chapter fourteen

Food allergy and food intolerance

T. Bruggink

14.1 Introduction

The cultural patterns of food consumption tend to change gradually with time. Although it is true that technology increasingly secures the safety of nutrients, this does not mean that

each food product is safe. In fact, with the introduction of food additives such as coloring agents and preservatives, the number of substances that may generate adverse reactions has increased, and it seems that the incidence of allergic reactions has, too. This may be explained by developments in technology such as high-temperature processing and irradiation of food, leading to the creation of new antigenic sites. Other factors may be involved as well. It is known, for example, that allergy to inhalants is on the increase. There are many mechanisms underlying adverse reactions to foods. Because of their complexity, there has been confusion about the terminology that should be applied for the different kinds of adverse food reactions. A lack of consensus can easily lead to misunderstanding. Therefore, a discussion about this problem has been started and this has led to the much wanted result: the term adverse food reaction has been defined as any kind of abnormal response to a food (product). This can be an immunologically mediated response or *food allergy*, or a non-immunologically mediated response or *food intolerance*. The latter is a general term which can in turn be further divided into different subcategories (see Table 14.1 and Section 14.2.3). A third type of adverse food reaction is *food aversion*, meaning a pure psychological effect evoked by a food. Within the framework of this chapter, no further attention will be paid to this type of reaction. For a better understanding of the mechanisms underlying the first two types of reactions, the basic principles of allergic reactions and of the normal functioning of the digestive tract will be discussed (Sections 14.2.2.1 and 14.2.2.2 respectively). The main causes of food-allergic and food-intolerance reactions are mentioned in Sections 14.2.4.1 and 14.2.4.2, respectively. It is often difficult to discriminate between a food-allergic reaction and a food-intolerance reaction on the basis of clinical data, as the symptoms can be similar (Sections 14.3.1). Further, there is an extensive differential diagnosis, which renders the problem of diagnosis even more difficult (Section 14.3.2). However, it is important to come to the right diagnosis, because only then is it possible to institute an effective treatment (see Section 14.3.3). Proper treatment has to start at the root, and therefore it is necessary to know the factors which determine the development of a disease.

All together, this issue should be handled with care, due to the chance of overestimation as well as underestimation, with all the related problems.

14.2 General aspects of allergy and intolerance

14.2.1 Definitions

Allergy is defined as an abnormal reaction of the immune system to foreign (not infectious) material, leading to injury to the body that may be either reversible or irreversible. In

Table 14.1 Food-allergic and food-intolerance reactions

Term		Definition
I	Food allergy	Immunological reaction to food or a food product
II	Food intolerance	General term describing an abnormal physiological response to food or food additives that does not appear to be immunological in nature
	a Pharmacological reaction	Reaction resulting from the pharmacological effect of (a) food (component)
	b Metabolic reaction	Reaction resulting from the effect of (a) food (product) on a metabolic abnormality of the host
	c Toxic reaction	Reaction caused by toxic food components
	d Idiosyncratic reaction	Individual intolerance of a certain food or additive. The underlying mechanism is unknown.
III	Food aversion	A psychogenic reaction to (a) food (product).

general, four different types of immunological hypersensitivity reactions are recognized. In a *food-allergic* reaction, this abnormal immunological response is directed against a specific protein or part of a protein in food. *Food-intolerance* reactions are defined as reactions caused by an abnormal physiological reaction of the body to a specific food (component).

14.2.2 Allergy

14.2.2.1 Types of hypersensitivity

There are four types of immunological hypersensitivity reactions. Of the four types of hypersensitivity reactions, type I reactions are probably the most important, as will become evident in this chapter. This does not mean though, that other types of reactions or combinations do not occur. A food-allergic reaction takes place only if the immune system of the body reacts to food in a specific way. This is the case if the food has antigenic potency and has the opportunity to stimulate the immune system.

To protect the body against unwanted effects of food, like allergic reactions, several defense mechanisms are available. The sites where food first makes contact with the body are the mucosa of the oropharynx and that of the digestive tract. The most important defense mechnisms are also located at these sites. For a better understanding of the pathological reactions to food, the normal functioning of the digestive tract is described first (Section 14.2.2.2).

14.2.2.1.1 Type I hypersensitivity. After contact with an allergen, certain white blood cells (B lymphocytes) are triggered to produce antibodies of a special type, namely the immunoglobulin E (IgE) antibodies. These antibodies bind to cells (mainly mast cells and basophils). When there is a subsequent exposure to the same allergen, the allergen becomes bound to two adjacent IgE molecules, resulting in degranulation of the cell to which the IgE is bound. Several types of (preexisting or newly formed) mediators are released, which results in a complex reaction: muscle contraction, dilatation, and increase of permeability of blood vessels, chemotaxis (a mediator-triggered process by which other cells are attracted to the site of reaction), and release of other immune mediators. The reaction occurs mostly within 1 hour, and is sometimes followed by a so-called late reaction which starts hours later.

