

Adverse reactions and intolerance to foods

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Food allergy is a form of adverse reaction to food in which the cause is an immunological response to a food. Common food triggers are eggs, cow's milk, peanuts and fish. Food allergy is most common in young infants, most of whom grow out of the allergy by the age of 5 years. The exception is allergy to peanuts, which is life-long. The term food intolerance does not imply any specific type of mechanism, and is defined as a reproducible adverse reaction to a specific food or food ingredient. Mechanisms for food intolerance comprise immunological reactions (*i.e.* food allergy), enzyme defects, pharmacological effects, irritant effects, and toxic reactions. Despite the popular phobia of food additives and food processing, and the obsession for so-called natural foods, the greatest dangers come from naturally occurring foods and food ingredients.

Over the years, a large number of disorders have been attributed to reactions to foods. The uncritical and over-enthusiastic nature of many claims, plus the anecdotal evidence upon which they were based, have generally discredited the whole subject. The introduction of double-blind provocation tests has placed studies on a more scientific footing, but they are impractical in routine management. The lack of objective and reproducible diagnostic laboratory tests which could eliminate bias has ensured that controversy about food intolerance continues.

After defining the key terms, this review describes immunological followed by non-immunological reactions to foods.

Definitions

The word allergy is frequently misused, and applied indiscriminately to any adverse reaction, regardless of the mechanism.

An **allergic response** is a reproducible adverse reaction to a substance mediated by an immunological response. The substance provoking the reaction may have been ingested, injected, inhaled or merely have come into contact with the skin or mucous membranes.

Food allergy is a form of adverse reaction to food in which the cause is an immunological response to a food.

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Food intolerance does not imply any specific type of mechanism, and is simply defined as a reproducible adverse reaction to a specific food or food ingredient.

Food aversion comprises food avoidance, where the subject avoids a food for psychological reasons such as distaste or a desire to lose weight, and psychological intolerance (see below).

Psychological intolerance is an unpleasant bodily reaction caused by emotions associated with the food rather than the food itself. Psychological intolerance will normally be observable when a food is given under open conditions, but will not occur when the food is given in an unrecognisable form. Psychological intolerance may be reproduced by suggesting (falsely) that the food has been administered.

The term **anaphylaxis** or **anaphylactic shock** is taken to mean a severe and potentially life-threatening reaction of rapid onset, with circulatory collapse. The term anaphylaxis has also been used to describe any allergic reaction, however mild, that results from specific IgE antibodies, but such usage fails to distinguish between a trivial reaction (*e.g.* a sneeze) from a dangerous event.

Food allergy – immunological reactions to food

Mechanisms of food allergy

Understanding of the mechanisms of food allergy is poor, and in many cases the precise mechanism is obscure.

Sensitisation

Possible factors which contribute to immunological sensitisation leading to food intolerance are listed in Table 1.

Immunological and molecular mechanisms

Despite the gastrointestinal barrier, small amounts of immunologically intact proteins enter the circulation. Normal individuals, although capable of mounting a rapid and potent response against foreign substances, develop tolerance to ingested food antigens¹. The means by which tolerance develops is poorly understood.

Heat treatment

Heat treatment renders certain (but not all) foods less likely to provoke an allergic reaction in a subject who is allergic². In cow's milk, whey proteins are easily denatured by heat but casein is highly resistant. Heat renders a large number of fruits and vegetables less likely to provoke

