such a way that they minimise the risk of severe reactions to food. Many children with allergies to milk and egg (but not usually to peanut) “grow out of” their allergies in the sense that they cease to have clinical manifestations (although some skin prick test sensitivity usually persists). In these children, the diagnosis should be reassessed at yearly intervals by SPT or FEIA (followed by food challenge if the reaction has declined). If there is no reaction, a normal diet may be cautiously reintroduced.

### ***Dietary management***

The key to the treatment of both established food allergy and non-allergic food hypersensitivity is dietary management. Once the offending foods have been identified, an appropriate elimination or exclusion diet can be recommended. The nature of the diet will vary, depending on the relevant allergens, and initial advice and continuing involvement from a dietician is very helpful.

Any elimination diet must be planned on the basis of full knowledge of potential hidden sources of the relevant allergens and of possible cross-reactivity between foods or with inhaled or contact allergens.

The nutritional adequacy of all elimination diets must be assessed and adjusted if necessary, especially in growing children. Elimination of cow’s milk may cause particular nutritional problems, as it is a basic calorie and protein source for infants and children in many countries. If an infant is being breast-fed, the mother

may also need to modify her diet to minimise the risk of allergen exposure via breast milk (e.g. by eliminating milk, egg or fish from her diet). For bottle-feeding, hydrolysed milk protein offers an alternative to cow’s milk. Soy-based milk substitutes may also be used, although some infants may then develop allergy to soy.

The efficacy of dietary elimination must always be assessed. Improvement within 10 days and total remission within one month are reasonable targets if a disorder is believed to be entirely due to food allergy or hypersensitivity.

### ***Extent of dietary exclusion***

Some patients with food allergy or hypersensitivity are exquisitely sensitive, and must avoid contact with even very small amounts of the problem food. This group includes those with classic IgE-mediated food allergy who are at particular risk of anaphylaxis (especially those with asthma and those who have had previous life-threatening attacks).

These individuals could be affected by microgram amounts of the culprit allergen, which could be present in food as a result of trace cross-contact during manufacture or cooking. They are also potentially vulnerable to airborne allergens from cooking, or from airborne dust in the bakery section of a supermarket or even from a packet of peanuts being opened nearby on an airplane. Fortunately anaphylaxis has not been reported in the latter circumstances, but significant oral and respiratory reactions can occur.

Other sufferers could be said to be very sensitive. They must be careful to avoid the problem food as much as possible, even when it is known to be used in quite small amounts in a manufactured product, but they do not need to worry about eating trace amounts that may

get into the food by cross-contact (although larger amounts such as an accidental chunk of nut could still cause major symptoms). This group includes many people with classic IgE-mediated food allergy, especially those who do not have asthma and are believed to be at lower risk of life-threatening anaphylaxis; those with eosinophilic food reactions; and some of those with food-related atopic disease.

Some individuals are moderately sensitive, as they can tolerate small amounts of the provoking substance used in manufactured food as a secondary ingredient (the milk used in some kinds of bread, for example). This group includes most people with food intolerance of unknown cause, once they have avoided the food completely for a while and are in good health; many of those with food-related eczema or asthma; and some people with milder manifestations of classic IgE-mediated food allergy.

One difficulty with patients with the milder manifestations of classic IgE-mediated food allergy is that their sensitivity may be affected by other factors. “Adjuvant” factors such as cigarette smoking, alcohol intake, exercise and recent infection may amplify the individual’s response to allergen exposure, leading to a greater risk of a severe reaction.

These categories are subjective, and an individual sufferer may move from one category to another over time or on the basis of experience. The ability to carry out these dietary recommendations depends on an accurate and detailed knowledge of the content of natural and manufactured foods.

### ***Drug treatment for food allergy***

Drug therapy has only a limited role in food allergy, as there are no medications that will truly prevent or cure allergic reactions.

A drug that could be taken in advance to protect the sufferer against the effects of accidental exposure to a known allergen, especially when eating out or travelling, would be of great value but does not exist. Sodium cromoglicate (cromolyn sodium), taken by mouth, may sometimes increase the threshold dose at which a reaction occurs, but its effects are unpredictable and it is rarely used.

Individuals at risk of anaphylaxis should carry a loaded epinephrine (adrenaline) syringe or “pen” with them at all times and be trained in its use. Self-administration (or administration by a friend or relative) in the early stages of anaphylaxis can be life saving. Epinephrine can also be delivered to the throat and lungs via an inhaler. A patient with anaphylaxis always requires further urgent treatment in hospital.

