

MIMICS OF FOOD ALLERGY

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ABSTRACT

Adverse reactions to food include diverse mechanisms, and distinguishing between true food allergy and other adverse reactions may not be easy as many may mimic food allergy. The differential diagnosis is wide, comprising psychological reactions (food aversion), organic or anatomical reactions, toxic reactions and non-toxic reactions (food allergy and food intolerance/non-immune mediated food hypersensitivity).

The classification and differential diagnosis of non-immune adverse food reactions is discussed and selected examples (lactose intolerance, sucrose intolerance, alcohol intolerance, pharmacological reactions and unabsorbable wax esters) are discussed in more detail.

Immune reactions (food allergies) may be difficult to diagnose (and to identify the causative food) where non-IgE mechanisms are implicated, where diagnostic tests are falsely negative despite true IgE-mediated allergy and where hidden ingredients or concomitant allergens are present.

INTRODUCTION

Up to 34% of individuals or parents think that they or family members have a food allergy and 22% avoid particular foods on the mere suspicion that the food may contain an allergen. In fact only between 1% and 6% test positive on full evaluation which may include double-blind placebo-controlled food challenges.^{1,4} Much

has been made of this discrepancy between perceived food allergy and true food allergy, but many people without true food allergy may indeed be suffering significant symptoms associated with ingestion of food which have other important and avoidable causative factors.

The potential mimics of food allergy are extensive and this review focuses on a limited number of more common causes.

CLASSIFYING ADVERSE REACTIONS TO FOODS

Adverse reactions to food can be categorised as psychological (food aversion), organic or anatomical, toxic and non-toxic reactions (Fig. 1).⁵

Psychological reactions to food (food aversion) manifest as food refusal, poor feeding, and somatic symptoms such as vomiting, gagging, irritability and failure to thrive. Food aversion leads to significant problems and may be very difficult to diagnose and manage. Psychological food refusal without any organic cause may have an onset of symptoms before age 2 and be present for longer than 1 month. Poor food intake, poor weight gain, and vomiting do not discriminate between organic and nonorganic causes, but factors indicating the presence of a behavioural cause include food refusal, food fixation, abnormal parental feeding practices, onset after a specific trigger and presence of anticipatory gagging.⁶

Organic and anatomical problems causing food-related problems include pyloric stenosis, hiatal hernia, Hirschprung's disease, tracheoesophageal fistula, irritable bowel syndrome and inflammatory bowel disease. Several other conditions, including ulcers and cancers of the gastrointestinal (GI) tract, may cause some of the same symptoms as food allergy. Frey's syndrome, or auriculotemporal gustatory sweating has been reported to occur with orange juice, tomato, onion, and certain non-chocolate candies and snack foods.⁷

Toxic reactions may manifest because of an inherent ingredient in a food that has a toxic potential in its own right. The reaction is not mediated through immune, intolerance or pharmacological reactions but through

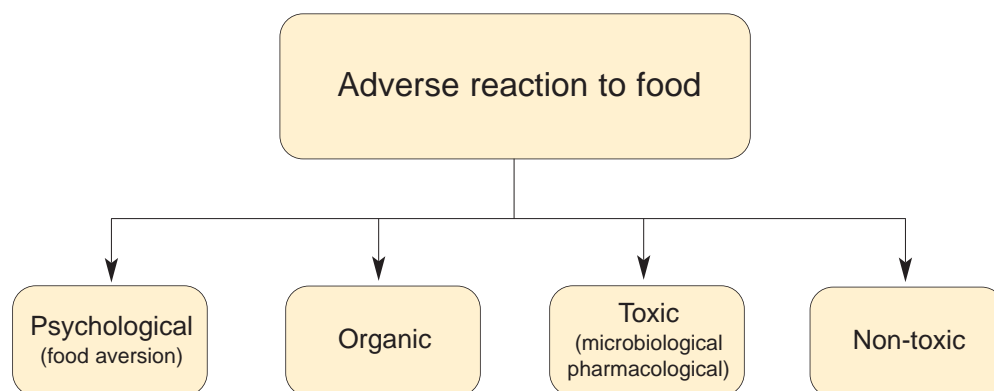


Fig. 1. Classification of adverse reactions to food.

the implicit toxicity of the ingredient. Toxic reactions may therefore occur in all individuals exposed to the food. Examples include bacterial toxins in spoilt food that may result in nausea and vomiting, which may be ascribed to an allergy. Another example is histamine poisoning (scombroid poisoning) resulting from the ingestion of tuna or yellowtail. Examples of toxic reactions are listed in Table I. Not all toxic reactions mimic allergic symptoms – some have explicit symptoms specific to that toxin.