Table 1 Possible factors which contribute to sensitisation to foods

Factor	Comments
Genetic predisposition	Food allergy is commonly familial, and commonly co-exists with atopic disease, suggesting the importance of genetic factors
Immaturity of the immune system or the gastrointestinal mucosal barrier in newborn infants	Studies to see if food allergy or atopic disease can be prevented by interventions during pregnancy or lactation are based on the idea that there is a critical period during which sensitisation can occur
Dosage of antigen	It is possible that high dosage leads to the development of tolerance, and low dosage leads to sensitisation. This might explain the development of allergy to traces of foods that reach an infant through mother's breast milk
Certain food antigens are especially likely to lead to sensitisation, for example egg, cow's milk, fish and peanut	We do not know why, for example, peanuts and fish are more capable of inducing allergic reactions than lamb or cauliflower. The molecular acrobatics that make one antigen an allergen and another antigen a non-allergen are not known
A triggering event, for example a viral infection	There is a suggestion that food allergy may develop in a previously non-allergic subject after a viral infection such as infectious mononucleosis (glandular fever)
Alteration in the permeability of the gastrointestinal tract, permitting abnormal antigen access	It is possible that acute viral gastroenteritis may damage the small intestinal mucosa, allowing abnormal absorption of food proteins, leading to sensitisation

adverse reactions in subjects who are intolerant. Thus, for example, it is not uncommon to see children who are allergic to raw potatoes or fresh pineapple, but almost all such children can tolerate cooked potatoes or tinned pineapples².

Prevalence of food allergy

Reports of food allergy from individuals or parents of children are notoriously unreliable. It is common for parents to believe that foods are responsible for a variety of childhood symptoms. Double blind provocation tests in children with histories of reactions to food only confirm the story in one-third of all cases³. In the case of purely behavioural symptoms, in one study the proportion that could be reproduced under blind conditions was zero⁴. Adults' beliefs about their own symptoms are just as unreliable^{5,6}.

The parents of 866 children from Finland were asked to provide a detailed history of food allergy, and for certain foods the diagnosis was further investigated by elimination and open challenge at home⁷. Food allergy was reported in 19% by the age of 1 year, 22% by 2 years, 27% by 3 years, and 8% by 6 years. In a prospective study of 480 children in

the US up to their third birthday, 16% were reported to have had reactions to fruit or fruit juice and 28% to other food⁸. However, open challenge confirmed reactions in only 12% of the former and 8% of the latter.

Prospective studies indicate that about 2.5% of infants experience allergic reactions to cow's milk^{1,9}. Allergic reactions to egg occur in about 1.3% of children¹⁰, and to peanut in about 0.5% of children in the UK and US¹. The prevalence of food allergy in adults is believed to be less than in children, but a recent national survey in the US suggested that peanut and tree nut allergy together affect 1.3% of adults. If one adds to this the estimated frequency of shellfish allergy (approximately 0.5%) it appears likely that 2% of the adult population in the US is affected by food allergy¹.

Natural history of food allergy

The natural history of food allergy is poorly documented. It is well known that a high proportion of children with food intolerance in the first year of life lose their intolerance in time¹¹. The proportion of children to which this happens varies with the food and probably with type of symptoms which are produced. Thus it is common for allergy to cow's milk or egg to spontaneously disappear with time^{2,11}, whereas peanut allergy is usually life-long. In the North American study referred to above, it was found that the offending food or fruit was back in the diet after only 9 months in half the cases, and virtually all the offending foods were back in the diet by the third birthday⁸. In a population based study from Norway, two-thirds of reactions to foods in children had disappeared within 6 months¹². A further study of 9 children with very severe adverse reactions to food showed that, despite the severity, 3 were later able to tolerate normal amounts of the offending food and a further 4 became able to tolerate small amounts¹³.

In adults with food allergy, the problem is far more likely to be life-long. Nevertheless, some adults do become tolerant to foods to which they were allergic. In one adult follow-up study, approximately one-third of adults were found to lose their allergy after maintaining an elimination diet for 1 year¹⁴.

Clinical features

The clinical features of an allergic reaction include urticaria (nettle rash), angioedema, rhinitis (sneezing, nasal discharge, blocked nose), worsening of pre-existing atopic eczema, asthma (wheezing, coughing, tightness of

Table 2 Cross reaction between foods of different species, and between foods and other antigens

Food item(s)	Cross reactions
Milk from cows, goats, sheep and horses	The marked antigenic similarity between the proteins in the milk of cows, goats, sheep and horses means that almost all subjects who are allergic to cow's milk protein are allergic to the milks of these other animals
Bird eggs	The eggs from turkeys, duck, goose and seagull all contain ovalbumin, ovomucoid and ovotransferrin, the major allergens in hens' eggs
Legumes (beans, peas, soya, lentils, peanuts, liquorice, carob and gum arabic)	Cross-reactivity is uncommon
Seafood	The taxonomic diversity (fish, molluscs, crustaceans) explains why complete cross-reactivity for all seafood is uncommon
Cross reactions between inhaled pollen and ingested food allergens	An example is the association between allergy to birch tree pollen combined with allergy to apple, carrot, celery, potato, orange and tomato

the chest, shortness of breath), vomiting, abdominal pain, diarrhoea, and anaphylactic shock.