The oral allergy syndrome, acute urticaria and angioedema often respond to prompt administration of an antihistamine by mouth, but this does not fully protect against the risk of anaphylaxis.

Patients with asthma, rhinitis or eczema in association with food allergy should receive the same drug treatments for these conditions as those who do not have food allergy. Unless the relevant food is easy to identify and avoid, such therapy is usually far more effective than attempts at dietary elimination.

Immunotherapy with relevant food extracts, in which a series of “desensitising” injections is given to suppress or block the patient’s IgE response to the allergen, could prove to have useful effects but has not been shown to be safe. Oral hyposensitisation, in which progressive doses of allergen are given by mouth, has not been shown to be effective and is hazardous in sensitive individuals.

## **RISK REDUCTION AND FOOD LABELLING**

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Individuals with known food allergy or hypersensitivity need to avoid ingestion of the relevant foods, especially when they are exquisitely sensitive and at risk of life-threatening reactions. This requires that affected individuals receive education and guidance on the likely sources of problem allergens. Avoiding allergens in fresh, unprocessed foods is relatively simple, although cross-contact is possible if foods are sold loose and unwrapped, or if they are inappropriately handled in home or restaurant kitchens. Cross-reactivity between allergens is a risk in all these settings.

Reducing the risk of unwanted allergen exposure from manufactured foods is a major concern for the food industry.

### ***Risk reduction in manufacturing processes***

With manufactured foods, and foods served by the catering industry, avoidance requires that the consumer has a detailed knowledge of the ingredients. Where a food is manufactured in a facility used for no other purpose, from a known list of pure ingredients (which could not themselves have been contaminated before delivery to the plant), such labelling is simple, but in the real world, this situation is rare.

Most foods, whether manufactured or catered, are made in facilities that produce many products simultaneously or sequentially. An allergen that is not intended to be part of a food product may become incorporated into the product if dust or scraps from previous production processes are inadvertently incorporated. In addition, many manufactured and catered foods contain

ingredients from other suppliers, who use different premises that are subject to similar risks. Also many manufactured foods (such as chocolate and baked goods) often contain “rework” materials – surplus material remaining from a previous batch after trimming, moulding, or other processing. This is another source of potential carry-over of unwanted allergens.

Good Manufacturing Practices (GMP) within the food industry can often prevent carry-over of unwanted allergens from one food to another, but frequently the risk of trace carry-over due to cross contact remains. In some cases thorough and adequate cleaning of equipment may not be possible (e.g. on lines producing sticky or fatty foods such as chocolate, where dry cleaning is inappropriate and would cause a greater microbiological hazard). Nut-containing chocolate products are often made on the same production line as nut-free products. Major contamination by nuts on the line can be avoided by Good Manufacturing Practice, but there is always the possibility that nut dust or fragments may have been trapped in the parts of the equipment, from where they may be blown out into the new batch of food. Fragments of nut carried over in this way could be large enough to contain a substantial amount of allergen. Similarly, if another production line in the same premises is making a nut-based product, airborne cross contact is possible. In these circumstances appropriate labelling is the only satisfactory option.

To minimise these risks in food production, guidelines that cover Good Manufacturing Practice and other issues in manufacturing, labelling and information provision to consumers should be followed. An allergen prevention plan (analogous to that used to prevent bacterial contamination; both are known as a “Hazard Analysis of Critical Control Points” plan – HACCP) should determine potential sources of contaminating allergens in food manufacture and enforce appropriate controls to prevent

their introduction into food products. These controls may include the following.

- Restricting the use of peanuts, tree nuts and other foods from “the big eight” to products in which they are an essential ingredient
- Adhering to strict rework policies (for example, like-into-like food only)
- Scheduling production of allergen-containing products at the end of manufacturing runs
- Thorough cleaning of lines after running allergen-containing food products
- Redesigning equipment
- The use of a separate plant in separate buildings or sites to prevent any risk of contamination by common allergenic foods (for example, a nut-free manufacturing plant)

Proper labelling and control of ingredients from suppliers and the training of employees are essential to this process.