Non-toxic reactions imply an individual hypersensitivity to the food, either immune mediated (food allergy) or not immune mediated (food intolerance) (Fig. 2). Non-toxic reactions only occur in susceptible individuals, and are not experienced by all people exposed to that particular food. New nomenclature⁹ refers to 'food intolerance' as 'non-allergic food hypersensitivity'.

FOOD INTOLERANCE/NON-ALLERGIC FOOD HYPERSENSITIVITY

Food intolerance may result from enzyme deficiencies, pharmacological reactions and other mechanisms.

Enzyme deficiencies

The most common cause of food intolerance is related to enzyme deficiencies. Table II lists a selected number of food intolerance reactions occurring as a result of enzyme intolerance.

Lactose intolerance

Approximately 2% of infants experience an adverse reaction to milk. A great deal of the time, the problem is not a milk allergy but caused by the body's deficiency of the β -lactase enzyme, known as lactose intolerance. After the age of 5, approximately 15-25% of Caucasian children and up to 95% of black individuals will develop a partial to complete deficiency of lactase enzyme. The symptoms are typically flatulence, abdominal cramps, and diarrhoea, but may be difficult to separate from those of non-IgE-mediated GI allergy.^{9,10}

The suspicion of lactase deficiency is raised by a history of GI symptoms, occurring after or aggravated by milk ingestion. This may respond or resolve completely with avoidance of dairy products. Subjects may be better tolerant of yoghurts and hard cheeses because of partial breakdown of lactose during the manufacturing process.¹⁰

Although rarely performed, laboratory confirmation may include a hydrogen breath test and lactose toler-

Table I. Toxic reactions from food

<i>Salmonella</i> , staphylococcus	Food spoilage
Cyanogenic glycosides	Kernel of almonds, apricots, cassava
Fungal aflatoxins	Peanut, apple juice
Trichothecenes	Wheat
Atropine	Mushroom
Ochratoxin	Various grains
Glucosinolates	Brassicaceous vegetables, e.g. cabbage
Pyrrrolizidine alkaloids	Comfrey
Haemagglutinins	Beans
Solanine	Potatoes (raw) and related plants
Seafood toxins	Spoiled fish, especially scombroid fish
Tetrodotoxin	Puffer fish
Saxitoxins	Clams, oysters
Neurotoxin (lathyrism)	Chickling Vetch / grass pea
Nitrates	Green vegetables, e.g. spinach

ance test. More commonly, a stool sample is taken which shows reducing substances or acidic pH. This indicates unabsorbed osmotically active substances. Occasionally a small intestinal biopsy is performed to assess direct lactase enzyme activity.¹⁰

Fructose intolerance

Although lactose intolerance is probably the most common enzymatic deficiency condition recognised, and often confused with allergic symptoms, the over-hasty diagnosis of lactose intolerance in infants and toddlers has probably caused many cases of fructose intolerance to be overlooked.¹¹

Fruit juice has become a significant part of young children's diets. Marketing surveys have shown that infants consume, on average, 150 ml of juice per day, and about 1% consume more than 600 ml daily.¹² Fructose malabsorption can occur as frequently in normal, healthy children and adults as in those with functional bowel disease (such as irritable bowel disease).¹³ Although symptoms may classically involve features of food intolerance, e.g. unexplained bloating, flatus, and distension, atypical features may be confused with symptoms of allergy.