Cross reactions

This term refers to: (i) cross-reaction between different food species; and (ii) cross-reactions between foods and non-food items. Most studies of cross-reactivity are based on skin prick and IgE antibody test results which are of little relevance to clinical sensitivity. The position is summarised in Table 2.

Timing of allergic reaction and delayed reactions

Most allergic reactions to foods occur within minutes of ingestion of the food; but sometimes a reaction may be delayed. For example, in cow's milk protein allergy, three types of reaction are recognised¹⁵. In the 'early skin reaction' group, symptoms begin to develop within 45 min of cow's milk challenge. In the 'early gut reaction' group, symptoms begin to develop between 45 min and 20 h after cow's milk challenge. In the 'late reaction' group, symptoms begin to develop about 20 h after cow's milk protein challenge.

Quantity of food required for allergic reaction

The quantity of food required to produce an allergic reaction varies. Some patients with cow's milk protein allergy, for example, are highly sensitive and develop anaphylaxis after ingestion of less than 1 µg of casein, β-lactoglobulin or α-lactalbumin. In contrast, there are children and adults who only react adversely to 200 ml or more¹⁶. There is a relationship between the quantity of milk required and the time of onset of symptoms. In one study, the median reaction onset time in those who reacted to 100 ml milk challenges was 2 h, but the median reaction onset time in those who required larger amounts of milk to elicit reactions was 24 h¹⁶.

Other factors required for an allergic reaction to occur

In some individuals, adverse reactions only occur when ingestion of a trigger food is combined with some other factor.

Food-dependant exercise-induced anaphylaxis

In this unusual condition, attacks only occur when the exercise follows within a couple of hours of the ingestion of specific foods such as celery, shellfish, squid, peaches or wheat².

Effect of disease activity

It is a common, but poorly understood, observation that children with eczema and food allergy can often tolerate some or all food triggers when the skin disease clears (usually when the child is on holiday in a sunny country).

Drug-dependant food allergy

There are individuals who only react to specific foods while taking a drug. The best recognised examples of this are individuals who only react to foods while taking salicylate (aspirin).

Diagnosis of food allergy

The diagnosis of food allergy is usually made from the history (*see* Table 3), supported by information about the response to the avoidance of specific food triggers. In practice, there are some common diagnostic difficulties.

Lack of simple reliable tests

The skin prick test and the radio-allergosorbent (RAST) blood test both detect specific IgE antibodies to individual antigens. These tests are easy

Table 3 Points to be noted when obtaining a history of reactions to foods

Points from history	Comments
Speed of onset	The quicker the onset of the allergic reaction, the more reliable is the history
Exclude co-incidences	If an individual becomes unwell (e.g. starts wheezing) an hour after eating a specific food, the wheezing could be caused by the food, or it could just be a co-incidence. The more times that such a sequence has been observed, the more likely it is that there is a cause and effect relationship
Seek evidence of internal consistency	(1) Have the same symptoms occurred on occasions when the trigger food was not taken? (2) Have there been occasions when the suspect food was taken without there being any adverse effects?
Need to probe a label of 'allergy'	It is common for people to believe they are allergic to something (1) Misdiagnosis based on flimsy evidence such as allergy test results (2) Misinterpretation of sequence of events such as attributing an allergic reaction to sesame seeds coated on a bun, in an infant, such reactions are more likely to be due an allergic reaction to the egg glaze that has been used as an adhesive for the seed coating

to perform, but difficult or impossible to interpret (see Table 4). They still have a place in research studies, but are of little use in clinical practice². The difficulties in interpretation of skin prick tests are summarised in Table 4. Depending upon the criteria used for positivity, there is a fair degree of correlation between RAST test and skin prick test results. Thus the clinical interpretation of RAST test results is subject to most of the same pitfalls as the interpretation of skin prick testing. Additional problems with RAST tests are the cost, and the fact that a very high level of total circulating IgE (e.g. in children with severe atopic eczema) may cause a false positive result.