Traces of many common food allergens can be detected in foods by immunological methods. These can be used to check the adequacy of cleaning processes, for cross-checking of food content, and to identify any points at which contamination has occurred. These methods may be useful for the detection of evenly distributed allergens, but they will not detect contamination by heterogeneously distributed material (e.g. occasional larger pieces of nut in chocolate, biscuit pieces, etc.).

Similar standards for the avoidance of common allergens should apply in the catering industry, but these have not been formalised, and good control is generally less likely to occur there than in large-scale food manufacturing.

## ***Labelling of allergen risk***

Comprehensive labelling of the ingredients of manufactured foods seems desirable to many consumers but carries some potential difficulties. Small amounts of some allergens (microgram amounts) can cause a reaction in some sensitive individuals. Many manufactured foods contain large numbers of ingredients in very small quantities, and detailed labelling can become very complicated, especially if multilingual labelling is required on a small package. Lengthy lists of complete contents may not always be useful to the consumer (because of their length, the obscure nature of many of the ingredients, and the doubtful relevance of such small amounts to many consumers). This approach could be refined if the threshold levels for response to different allergens were better defined in the future.

The “25% rule,” which has exempted food manufacturers from listing the individual ingredients of a compound ingredient which constitutes less than 25% of a product (slices of sausage on a pizza, for example) was insufficient to protect consumers from food allergens, and an amendment of a European Union (EU) Directive recently changed this rule. In addition, all allergens must be labelled, whether they are ingredients, parts of compound ingredients, additives or carriers of additives or flavourings. The allergens covered by the EU directive are listed in Table 4. Again, such labelling may result in very long lists of ingredients, which are difficult to read in full.

Guaranteed free labelling is an alternative approach that is relevant to particular groups of consumers. Here the food is labelled as required by law, and trace ingredients are not all quantified or listed. However, a specific declaration is made that the product is “guaranteed peanut-free” or “guaranteed gluten-free,” for example. In practice it is usually impossible to guarantee

**TABLE 4**

<b>Key features of different adverse reactions to food</b>					
	<b>Codex Alimentarius Commission of FAO/WHO (CODEX)</b>	<b>Draft Amendment of European Union (EU) Directive</b>	<b>International Alliance of Food Products Associations (IAFPA)</b>	<b>ILSI Food Allergy Task Force [3] (ILSI)</b>	<b>Food and Drink Federation<sup>1</sup> (FDF)</b>
<b>Criteria for inclusion of foods and products derived from them</b>	<b>Most common allergenic foods</b>	<b>Recognised as causing food allergy or intolerance</b>	<b>Foods or food ingredients that can trigger IgE-mediated reactions</b>	<b>Foods shown to be positive in DBPCFC test and cause of anaphylactic reaction</b>	<b>Foods or food ingredients that can trigger IgE-mediated anaphylactic reactions</b>
<b>Allergen</b>					
Peanut	X	X	X	X	X
Tree nuts	X	X	X	X	X
Egg	X	X	X	X	X
Fish	X	X	X	X	X
Cow's milk	X	X	X	X	X
Crustaceans, molluscs, shellfish	X	X		X	X
Sesame seeds		X		X	X
Soya	X	X	X	X	X
Sulphite <sup>2</sup>	X	X			
Cereals containing gluten <sup>3</sup>	X	X			
Wheat				X	
Celery		X			
Mustard		X			

1 The FDF recognises that highly processed materials may no longer be allergenic.

2 Where the concentration is 10 mg/kg or higher.

3 Wheat, rye, barley, oats, spelt or their hybridised strains (the CODEX and EU lists included gluten-sensitive enteropathy [coeliac disease] as a food allergy, while the other three lists did not).

complete freedom from any allergen, but guarantees of very low content are possible (e.g., a guarantee of less than 0.01% gluten content). If accurate, such labelling is very helpful to the target group, but less so to those who have other significant allergies. Peanut-free would be helpful to an individual with peanut allergy, for example, but unhelpful to someone with sesame seed allergy who may be worried about the possible presence of trace amounts of that allergen.

Positive declaration labelling is a third approach that is favoured by many, including the FAO/WHO Codex committee, ILSI and the EU. Foods and additives from an agreed list (see Table 4) are always declared in the ingredients, even if they are present only in trace amounts. This approach is potentially very helpful to those with allergies to the food groups included in an agreed list if it is applied accurately and honestly.