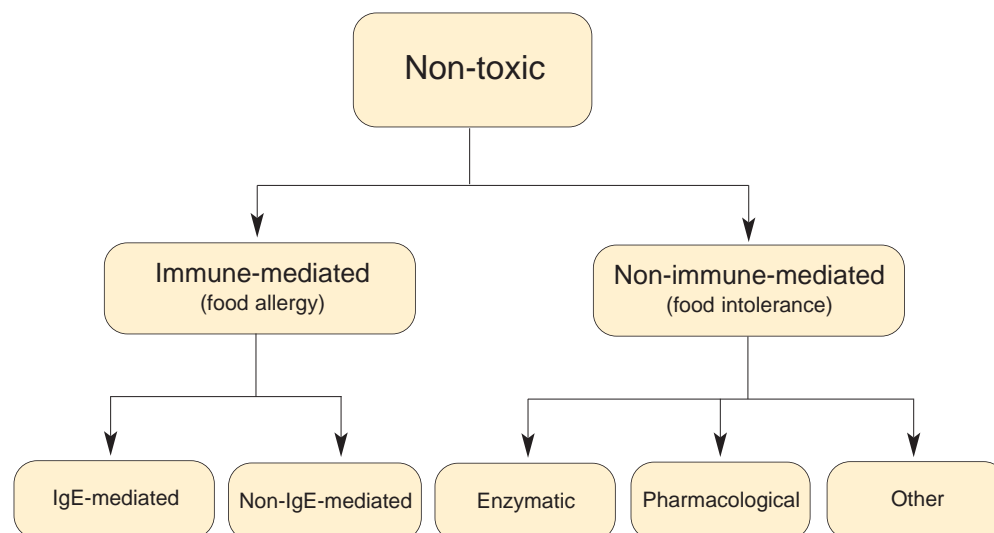


Fig. 2. Classification of non-toxic reactions to food.

Table II. Enzyme deficiencies

Lactase deficiency	Lactose (milk)
Fructose intolerance	Fructose, especially fruit juices
Sucrose intolerance	Sucrose and starch
Alcohol intolerance	Alcohol
Sulphite intolerance	Sulphite preservatives
G6PD deficiency	Fava (broad) beans
Pancreatic insufficiency	Fatty food
Galactosaemia	Lactose and galactose (milk and legumes)
Phenylketonuria	Phenylalanine (high protein foods) and aspartame sweetener

The mechanism of fructose absorption is not completely understood. The absorption capacity of fructose is much more complete when fructose is given either as sucrose to be broken down or with glucose than when it is ingested alone. Clinical studies have demonstrated this, with malabsorption being more apparent when the fructose concentration exceeds that of glucose (e.g. in apple and pear juice) than when the two sugars are present in equal concentrations (e.g. in white grape juice). However, when provided in appropriate amounts (10 ml/kg body weight), these different juices are absorbed equally well.¹⁴ Whereas orange juice was the major juice produced 50 years ago (primarily to prevent scurvy), now apple juice is the juice of choice for the under-5 age group. The result is a higher fructose intake.¹⁵ Fifty per cent of juice consumed by young children is apple juice.¹² Even at intakes of 15 ml/kg (or 240 ml in another study) at a time, which is generally seen as an acceptable serving size, apple juice has been associated with symptoms. Fruit juice manufacturers often use de flavoured apple juice to increase the volume of other fruit juices, which increases their fructose content. Interestingly, a study has shown that freshly pressed and unprocessed ('cloudy') apple juice did not influence stool frequency and consistency, compared with enzymatically processed ('clear') apple juice, which significantly promoted diarrhoea. It was suggested that, in addition to fructose, the increased availability of non-absorbable monosaccharides and oligosaccharides as a result of the enzymatic processing of apple pulp is an important aetiological factor in apple juice-induced chronic non-specific diarrhoea.¹⁵

Alcohol intolerance

Alcoholic drinks are complex, consisting of hundreds of components, which play a role in the flavour and character of these drinks. Alcoholic drinks are involved in a variety of reactions.