The results of these tests cannot be taken alone, and standard textbooks of allergy acknowledge that 'the proper interpretation of results requires a thorough knowledge of the history and physical findings'. The problems in clinical practice are, for example, whether an individual with symptoms suggestive of food intolerance will benefit from attempts to avoid certain foods or food additives. However, skin prick test results are unreliable predictors of response to such measures.

Skin prick tests and RAST tests mainly detect IgE antibody. However, many adverse reactions to food are not IgE mediated, in which case these tests can be expected to be negative. Taking cow's milk protein intolerance as an example, patients with quick reactions often have positive skin prick tests to cow's milk protein, but those with delayed reactions usually have negative skin prick tests¹⁵.

Table 4 Practical difficulties in the interpretation of skin prick test results

- **False positive tests** a positive skin prick test may be present in subjects with no clinical evidence of allergy – sometimes described as ‘asymptomatic hypersensitivity’ or ‘subclinical sensitisation’ Positive results may persist after a child has grown out of a food allergy
- **False negative tests** skin prick tests are negative in some subjects with genuine food allergies False negative results are a special problem in infants and toddlers
- **Lack of agreed definition** about what constitutes a positive reaction
- **Size of the skin reaction** depends to some extent on the potency of the extract
- **Antihistamines and related drugs** (e.g. tricyclic antidepressants) suppress, for days, weeks or even months, the histamine-induced weal and flare response of a skin test
- **Poor correlation** between the results of provocation tests (e.g. double-blind food challenges) and skin prick tests. For example, in one study, of 31 children with a strongly positive (weal > 3 mm in diameter) skin prick test to peanut, only 16 (56%) had symptoms when peanuts were administered
- **Commercial food extracts** (sometimes heat treated) and fresh or frozen raw extracts may give different results (more positives with raw foods), reflecting the fact that some patients are allergic to certain foods only when taken in a raw state In others the reverse is the case

Inability to predict outcome

In many clinical situations (e.g. a child with severe eczema), the subject wants to know whether there will be any benefit from food avoidance (e.g. not drinking cow’s milk or not eating apples). Even if there were valid tests for the diagnosis of food intolerance, the outcome of avoidance measures depends on a number of other variables. Allergen avoidance may succeed for a number of quite unrelated reasons, such as: (i) the patient was intolerant to the item; (ii) co-incidental improvement; or (iii) placebo response.

Table 5 Reasons why a trial of avoidance of a specific food may fail to help

- The subject is not allergic to the food
- The period of elimination was too short For example, where a child has an enteropathy (damage to the small intestine) due to food allergy, it may take a week or more for improvement in symptoms to occur
- The food has been incompletely avoided, as in a subject supposed to be on a cow’s milk protein free diet who still continues to receive food which contains cow’s milk proteins such as, for example, casein or whey
- The subject is allergic to other items which have not been avoided, such as a child with cow’s milk protein allergy who fails to improve when given a soya based milk to which there is also an allergy
- Co-existing or intercurrent disease, for example gastroenteritis in a child with loose stools who is trying a cow’s milk-free diet
- The patient’s symptoms are trivial and have been exaggerated, or alternatively do not exist at all and have either been imagined or fabricated

Even if an individual is allergic to a food, a trial of food avoidance may fail to help for a number of reasons (see Table 5).

Provocation tests

The aim of a food challenge is to study the consequences of food or food additive ingestion. An **open challenge** is where the subject and the observer know the identity of the administered material. In a **single-blind challenge** the observer but not the patient or family know the identity of the test material. In a **double blind challenge**, neither the subject nor the observer know the identity of the administered material. Provocation tests are helpful either to confirm a history or diagnosis, to see if a subject has grown out of a food intolerance, and as a research procedure.