Positive declaration labelling has led to large numbers of products being labelled “May contain traces of nuts” and, to a lesser extent, bearing similar labels warning of possible milk and egg content. The Food Standards Agency in the UK has recently researched the use of such labelling from the consumer’s point of view [5]. Such labelling is viewed with suspicion by some consumers, who may regard it as essentially a defensive move by the food industry. It is generally agreed that “may contain” labelling should be used only as a last resort. However, this label still reflects a real and sometimes unquantifiable risk of manufacturing carryover of allergens into a product that does not contain them by design. Its intention is to warn individuals with food allergy of the risk of exposure to otherwise unexpected allergens and allow them to make an informed decision – if necessary, in consultation with their medical advisers.

## *Novel food proteins*

As discussed earlier, allergies to “new” foods commonly emerge as these foods are introduced to a new population. Thus kiwi fruit allergy has become a significant problem in the UK over the past few years, and cross-reactive lupin allergy is a problem for some with peanut allergy.

Novel food proteins from genetically modified (GM) organisms or from new manufacturing processes applied to existing foods could also carry a risk of food allergy. For example, a new GM variety of soybean, developed in Brazil for animal feed, contained a gene transferred from Brazil nut. The aim of this gene transfer was to enhance the nutritional value of the soybean by making it methionine rich. When the new soy was tested before release, cross-reactivity was found in individuals allergic to Brazil nut. Development of the new variety of soybean stopped, even though it was intended for use only in animal feed. Vigilance was effective in this case, and it is important that similar vigilance be applied to new foods in the future – whether of GM or of other origin.

The need for vigilance has been addressed by regulatory agencies and by food manufacturers. In its 1992 biotechnology policy statement, the US Food and Drug Administration stated that “a protein copied by genetic engineering from a food commonly known to cause an allergic reaction is presumed to be allergenic unless clearly proven otherwise. Any food product of biotechnology that contains such proteins must list the allergen on the label.” This rule is generally applied.

More recently, a number of working parties have considered the issue of novel food proteins in more detail. It is not possible to determine in advance whether a protein source will prove to be a food allergen, so the

properties of a new protein must be compared with those of known allergenic proteins. In 2001, the Joint FAO/WHO Expert Consultation on Allergenicity of Foods Derived from Biotechnology [6] produced guidelines for the assessment of potential allergenicity of novel foods, which included the following.

- Whether or not the gene source is known to be allergenic, a structural assessment of the novel protein is required.
- If the new protein shows a sequence homology with a known allergen (i.e., if it contains a similar sequence of amino acids to a known epitope), the risk of allergenicity in the new protein is clear.
- If there is no sequence homology, testing against serum from known sufferers of related food allergy should be carried out.
- If such testing gives negative results, further testing using measures of pepsin resistance (resistance to digestive breakdown of the protein) is required to establish the probable level of risk of allergenicity.

Novel foods derived from sources or methods other than biotechnology can follow a similar safety assessment.

If a novel food is marketed after these studies, post-launch monitoring (post-marketing surveillance) is essential to verify the safety assessment and detect any unexpected and rare adverse events.

An interesting possibility is that genetic modification might be used to develop hypoallergenic novel food proteins. For example, it might be possible to modify a plant so that it no longer produces an allergenic protein, but instead produces a protein that is much less likely to generate an allergic response. This possibility is

complicated by the fact that many problem foods contain multiple allergens, but one technique – introducing copies of a gene in the ‘antisense’ orientation – has already been proved effective in reducing allergen levels in rice, and another technique – site-directed amino acid substitution – may be possible in soybean. Again, full pre-marketing risk assessment and post-marketing surveillance will be required.

## CONCLUSIONS

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Food allergy is a major problem for a small proportion of the population, and a less severe problem for at least 2% of children and 1% of adults in most European countries. Food hypersensitivity, involving non-allergic mechanisms, affects at least an additional 3%–6% of children and 1% of adults. Like other allergies, food allergy is probably becoming more common in the population of the developed world.

Classic IgE-mediated food allergy causes a characteristic range of symptoms, which develop rapidly after exposure to the food and which can also be caused by non-food allergens and closely mimicked by rarer non-allergic reactions. The most severe manifestation of IgE-mediated food allergy is anaphylaxis, a dangerous condition that can be rapidly fatal without appropriate treatment. Unfortunately, the strength of reaction in an individual is difficult to predict, so many people with IgE-mediated food allergy must be considered at risk of a severe reaction.