14.2.2.1.2 Type II hypersensitivity. Antibodies of the immunoglobulin G (IgG) or immunoglobulin M (IgM) class are generated against a cell-surface antigen or an antigen bound to a cell surface. This leads to an inflammatory reaction by which the cells are destroyed. Transfusion reactions due to blood incompatibility work according to this mechanism. There is no evidence that this type of allergic reaction plays a role in food allergy.

14.2.2.1.3 Type III hypersensitivity. Antibodies of the types IgG and IgM are formed against antigens that circulate in the blood. This results in the formation of antigen–antibody complexes which activate the complement system, followed by the release of different mediators from mast cells and basophils. When there is an optimal ratio of antibody to antigen, the complexes may precipitate at different sites in the body, e.g., the joints, the kidneys, and the skin. This type of reaction may play a role in some types of food-allergic reactions. However, it remains difficult to find conclusive evidence. Immune complexes may also be found in the bloodstream of normal individuals shortly after a meal. Type III hypersensitivity reactions also include a number of drug reactions and a few types of vasculitis.

14.2.2.1.4 Type IV hypersensitivity. In contrast to the above types of allergic reactions, no antibodies are involved in this type of reaction. After contact with an antigen, T-lymphocytes are sensitized. These T-lymphocytes then produce cytokines which activate other cells. An example is contact allergy of the skin due to cosmetics. In food allergy, this type of reaction is sometimes seen when food comes into contact with the skin in a person allergic to that specific food.

14.2.2.2 Defense mechanisms in the digestive tract

A major function of the digestive tract is to process food ready for absorption and to exclude harmful substances in the food. Proteins undergo enzymatic degradation to amino acids and dipeptides, fats to fatty acids and diglycerides, and carbohydrates to monosaccharides. Subsequently, absorption by gut enterocytes can take place. There are two types of defense mechanisms in the digestive tract. First, there is a *non-immunological defense* mechanism. The mucus membrane of the gut forms a protective barrier against penetration of pathogenic microorganisms and allergens. Also, the secretion of certain enzymes and gastric acid (which may lead to degradation of unwanted substances) and the enteric motility (which prevents excessive proliferation of bacteria in the small intestine as well as absorption of macromolecules through the digestive mucosa), contribute to the non-immunological defense.

Secondly, there is the *immunological defense*, formed by the gut-associated lymphoid tissue (GALT). The GALT consists of lymphoid organs (follicles, appendix, tonsils, and Peyer's patches) and solitary lymphocytes. Lymphoid organs contain B and T lymphocytes as well as antigen-presenting cells (APCs), mast cells, eosinophils, and basophils. Much research has been carried out on the anatomy and function of the Peyer's patches, which can be found in the small intestine. They are situated just beneath the mucous membrane and are covered by epithelial cells. Between the latter, the so-called M cells (microfold cells) are found, which transport the antigens from the gut lumen to the dome area by pinocytosis. The dome area consists of B cells, plasma cells, T cells and APCs. The APCs present the antigen to the B and T cells. The T cells produce cytokines which stimulate the B cells to switch from IgM production to immunoglobulin A (IgA) production, and activate the B cells to proliferate. The B cells migrate to other parts of the body, such as the respiratory mucosa. Meanwhile, they can receive other T-cell signals which stimulate differentiation to Ig-producing plasma cells. After this, a number of these plasma cells return to the GALT. Most of the plasma cells produce IgA (70 to 90%), some of them IgM (20%), and only a few IgG or IgE. The IgA binds not only to antigens, but also to microorganisms, to prevent infection. A small number of antigens, bound to IgA, are taken up and transported by the portal system to the Kupffer cells in the liver, and eliminated. Also, in healthy individuals, these immune complexes circulate in the blood shortly after a meal. Thus, both immunological and non-immunological mechanisms are involved in preventing food allergens penetration into the gut. In combination, they form the *mucosal barrier*.

Most food allergic reactions occur in infants. This can partly be explained by the fact that the permeability of the intestine in neonates is high, so that proteins can pass across the intestinal mucosa and interact with the immune system. Further, because of the immaturity of the immune system, defensive responses to antigens mediated by secretory IgA in the GALT are only poor. The complete development of both intestinal defense mechanisms takes months. In certain adults, allergic reactions to food occur, even though the defense mechanisms are present in the intestine. The defense can be insufficient at several levels. Mucosal factors as well as intraluminal factors may be responsible for an insufficient elimination of potentially harmful substances.