Open food challenges are the simplest approach, but open food challenges run the risk of bias influencing parents', patients' or doctors' observations. Often this is unimportant. Where belief in food intolerance may be disproportionate, and there is no substitute for a double-blind placebo-controlled challenge. For example, in Britain, parents widely believe that there is an association between reactions to food additives and bad behaviour, but in one series, double-blind challenges with tartrazine and benzoic acid were negative in all 24 children with a clear parental description of adverse reaction⁴.

The double-blind placebo-controlled challenge is regarded as the state-of-the-art technique to confirm or refute histories of adverse reactions to

Table 6 Limitations and difficulties with double-blind placebo-controlled challenges

Problem	Comment
Effect of dose	In some, microgram quantities are sufficient to provoke symptoms. In others, much larger quantities of food are required.
Concealing foods can be difficult	Standard capsules which contain up to 500 mg of food are suitable for validation of immediate reactions to tiny quantities of food, but concealing much larger quantities of certain foods (especially those with a strong smell, flavour or colour) can be very difficult.
Route of administration	Reactions to food occurring within the mouth will be missed if the challenge by-passes the oral route, for example by administration of foods in a capsule or via a nasogastric tube.
Capsule problems	Capsules are unsuitable for use in children who cannot swallow large capsules, a major limitation as most cases of suspected food allergy are in infants and toddlers. It is unsatisfactory to allow patients or parents to break open capsules and swallow the contents mixed into food or drink, as the colour (e.g. tartrazine) or smell (e.g. fish) will be difficult or impossible to conceal and the challenge will no longer be blind.
Danger of anaphylaxis	There is a danger of producing anaphylactic shock, even if anaphylactic shock had not occurred on previous exposure to the food. For example, in Goldman's classic study of cow's milk protein intolerance, anaphylactic shock had been noted prior to cow's milk challenge in 5 children, but another 3 out of 89 children developed anaphylactic shock as a new symptom after cow's milk challenge ¹⁶ .
Additive effect of triggers	Although some patients react repeatedly to challenges with single foods, it is possible (but unproven) that some patients only react adversely when multiple allergens are given together. Also, there are some subjects who only react in the presence of a non-food trigger, such as exercise or taking aspirin.

foods^{17,18}. However, the technique is subject to a number of potential limitations, not all of which can be overcome (see Table 6).

Mechanisms of food intolerance

The principal mechanisms resulting in food intolerance and the pathophysiology (where this is understood) are discussed below.

Food allergy

As described in the earlier part of this review, the term allergy implies a definite immunological mechanism. This could be antibody mediated, cell mediated, or due to circulating immune complexes.

Enzyme defects

Inborn errors of metabolism due to enzyme defects may affect the digestion and absorption of carbohydrate, fat or protein. In some subjects the enzyme defect is primarily gastrointestinal, causing defects in digestion or absorption. An example is lactase deficiency, described below. In other subjects, the enzyme defect is systemic. An example is the rare disorders of hereditary fructose intolerance, also described below.

Lactase deficiency

In this condition, there is a reduced or absent concentration of the enzyme lactase in the small intestinal mucosa^{19,20}. Affected subjects are unable to break down ingested lactose, which is the main sugar found in milk. If unabsorbed, lactose passes into the large intestine. One consequence is an osmotic diarrhoea. Another is that some of the unabsorbed lactose is broken down by intestinal bacteria, accompanied by the production of gas and organic acids. The clinical symptoms that result comprise loose stools, flatus, and perianal soreness and excoriation.

The diagnosis of lactase deficiency is made most simply by observing disappearance of symptoms when lactose is withdrawn from the diet, and re-appearance of symptoms when lactose is re-introduced. The diagnosis can be confirmed by the breath hydrogen test. In this test, the subject swallows a dose of lactose. Breath is collected every 30 min and the hydrogen content is measured. In the normal individual, the sugar is absorbed and hydrogen is not produced. In the intolerant individual, the sugar is not absorbed, hydrogen is produced, and a steep rise in hydrogen concentration is found in the exhaled air.