True allergy

Ethanol may rarely be responsible for anaphylactic reactions. A 25-year-old patient suffered from urticaria and acute anaphylactoid symptoms after ingestion of alcoholic beverages. The skin-prick test for acetic acid (5%) and for acetaldehyde (50% and 100%) was positive. The symptoms could be reproduced in an oral provocation test with pure ethanol (20%).¹⁷

True food allergy may be experienced to a number of minor constituents of alcoholic beverages. This may cause diagnostic difficulty because the allergen is 'occult' or 'hidden'. Examples include allergy to wheat in beer¹⁸ or residual lipid transfer proteins from barley or malt in beer.^{19,20} Adverse effects to the lipid transfer

proteins in beer may be a result of cross-reactivity due to primary peach allergy.²¹

Alcohol may trigger asthma, food allergy or exercise-induced anaphylaxis in susceptible subjects. In addition, there is increasing evidence that alcohol intake may play a role as a promoter of the development of IgE-mediated hypersensitivity to different allergens²² and act as a histamine liberator.²³ Furthermore, alcohol consumption is associated with increased serum IgE of unknown specificity.²⁴

A case report has been described of an 18-year-old woman with alcohol-induced anaphylaxis to grape.²⁵ Her first episode comprised generalised urticaria, facial angio-oedema and nasal obstruction 20 minutes after ingesting grape and a glass of champagne. A year later, 10 minutes after ingesting the same combination she developed abdominal pain, vomiting, facial angio-oedema and nasal obstruction. She remained asymptomatic if she ate the fruit alone but not if grape was associated with alcoholic drinks. Skin-prick test with a commercial extract of white and red grape was negative. No grape-specific IgE could be demonstrated and oral challenge with grapes and champagne together were positive (negative for 1 grape and 5 ml champagne but positive for 12 grapes and 50 ml champagne).²⁵

Intolerance

Often not considered, alcohol intolerance results in a number of symptoms that may mimic allergy or result in an aggravation or enhancement of allergic symptoms. These include flushing syndrome and anaphylactoid reactions such as urticaria/angio-oedema and even shock.

Approximately 45% of Japanese people have a partial to severe acetaldehyde dehydrogenase 2 (ALDH2) enzyme deficiency which may result in alcohol-induced asthma and other symptoms.²⁶⁻²⁸ This is the same enzyme that is blocked by disulfiram in order to cause reactions with alcohol ingestion in an attempt to contain or cure alcoholism. Other drugs that cause a disulfiram-like reaction include antibiotics (e.g. metronidazole, sulphonamides, some cephalosporins, nitrofurantoin, chloramphenicol), antifungals (griseofulvin) and chloral hydrate. Rarer causes include exposure to industrial solvents and pesticides (e.g. carbamates, monosulfiram [Tetmosol]) and ingestion of mushrooms (notably the otherwise delicious common ink-cap *Coprinus atramentarius*).

Alcoholic drinks are complex and adverse reactions may occur as a result of a number of other causes which are better categorised as pharmacological or immune related, including adverse reactions to sulphites in wine and beer.²⁹ Sulphur dioxide and the sulphite preservatives are well-known preservatives used in a wide range of foods including alcoholic beverages and soft drinks. They are well-known triggers of asthma. Although not fully elucidated, the mechanism has been considered to be sulphite oxidase deficiency, which would classify it as an enzymatic reaction. In this case, the deficiency is variable in severity in different individuals, resulting in different levels of tolerance to drinks containing sulphites.^{30,31} However, the ability of the cellular antigen stimulation test (CAST) to often accurately indicate sulphite sensitivity suggests that other mechanisms may also contribute.

Pharmacological reactions

Pharmacological reactions refer to constituents that are normally present in foods, that when ingested in excess will result in a dose-dependent drug-like effect. However, this category is blurred by the fact that some

people have a partial to complete, temporary or permanent deficiency of an enzyme required to break down the constituent, or that someone may have a heightened sensitivity to the constituent, resulting in adverse effects when the food is ingested in an average serving. These include histamine (wine, certain cheese, spinach, strawberry, tomato, sauerkraut and other fermented food), caffeine (coffee, tea, cola drinks, cocoa, chocolate), tyramine³² (cheese, beer, chocolate, cured meat, pickled herring, Marmite), theobromine (chocolate), alcohol and serotonin (tomato, banana, pineapple, walnuts). All vasoactive amines, which include dopamine, histamine, norepinephrine, phenylethylamine, serotonin and tyramine, have been implicated in pharmacological reactions.³³ In scombroid poisoning (histamine poisoning) (pharmacological reaction), the level of histamine in the spoiled fish is markedly high, resulting in almost everyone ingesting the fish being affected, whereas in people with a diamine oxidase (DAO) deficiency, histamine in wine, tomato, etc., may result in symptoms. Also, certain drugs, e.g. isoniazid, may impair DAO activity.^{34,35} This similarly occurs for other constituents listed in Table III.