A number of types of food provoke IgE-mediated food allergy, and some seem more likely to produce severe reactions than others. Current management of patients involves accurate diagnosis, elimination of the problem food from the diet, and the provision of “rescue” medication for immediate self-administration in severe attacks. Elimination of the problem food is relatively easy if the allergen is from an unusual or discrete food source, but it is much more of a challenge for the sufferer if the food source is commonly used (e.g. peanut) or almost ubiquitous (milk, egg, or wheat protein) in manufactured food.

Other forms of allergy to food involve less rapid mechanisms. Coeliac disease is a chronic and potentially

serious condition in which a non-IgE-mediated allergic reaction to gluten plays a key role (although it may not be the cause of the condition). Dietary elimination of gluten controls symptoms and reverses the changes in the gut. Delayed food-related reactions can occur in other conditions, such as atopic eczema, but these are more difficult to diagnose than immediate reactions, and the effect of eliminating the problem food is often less marked. Food allergy is probably a contributor to these conditions rather than their sole cause.

The food industry recognises the significance of allergens to individuals who have food allergy, and responsible manufacturers have systems in place to identify and minimise risk for those with common food allergies. These are limited to some extent by the nature of food manufacturing processes and by the demand to provide a full range of palatable and enjoyable food to the majority of the population who do not have food allergies. The accurate labelling of food is essential, but the indication of a risk of the presence of trace amounts of allergens, or a remote risk of the presence of a larger amount, can make choice of food difficult for the allergy sufferer. Much research is in progress with the aim of minimising the allergenicity of natural and manufactured foods in the future.

Restaurant, canteen and take-away food is a weak link in the protection of food allergy sufferers, and many of the reported severe reactions in the UK, the USA, Sweden and other countries have followed consumption of food from these sources.

Currently, the medical profession can offer only symptomatic treatment for food allergies. Much medical research is directed towards the future prevention of allergies to food and other allergens, with particular attention being devoted to the sensitisation process, which usually takes place in infancy or even during

pregnancy. Drugs that protect against attacks in an individual who is already sensitised would also be of great value.

The individual with food allergy (or the carer of an infant or child with food allergy) has a responsibility for constant vigilance in the selection and exclusion of foods. This requires education, guidance, information, consideration and practical help from doctors, dieticians, caterers and food manufacturers. The quality of life of those with serious food allergies would be greatly improved if this support were consistently available from all parties.

## **GLOSSARY**

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- Allergen:** A foreign substance or protein (antigen) that stimulates an allergic reaction.
- Allergy:** A state in which objectively reproducible symptoms or signs can be initiated by immunologic mechanisms after exposure to a defined stimulus at a dose tolerated by normal subjects.
- Anaphylaxis:** A generalised inflammatory immunologic reaction to a foreign protein in a sensitised individual, which may be severe enough to be life-threatening.
- Angioedema:** Swelling of the skin or mucous membrane and underlying tissue. Usually associated with urticaria.
- Antibody:** A protein molecule (immunoglobulin) produced and secreted by B lymphocytes in response to an antigen, which is capable of binding to that specific antigen.
- Antigen:** A foreign substance (usually a protein) that is recognised by the immune system when introduced into the body.
- Asthma:** A disorder characterised by recurrent cough and wheeze, caused by reversible inflammation and narrowing of the lower airways, in which many cells play a role, especially mast cells and eosinophils.
- Atopy:** A personal or familial tendency to produce IgE antibodies in response to low doses of allergens, and to develop typical symptoms such as asthma, rhinitis or eczema or dermatitis.
- B cell (or B lymphocyte):** A subset of lymphocytes that can develop into antibody-producing cells.
- Basophil:** A type of circulating white blood cell that contributes to inflammatory reactions and symptoms of allergy and is closely related to the mast cell.
- Challenge test:** Test administration of a food or allergen to investigate the possibility that it will cause an adverse reaction.
- Coeliac disease:** A disease in which the mucosa of the small intestine is damaged by exposure to gluten (also known as gluten sensitive enteropathy).
- Crohn's disease:** A chronic inflammatory disease of the gut. The cause is unknown.
- Dermatitis:** Inflammation of the skin. Atopic dermatitis is synonymous with atopic eczema.
- Double-blind placebo-controlled food challenge (DBPCFC):** Challenge test in which neither the patient nor the clinical investigator knows the identity of the administered substance, which may be food (or allergen) or placebo.
- Eczema:** An itching red inflammatory skin disorder, often on the face, hands or skin folds, which oozes and crusts if scratched; it is common in individuals with atopy.
- Enzyme:** Proteins that catalyse the reactions of metabolism, speeding them up without themselves being used up in the reaction. Each enzyme is specific for a given substrate or reaction.
- Epithelium:** The surface layer of the skin, and the lining layer of the gut, air passages of the lungs, and other hollow organs of the body.
- Epitope:** A portion of an allergen that combines with a matching portion of an antibody (the paratope).
- Gastrointestinal tract:** The organs along which food travels from the mouth, within which food is digested and absorbed, and from which the undigested remnants emerge as stools.