The management of lactose intolerance is to avoid foods that contain lactose, mainly cow's milk and its products.

In infants and young children, lactase deficiency is usually a transient problem occurring after an episode of viral gastroenteritis, but it can be a feature of any disease (such as coeliac disease) which causes damage to the intestinal mucosa. Levels of lactase tend to fall during mid to later childhood, and in a number of populations (*e.g.* Africa, Mexico, Greenland Eskimo) a high proportion of adults have very little lactase activity. This adult deficiency is believed to have a genetic basis.

Hereditary fructose intolerance

This condition is inherited as an autosomal recessive. Deficiency of the liver enzyme fructose 1,6-bisphosphate aldolase results in the accumulation of fructose-1-phosphate in liver cells, and acts as a competitive inhibitor for phosphorylase. The resulting inhibition of the conversion of glycogen to glucose leads to hypoglycaemia²¹.

Affected infants are symptom-free as long as their diet is limited to human milk. Once patients receive a milk formula, or any food that contains fructose, they develop hypoglycaemia. There may also be jaundice, an enlarged liver, and sometimes progressive liver disease. Treatment requires the complete elimination of fructose from the diet. The need to avoid many types of confectionery leads to one advantage, a reduction in dental caries.

Pharmacological mechanisms

Pharmacological substances present in food can be responsible for adverse reactions to the food. Some examples are given below.

Caffeine

The stimulant effects of 60 mg caffeine in a cup of tea or 100 mg caffeine in a cup of coffee are well recognised, as is the diuretic effect. Less well known is that those who regularly consume large quantities of caffeine can suffer a number of other side effects, including heartburn, nausea, vomiting, diarrhoea, intestinal colic, tachycardia, arrhythmia, sweating, tremor, anxiety and sleeplessness.

Sodium nitrite

Sodium nitrite is an antioxidant used as an anti-bacterial agent, and in quantities of 20 mg or more it can cause dilatation of blood vessels causing flushing and headache²², and urticaria²³.

Tyramine, histamine and other vasoactive amines

Vasoactive amines, such as tyramine, serotonin, tryptamine, phenylethylamine and histamine, are the normal constituents of many foods, which include tuna, pickled herring, sardines, anchovy fillets, bananas, cheese, yeast extracts (such as Marmite), chocolate, wine, spinach, tomato and sausages. Vasoactive amines arise mainly from the decarboxylation of amino acids, but they may also develop during normal food cooking and during the storage of food. The largest amount of histamine and tyramine are found in fermented foods such as cheese, alcoholic drinks, sausage, sauerkraut and tinned fish^{24,25}. Badly stored food such as mackerel and tuna can contain large amounts of histamine

Adverse effects can occur as the result of:

- 1 An abnormally high intake: for example a high intake of histamine or tyramine, due to either a high content in food or because of synthesis of these substances in the gut as the result of action by bacteria.
- 2 Pharmacological substances in food which interfere with the enzymatic breakdown of vasoactive amines.
- 3 Release from mast cells of histamine and other mediators of inflammation, triggered by eating certain foods such as strawberries, shellfish and alcohol.

The effects of large doses of tyramine, histamine and other vasoactive amines are extremely variable. Histamine causes flushing, constriction of smooth muscle in the intestine and the bronchi, increased heart rate, headache, fall in blood pressure and asthma. Tyramine causes constriction of blood vessels, stimulates the release of noradrenaline, and can also cause the release of histamine and prostaglandins from mast cells. Dietary tyramine is known to induce hypertension and headache in patients who are taking monoamine oxidase inhibitor drugs. This effect has been shown to be due to inhibition, by these drugs, of intestinal and hepatic metabolism of tyramine, so that the amine accumulates.