Other food intolerance

Selected examples of food intolerance with non-enzymatic and non-pharmacological mechanisms include aspirin hypersensitivity (leading to asthma and urticaria), sensitivity to monosodium glutamate³⁵ (leading to headache and flushing) and unabsorbable wax esters in fish (leading to diarrhoea). In European countries, acetyl-salicylic acid may be added to homemade canned fruits, berries and vegetables, which may result in urticaria in acetyl-salicylic-sensitive individuals.³⁷ Acetyl-salicylate sensitivity needs to be differentiated from sodium salicylate sensitivity, a controversial clinical entity.^{38,39} Additives used in foods, including food dyes, can also trigger allergies and intolerances. The dyes most frequently associated with allergy or adverse reactions include: carmine, tartrazine, red FD&C No. 2, and brilliant blue.⁴⁰ These same dyes are also used to colour certain oral medications.⁴¹ Reports of allergy-like reactions to sodium benzoate are increasing.⁴²⁻⁴⁴

Unabsorbable wax esters

The passage of oil through the rectum has been observed following the ingestion of 'butterfish'. Anecdotally this condition occurs more commonly than reported in the literature. There have only been a few articles in the literature on this subject: one in a South African journal⁴⁵ and three in one issue of *Communicable Diseases Intelligence* in 2002.⁴⁶⁻⁴⁸ The incidence is likely to increase as butterfish is eaten more commonly, especially as sushi. In the literature, there is some confusion about the correct names of the fish that cause this passage of oil per rectum. Reactions

have been associated with 'escolar', 'oilfish', 'rudderfish' and '*Lepidocybium flavobrunneum*,' the latter given as the scientific name for butterfish when this is in fact *Scatophagus* spp.

In those who are susceptible, the onset of symptoms occurs at a median of 2.5 hours and within a range of 1 to 90 hours after consumption of raw or baked fish.⁴⁸ The predominant symptom is oil being passed per rectum (kerriorrhoea). It is difficult to contain the oil that pools in substantial quantities in the lower rectum, and therefore frequent evacuation is required. If prophylactic visits to pass stools are not performed, inability to retain rectal contents may result in soiling of clothing.⁴⁵ Approximately 10 ml of inoffensive, clear orange or green oil is passed per occasion. Oil is mostly not contaminated significantly by faecal material. Because most experiences occur in the absence of bowel cramps or abdominal discomfort, this would imply that the frequent calls to stool are caused by the lubricant effect of the oil, and not by an irritant action. In selected cases severe diarrhoea with abdominal pain, nausea, headache and vomiting may occur.⁴⁸ Most people recover within 24 hours.⁴⁹

COMPLICATIONS OF TRUE FOOD ALLERGY

True immune-mediated food allergy can be divided into two subgroups on the basis of the immunological mechanisms involved: food allergen-specific IgE responses, and non-IgE-dependent immunological responses, either of which may be immediate or delayed. The latter may be divided into non-IgE-mediated reactions resulting in, among others, delayed allergy reactions, and other immune reactions such as coeliac disease, an autoimmune disorder of the GI tract triggered by ingestion of gluten (wheat, barley, and rye). It occurs in approximately 1% of the population and is influenced by a variety of genetic and environmental factors.⁵⁰

IgE-dependent reactions are further classified by symptom complexes developed in the primary target organs. Food-related allergic reactions are the leading cause of anaphylactic reactions treated in the emergency department, accounting for approximately 30 000 emergency department visits in the USA each year, and 150-200 deaths.⁵¹

Even when symptoms may be truly allergic in nature, there are two scenarios where the causative food may not be easily identifiable.

- When diagnostic tests are negative
- When an associated allergen is responsible for the symptoms.

Diagnostic tests are negative

True food allergy may occur with negative diagnostic tests when the cause is a non-IgE mechanism or in cases where diagnostic tests are negative in spite of a clear IgE mechanism.