**HACCP plan:** Hazard Analysis of Critical Control Points plan. A document prepared to ensure control of hazards that are significant for food safety in the segment of the food chain under consideration.

**Histamine:** An amine derived from the amino acid histidine. Large amounts are released by mast cells when the body encounters an allergen (or other substance) to which it is sensitive, thereby triggering symptoms of an immediate allergic reaction.

**Hydrolysis:** The splitting of a chemical compound into its constituents by addition of water, thus breaking one chemical bond. The process may be purely chemical or catalysed by enzymes. Digestion is normally achieved by enzyme-catalysed hydrolysis.

**Hypersensitivity:** A state in which objectively reproducible symptoms or signs can be initiated by exposure to a defined stimulus at a dose tolerated by normal subjects.

**IgA, IgD, IgE, IgG, IgM:** Classes of immunoglobulin.

**Immunoglobulin:** A protein molecule produced and secreted by B lymphocytes in response to an antigen, which is capable of binding to that specific antigen (also known as an antibody).

**Inflammation:** General term for the reaction of tissues to injury, infection or a localised immune (allergic) response; characterised by the infiltration of inflammatory cells and clinically by heat, redness, swelling and pain.

**Lactose intolerance:** A state in which an individual is unable to digest significant amounts of lactose, the predominant sugar in cow's milk. This results from a deficiency of the enzyme lactase, normally produced by the mucosal cells of the small intestine.

**Leukotrienes:** Chemical mediators of the inflammatory response, released by various white blood cells and by mast cells and basophils.

**Lymphocytes:** White blood cells that are part of the body's immune system.

**Mast cells:** Granule-containing cells found in tissue whose inflammatory responses contribute to the symptoms of allergy by release of histamine and other mediators. Closely related to basophils.

**Migraine:** Recurrent headaches, often mainly on one side of the head and often preceded by flashing lights, nausea or other warning symptoms.

**Mucosa:** The lining membrane of tubular organs.

**Oral allergy syndrome:** Acute onset of tingling, itching and swelling of the lips and mouth as the result of an allergic reaction.

**Peyer's patches:** Specialised groups of cells in the wall of the small intestine, composed of lymphocytes and other immune cells.

**Placebo:** A harmless and pharmacologically inactive substance, usually disguised, given to compare its effect with that of an active material. It is used to assess whether there is any psychological effect arising from consumption.

**Prevalence:** The number of existing cases of a disease in a defined population at a specified time.

**Prostaglandins:** Fatty acid derivatives synthesised by various white blood cells and at the surface of mast cells that can cause contraction or relaxation of smooth muscles in the airways, blood vessels and elsewhere.

**Rhinitis:** An inflammatory disorder of the nose that may be caused by allergy (allergic rhinitis) and associated with inflammation of the eyes (rhinoconjunctivitis).

**Sulphite:** Anion derived from sulphur, commonly used in wine and on salads and other foods as a preservative.

**T cells (or T lymphocytes):** A subset of lymphocytes that induce, regulate, and effect specific immune responses after stimulation by antigen.

**Urticaria:** A raised, itching rash, characterised by transient raised areas (weals) with reddened margins and pale centres. May result from allergy or other causes.