14.2.3 Intolerance

Various mechanisms may be responsible for food intolerance reactions. The different types of reactions, which are summarized in Table 14.1, will be briefly discussed.

Pharmacological reactions (Table 14.1, Food intolerance reaction IIa). The intensity of biological effects of substances may differ from individual to individual. A well-known example is *caffeine*, a methylxanthine derivative present in tea and coffee. Its biological action includes stimulation of the heart muscle, the central nervous system, and the production of gastrin. People who drink a large amount of coffee may experience restlessness, tremors, weight loss, palpitations, and alterations in mood. Another group of biologically active substances include the vasoactive amines such as histamine and tyramine, and histamine releasers. Excessive intake of *histamine* can cause headache, abdominal cramps, tachycardia, urticaria and, in severe cases, hypotension, bronchoconstriction, chills, and muscle pain. These symptoms appear within 1 hour after ingestion and may last for several hours. Histamine is normally present in food products such as cheese, wine, cream, fish (especially sardine, spatin), sauerkraut, and sausages. It can also be produced by bacteria in the gut. It is metabolized very quickly by enzymes in the gut mucosa and liver. *Tyramine* can be found in French cheese, cheddar, yeast, chianti, and canned fish, and can also be produced by microorganisms in the gut. Symptoms like migraine and urticaria can occur in sensitive persons. *Phenylethylamine* occurs in chocolate, old cheese, and red wine, and can provoke migraine attacks. *Histamine releasers* can function in a non-IgE-mediated way. Known histamine releasers are lectins, present in certain legumes, fruits, and oat. Also, chocolate, strawberry, tomato, fish, egg, pineapple, ethanol, and meat can cause histamine release. Symptoms following non-IgE-mediated histamine release resemble real allergic symptoms (Table 14.2). In children, the above foods may aggravate symptoms of atopic dermatitis.

Metabolic reactions (Table 14.1, Food intolerance reaction IIb). Several metabolic disorders in the recipient may result in adverse reactions to foods. The most important in this respect is enzyme deficiencies. The most frequently occurring, especially in Asian countries, is lactase deficiency, leading to intolerance of lactose. After lactose (a carbohydrate in milk or milk products) is ingested, it is not metabolized in the usual way and therefore not taken up by the gut mucosa. It is transformed by the intestinal microflora into a hyperosmolar product that causes diarrhea. Enzyme deficiency may also concern the enzymes disaccharidase and glucose-6-phosphate dehydrogenase, and the disorder phenylketonuria.

Toxic reactions (food poisoning) (Table 14.1, Food intolerance reaction IIc). The presence of toxic components in food has been discussed in Part 1, and their toxic effects in the preceding chapters of Part 2.

Idiosyncratic reactions (Table 14.1, Food intolerance reaction IId). The mechanism underlying this type of food reaction is unknown. It includes reactions to food and the majority of the reactions to food additives. Although the group of additives used in the food industry is very large, only a few have been found to be potentially unsafe for certain individuals. The most important additives in this respect are the azo dyes, sodium benzoate, sulfiting agents, monosodium glutamate, and annatto. They will be discussed separately. It is possible that in the future, some of these reactions will be considered metabolic or toxic, if more is known about their mechanisms.

14.2.4 Food components

14.2.4.1 Allergens

Allergens in food are either proteins, glycoproteins, or polypeptides. The allergenicity can be associated with the type of structure of the proteins and the peptides: primary, second-

ary, or tertiary. In the case of tertiary structures, allergenicity often disappears on denaturation, whereas in the case of primary structures allergenicity remains. Further, the protein has to be large enough to be recognized by the immune system as a foreign compound. In general, the allergenicity of molecules with a molecular mass lower than 5000 is low, unless they are bound to endogenous proteins. On the other hand, substances with a molecular mass higher than 70,000 are not absorbed, and do not come into contact with the immune system. There is a large number of foods wich may cause allergic reactions, but of only a few the allergens have been isolated and identified. The most common causes of allergic reactions are cow's milk, soy, fish, egg, nuts, peanuts, and wheat. These will be discussed briefly.