Non-IgE mechanisms

The severity and immediacy of IgE-mediated food reactions such as anaphylaxis and urticaria/angio-oedema, (as well as easier diagnosis) results in an under-appreciation of the significance of non-IgE-mediated mechanisms. Non-IgE-mediated food allergy may be responsible for approximately 30% of delayed immune-mediated reactions to food.⁵² This is illustrated in Fig. 3.

In this Australian study, three groups of reactors were characterised: immediate, intermediate and late. Although all patients were milk allergic, only the *immediate* group (reactions within minutes of ingestion) con-

Table III. Substances in foods responsible for pharmacological reactions

Histamine	Spoilt fish (scombroid poisoning), wine, certain cheese, spinach, strawberry, tomato, sauerkraut and other fermented food
Tyramine	Cheese, beer, chocolate, cured meat, pickled herring, Marmite
Serotonin	Tomato, banana, pineapple, walnuts
Theobromine	Chocolate

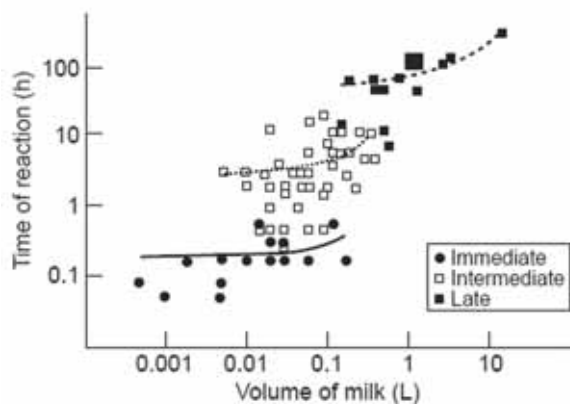


Fig. 3. Relationship between time of onset of adverse reactions and volume of milk ingested at that time for 100 Australian infants.⁵²

sistently had laboratory evidence of IgE sensitisation with positive skin tests and radioallergosorbent tests (RASTs). The *intermediate* group (reactions occurring from 1 to 24 hours after ingestion) displayed predominantly GI symptoms, including vomiting and diarrhoea, and most did not exhibit features of IgE sensitisation. The late group (symptoms occurring from 24 hours and up to 5 days after the commencement of the challenge procedure) presented with flares of eczema or development of cough and wheeze and showed no IgE sensitisation but rather *in vitro* evidence of T-cell sensitisation to milk.⁵² Thus a true food allergy may not have demonstrable IgE, may manifest some hours or even days after ingestion, and may require larger intakes of a food than customarily expected, all potentially resulting in a diagnosis of food allergy being rejected.

Negative tests despite IgE mediated food allergy

Skin-prick tests and serum specific IgE tests may be negative in spite of an overwhelmingly positive history for an acute IgE-mediated allergy. This may occur for a variety of reasons and depend on the diagnostic modality. Causes for skin-prick test being negative include defective technique, decay of allergen in the test material, concurrent use of antihistamines⁵³ as well as rarer cases where the individual may be sensitive to a specific allergen found in a low concentration or not present in the skin-prick test extract.

The specificity and sensitivity of serum specific IgE measurement varies widely between different allergens and may be low in certain food allergens. The allergen profile of the serum specific IgE reagent may not cover every relevant allergen present in a particular food. For example, in a report of 2 patients who developed anaphylactic reactions after the ingestion of fresh mango, a skin-prick test and CAST were positive. However, serum specific IgE tests were negative. Both patients were sensitised to allergens which appear not to be present in the extract used for the serum specific IgE assay.⁵⁴

A proper history is the most important factor in the diagnosis of food allergy. Ancillary tests such as skin-prick tests and serum specific IgE are of value in confirming diagnosis or guiding one towards the correct diagnosis. Cut-off ranges for 95% positive predictive values of skin tests⁵⁵ and IgE⁵⁶ have been identified for a limited number of allergens in specific populations. Both tests need to be interpreted in the light of the pre-test probability which depends greatly on the clinical diagnosis.⁵⁷ This is particularly important where results

fall in the non-predictive range, but also when they are in the ranges usually regarded as negative or conclusive. Specialised tests such as the CAST, basophil activation test and others, may contribute to the diagnosis. Although the double-blinded placebo-controlled food challenge is regarded as the gold standard in making a food allergy diagnosis, even this test may be unhelpful in a number of situations, e.g. if not tailored for delayed immune mechanisms or food-dependent exercise-induced symptoms such as asthma or anaphylaxis.