**Weal (also wheal):** A short-lived, well-circumscribed raised area of skin, often white in colour and usually itchy.

## REFERENCES

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- [1] Young, E., Stoneham, M.D., Petruckevitch, A., Barton, J., Rona, R. A population study of food intolerance, *Lancet*. 1994; 343:1127–1130.
- [2] Johansson, S.G.O., Hourihane, J.O'B., Bousquet, J., *et al.* (the EAACI Nomenclature Task Force). A revised nomenclature for allergy (position paper), *Allergy*. 2001; 56:813–824.
- [3] Bousquet, J., Björkstén, B., Brujnzeel-Koomen, C.A.F.M., Huggett, A., Ortolani, C., Warner, J.O., Smith, M., for the ILSI Europe Food Allergy Task Force. Scientific criteria and the selection of allergenic foods for product labelling, *Allergy*. 1998; 53:3–21.
- [4] Sethi, T.J., Kemeny, D.M., Tobin, S., Lessof, M.H., Lambourn, E., Bradley, A. How reliable are commercial allergy tests? *Lancet* 1987; 1:92–94.
- [5] Food Standards Agency. “May Contain” Labelling: The Consumer’s Perspective. London: Food Standards Agency, 2002. Available online at: <http://www.foodstandards.gov.uk/foodlabelling/policiesandregulations/maycontainsummary>
- [6] Food and Agriculture Organization of the United Nations (FAO) and World Health Organization (WHO). Evaluation of Allergenicity of Genetically Modified Foods: Joint FAO/WHO Expert Consultation on Allergenicity of Foods Derived from Biotechnology. Rome: FAO, 2001.

## **FURTHER READING**

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- Bruijnzeel-Koomen, C., Ortolani, C., Aas, K., Bindslev-Jensen, C., Björkstén, B., Moneret-Vautrin, D., Wöhrich, B. Adverse reactions to food (position paper), *Allergy*. 1995; 50:623–635.
- BSACI working party: Lack, G., Chapman, M., Kalsheker, N., King, V., Robinson, C., Venables, K. Report on the potential allergenicity of genetically modified organisms and their products, *Clin Exp Allergy*. 2002; 32:1131–1143.
- Cochrane, G.M., Jackson, W.F., Rees, P.J. *Asthma: Current Perspectives*. London: Mosby-Wolfe, 1996.
- Committee on Toxicity of Chemicals in Food, Consumer Products, and the Environment. Adverse Reactions to Food and Food Ingredients. London: Food Standards Agency, 2000. Available online at: <http://www.foodstandards.gov.uk/science/ouradvisors/toxicity/reports/foodreactions>
- David, T.J., Patel, L., Ewing, C.I., Stanton, R.H.J. Dietary factors in established atopic dermatitis, in Williams, H.C., ed., *Atopic Dermatitis: The Epidemiology, Causes, and Prevention of Atopic Eczema*. Cambridge, UK: Cambridge University Press, 2000:193–204.
- Dreborg, S., Höst, A., Murano, A., eds. Food allergy, atopic dermatitis, and the allergy march, *Pediatric Allergy and Immunology*. 2001; 12(suppl. 14):1–107.
- Emerton, V., ed. *Food Allergy and Intolerance: Current Issues and Concerns*. Leatherhead, UK: Leatherhead Publishing, 2002.
- Huggett, A.C., Hischenhuber, C. Food manufacturing initiatives to protect the allergic consumer, *Allergy*. 1998; 53(suppl 46):89–92.
- Institute of Grocery Distribution (IGD). *Voluntary Labelling Guidelines for Food Allergens and Gluten*. Letchmore Heath, UK: IGD, 2000.
- Jackson, W.F., ed. *Allergic Disorders*. London: Mosby-Wolfe, 1997.
- Langseth, L. *Nutrition and Immunity in Man*. ILSI Europe Concise Monograph Series. Washington, DC, and Brussels: International Life Sciences Institute, 1999.
- Metcalfe, D.D., Sampson, H.A., Simon, R.A., eds. *Food Allergy: Adverse Reactions to Foods and Food Additives*, 2nd ed. Cambridge, MA, USA: Blackwell Science, 1997.
- Morgan, M., Ortolani, C., eds. Symposium on immunological, chemical, and clinical problems of food allergy, *Allergy*. 2001; 56(suppl 67):1–130.
- Sicherer, S.H. Food allergy: when and how to perform oral food challenges, *Pediatric Allergy and Immunology*. 1999; 10:226–234.
- Warner, J.O. Food allergy: how much is there and how do we prevent it? *BNF Nutrition Bulletin*. 1998; 23(suppl 1):55–64.
- Warner, J.O. Peanut allergy: a major public health issue, *Pediatric Allergy and Immunology*. 1999; 10:14–20.
- Warner, J.O., Jackson, W.F. *Color Atlas of Pediatric Allergy*. London: Wolfe, 1994.

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