There is uncertainty about tyramine as a trigger of migraine². Most attempts to induce migraine by tyramine challenge in children and adults have been unsuccessful. In addition, a controlled study of exclusion of dietary vasoactive amines in children with migraine failed to demonstrate benefit²⁶. In this study, patients were randomly allocated to either a high fibre diet low in dietary amines or a high fibre diet alone. Both groups showed a highly significant decrease in the number of headaches, emphasising the need for a control diet in studies designed to show that dietary manipulation improves symptoms.

Of the foods reported to be common triggers of attacks of migraine, only cheese is rich in tyramine. Chocolate is low in this and other vasoactive amines, and red wine usually contains no more tyramine than white wine. Alcoholic drinks, particularly red wine, are commonly

Table 7 Naturally occurring toxins in foods

Substance	Comments
Protease inhibitors	Widely distributed throughout the plant kingdom, particularly in legumes, but to a lesser extent in cereal grains and tubers Heat labile
Lectins	Present in most legumes and cereals Some lectins, such as ricin from the castor bean, are extremely toxic. Others, such as those in the soya bean, are non-toxic Heat labile, e.g. inadequate cooking of red kidney beans can cause severe gastrointestinal upset, with vomiting and diarrhoea
Lathrogens	Lathyrism is a paralytic disease that is associated with the consumption of chickling pea or vetch, <i>Lathyrus sativus</i> The causative factor is an amino acid derivative, β -N-oxalyl- α , β -diaminopropionic acid, a metabolic antagonist of glutamic acid
Mimosine	An amino acid that comprises 1–4% of the dry weight of the legume <i>Leucaena leucocephala</i> Consumption of the leaves, pods and seeds leads to hair loss
Djenkolic acid	The djenkol bean (from Sumatra) is a seed of the leguminous tree, <i>Pithecolobium lobatum</i> Consumption leads to renal failure
Goitrogens	Present in cabbage, turnip, broccoli, cauliflower, brussel sprouts, kale, rape seed and mustard seed
Cyanogens	The most common plants that contain glycosides from which hydrogen cyanide may be released by enzymatic hydrolysis are lima beans (<i>Phaseolus lunatus</i>), sorghum, cassava, linseed meal, black-eyed pea (<i>Vigna sinensis</i>), garden pea (<i>Pisum sativum</i>), kidney bean (<i>Phaseolus vulgaris</i>), Bengal gram (<i>Cicer arietinum</i>) and red gram (<i>Cajanus cajan</i> s)
Vicine and convicine	These are β -glucosides that are present in broad beans (<i>Vicia faba</i>) When consumed by individuals with deficiency of the enzyme glucose-6-phosphate dehydrogenase, these substances precipitate haemolytic anaemia (favism)
Cycasin	Cycad seeds or nuts are obtained from <i>Cycad circinalis</i> , a tropical palm-like tree The toxic ingredient methyl-azoxymethanol, the aglycone of cycasin, is released on hydrolysis of cycasin by intestinal bacteria
Pyrrrolizidine derivatives	Pyrrrolizidine alkaloids are found in a wide variety of plant species Poisoning has resulted from the consumption of contaminated cereal and grain crops, and possibly also from milk from cows that have consumed pyrrrolizidine containing plants
Lupin alkaloid	Milk from animals that have eaten plants from the lupin family, notably <i>Lupinus latifolius</i> , may contain quinolizidine alkaloids such as anagryrine, which are teratogenic in animals and possibly also man

reported to provoke attacks of migraine. Whether these attacks are due to alcohol itself or some other compound is unclear.

11 β -hydroxysteroid dehydrogenase and liquorice

Liquorice contains an enzyme that inhibits 11 β -hydroxysteroid dehydrogenase, resulting in sodium and water retention, hypertension, hypokalaemia, and suppression of the renin-aldosterone system²⁷.

Irritant mechanisms for food intolerance

Certain foods have a direct irritant effect on the mucous membranes of the mouth or gut, such as the irritant effect of coffee or curry. In some

individuals, food intolerance only occurs in the presence of a co-existing medical disorder. For example, the ingestion of spicy food, coffee or orange juice provoke oesophageal pain in some patients with reflux oesophagitis.