An associated allergen is responsible for the symptoms

One of the authors has documented five mechanisms that may be important in the assessment of associated allergens responsible for symptoms in an individual, and formulated the concept of concomitant clinical sensitivity (CCS).⁵⁸ CCS is defined as 'the propensity for a patient to be allergic to other allergens due to one or more of five associative mechanisms'. Proximal CCS occurs when an adverse effect is caused not by the apparent allergen, but by another allergen proximal to or physically associated with it. A familiar example is *Anisakis* in fish,⁵⁹ but less common examples include red spider mite on tomato⁶⁰ or orange,⁶¹ storage mites in baker's asthma,⁶² and hidden allergens in food,⁶³ medications and cosmetics.⁵⁸

Hidden allergens in food are recognised throughout the world as a significant risk to individuals with known food allergy.^{63,64} An added diagnostic dilemma occurs when an individual reacts for the first time to a food allergen hidden in another food. For example, anaphylaxis caused by the unexpected presence of casein in salmon has been reported.⁶⁵ Buckwheat added as a bulking agent to pepper has caused anaphylaxis.⁶⁶ Although pine nuts are traditionally used in pesto sauce, a clinician may not consider systemic contact dermatitis following ingestion of a pesto sauce to be the result of allergy to raw cashew nuts.⁶⁷ An anaphylactic reaction following ingestion of apple juice was found to be as a result of the inclusion of juice of the acerola fruit.⁶⁸

Hidden allergens may not necessarily be of food origin: mite and storage mite contamination of flour and pancakes have resulted in allergic reactions including anaphylaxis as described in numerous studies,⁶⁹⁻⁷¹ including a study of 30 atopic subjects who were first seen with systemic anaphylaxis precipitated by the ingestion of wheat-containing foods, of whom 16 had anaphylaxis triggered by pancakes.⁷⁰ Similarly, allergic symptoms in 8 patients, previously diagnosed as having *Anisakis simplex* sensitisation, occurred after they ate chicken meat. Chicken feed usually contains a high proportion of fishmeal, which might possibly be contaminated by this nematode. All 8 patients presented positive prick-tests and challenges to *A. simplex*.⁷²

In honey-allergic individuals primary sensitisation may be due either to the honey itself, to airborne Compositae pollen, sunflower pollen, or even to cross-reacting bee venom components.^{73,74} The software program, Allergy Advisor^{®75}, contains over 180 examples of 'proximal sensitisation'.

CONCLUSION

Differential diagnosis of adverse reactions to food must take into account psychological reactions, organic or anatomical reactions, toxic reactions and non-toxic reactions. Non-toxic reactions imply an individual hypersensitivity to the food, either immune mediated (food allergy) or not immune mediated (food intolerance). Distinguishing between true food allergy and food intolerance may not be easy, and a wide differen-

tial should be considered. This should include enzymatic, pharmacological and other food intolerances, and both IgE-mediated and non-IgE-mediated food allergy. Hidden food allergens may further complicate diagnosis of food allergy in the case of concomitant clinical sensitivity to associated allergens hidden in or proximal to the food.

Declaration of conflict of interest

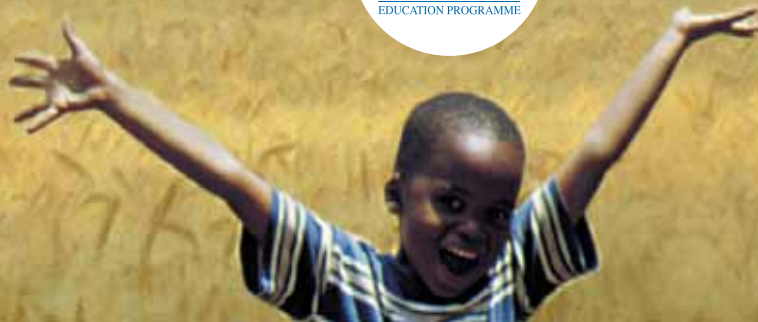
Dr Steinman has acted as a consultant to Phadia, Sweden.

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