Specific drug–food combinations

One example of drug-induced food intolerance is potentiation of the pressor effects of tyramine-containing foods (*e.g.* cheese, yeast extracts and fermented soya bean products) by monoamine oxidase inhibitor drugs. Another is the effect of taking alcohol in patients with alcohol dependence during treatment with disulfiram (Antabuse). The reaction, which can occur within 10 min of alcohol and may last several hours, consists of flushing and nausea.

Toxic mechanisms

Nature has endowed plants with the capacity to synthesise substances that are toxic, and thus serve to protect them from predators whether they be fungi, insects, animals or humans²⁸. Many plant foods contain naturally occurring toxins which protect the plant from predators such as fungi, insects or animals. Some examples are given in Table 7. There are numerous other examples of toxic substances present in food-stuffs. These include solanidine in potatoes, cyanide in tapioca, mycotoxins in mushrooms and cereal grains, and phototoxic furocoumarins in angelica, parsley, dill and celeriac, which in sufficient quantities can give rise to a wide variety of toxic reactions.

Food storage

Chemical changes in food during storage can produce substances which cause food intolerance. One example is the production of histamine in badly stored mackerel. Another example is intolerance to ripe or stored tomatoes in subjects who can safely eat green tomatoes, where ripening of the fruit produces a new active glycoprotein. Contamination of food by antigens such as storage mites or microbial spores may give rise to adverse effects, particularly asthma and eczema. Contamination of food by micro-organisms may result in adverse effects. For example, celery, parsnip and parsley may become infected with the fungus *Sclerotinia sclerotiorum* ('pink rot'), resulting in the production of the photosensitising chemicals psoralen, 5-methoxypsoralen and 8-methoxypsoralen.

Conclusions

Food arouses not only the appetite but also the emotions. The current phobia of food additives and food processing, and the obsession for so-called natural or health food arises largely out of misinformation and ignorance. Obsession with so-called natural or health food ignores the wide range of naturally occurring toxins in foods. For example, a survey of 'crunchy' peanut butter showed that 11 out of 59 samples from health food producers contained over 100 µg/kg of aflatoxins, over 10 times the proposed maximum permitted level for total aflatoxins²⁹. Only one of the 26 samples from other producers contained aflatoxins in excess of 10 µg/kg, and none contained more than 50 µg/kg. By far the greatest danger comes from allergy to naturally occurring allergens present in foods such as peanut, fish, egg and cow's milk. At present, the only practical management is specific food avoidance.

Key points for clinical practice

- Food allergy is a form of adverse reaction to food in which the cause is an immunological response to a food. The word allergy is frequently misused, and applied indiscriminately to any adverse reaction, regardless of the mechanism.
- Heat treatment renders certain (but not all) foods less likely to provoke an allergic reaction in a subject who is allergic.
- Reports of food allergy or intolerance from individuals or parents of children are notoriously unreliable, and when tested by double-blind placebo-controlled challenge not all reports of reactions can be verified.
- A high proportion of children with food intolerance in the first year of life lose their intolerance in time. The notable exception is allergy to peanut, which is life-long.
- Most allergic reactions to foods occur within minutes of ingestion of the food.
- The quantity of food required to produce an allergic reaction varies. Some patients are highly sensitive and develop reactions after ingestion of less than 1 µg of a food trigger. In contrast, there are children and adults who, for example, only react adversely to 200 ml or more of cow's milk.

- The diagnosis of food allergy is usually made from the history, supported by information about the response to the avoidance of specific food triggers.
- There is a lack of clinically useful simple diagnostic tests for food allergy. Skin prick tests and radio-allergosorbent tests, both of which detect specific IgE antibodies, are unreliable because of a large number of false positive and false negative reactions.
- Intolerance to food can result from enzyme defects. Examples are lactase deficiency and hereditary fructose intolerance.
- Pharmacological substances present in food such as caffeine, sodium nitrite or vasoactive amines such as histamine and tyramine, may be responsible for some adverse reactions to food.
- Food intolerance can also result from a direct irritant effect, for example from spicy food, or from toxins present in food

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