14.2.4.1.1 Cow's milk. Cow's milk contains 30 to 35 g protein per liter, which include a large number of antigens. The main antigens are β-lactoglobulin, casein (about 30 g/l!), α-lactalbumin, serum lactalbumin and the immunoglobulines. β-lactoglobulin and α-lactalbumin are referred to as the whey proteins. Casein and β-lactoglobulin are the most heat-resistant. Cow's milk allergy (CMA) is most frequently seen in children. In 10% of the cases, the symptoms appear in the first week of life; in 33%, in the 2nd to 4th week and in 40%, during the following months. The main symptoms are eczema and gastro-intestinal complaints such as diarrhea, cramps, vomiting, and constipation. Also, rhinitis, asthma, and rash may develop. An often obvious feature is irritability and restlessness. There are some specific syndromes (protein-mediated gastroenteropathy and the Heiner syndrome) which are attributed to CMA, but these will not be discussed in this context. In the older child, rhinitis and asthma, and skin disorders such as urticaria and rash dominate. If the diagnosis is CMA, a few alternatives for cow's milk are available. One of them is soy milk as far as nutritional value and costs are concerned, although 20 to 35% of the children develop an allergy to soy. This may be partly explained by the fact that soy milk is often given directly after a period of cow's milk feeding. CMA causes an increase in gut permeability, possibly resulting in an increase in absorption of soy protein, and eventually in a more extensive interaction between soy protein and the immune system.

A second alternative to cow's milk is the protein hydrolysates, which may be considered hypo-allergenic as they contain no or few allergens. Goat's milk is sometimes also mentioned as an alternative. However, this should be discouraged, because goat's milk is strongly cross-reactive and deficient in folic acid. The prognosis of CMA is good; 50 to 90% of the children can tolerate cow's milk by the age of 2-3 years.

14.2.4.1.2 Vegetable allergy. This kind of allergy may be provoked by beans (soy), peas, and peanuts. Especially, peanut allergy is well-known. Extensive reactions with urticaria, angioedema, nausea, vomiting, rhinitis, and dyspnea have been reported. Anaphylactic shock is not uncommon. The peanut allergen is very stable. It is resistant against all kinds of processing. In peanut butter and peanut flour (which is added to quite a few food products), the peanut allergen is still detectable. In peanut oil, the allergen is not or seldom present. Similarly, the soy allergen is rarely found in soy oil. Allergy to a particular legume does not invariably imply allergic sensitivity to all members of the legume family. Children with a peanut allergy seldom grow out of it.

14.2.4.1.3 Fish allergy. Allergic reactions to fish are often serious. The cod-fish allergen is heat stable and resistant to proteolytic enzymes. In addition to symptoms such as rhinitis, dyspnea, eczema, urticaria, nausea, and vomiting following digestion of food, urticaria may occur after skin contact with fish. Also, shellfish can cause strong allergic reactions. Probably, fish families have a species-specific antigen as well as cross-reactive antigens. Allergies may be directed against a specific fish or multiple fish families.

14.2.4.1.4 Egg allergy. Egg white is the most frequent cause of egg allergy. Egg white contains about 20 allergens, the most important being ovalbumin, ovotransferrine and ovomucoid. The latter is heat-resistant. Other egg allergens that have been isolated are lysozyme and ovomucine. There is evidence that some cross-reactivity exists between the allergens of the egg white and the egg yolk. Egg allergy is more frequently encountered in children (appearing in the first 2 years of their life) than in older people. Children may eventually lose their allergy for egg.

14.2.4.1.5 Tree nut allergy. In several studies, a cross-reactivity has been reported between birch pollen, and nuts. This cross-reactivity shows itself in a syndrome that is known as the para-birch-syndrome. The complaints of people suffering from this syndrome result from a birch pollen allergy (sneezing, nasal obstruction, and conjunctivitis during the birch pollen season), and also from an allergy to nuts and/or certain fruits. The allergic reactions to these foods mainly cause symptoms such as itching in and around the mouth and pharynx, and swelling of the lips. In some cases, however, more severe reactions occur. Related fruits in this context are apple, peach, plum, cherry, and orange. Also, some vegetables such as celery and carrot have been shown to be cross-reactive with the birch allergen. The patient is probably allergic to bread. Other known cross-reactivity combinations are graspollen with carrot, potato, wheat, and celery. A graspollen-allergic person may become allergic to, for example, wheat as well, which may eventually lead to symptoms such as dyspnea. The exact mechanisms underlying these phenomena are not known. It might be that wheat allergens are inhaled during the ingestion of bread. Another explanation might be that an allergic reaction is caused in the gut, where mediators are released which, after absorption, may be transported to the lungs.

14.2.4.1.6 *Wheat allergy.* Wheat contains water, starch, lipids, and the proteins albumin, globulins, and gluten. Gluten consists of gliadin and glutenine. The various proteins in wheat can cause different symptoms. One example is the so-called baker's asthma in bakers allergic to wheat albumin. This reaction shows itself when wheat dust is inhaled. In food allergy, globulins and glutenine are the most important allergens. Allergic reactions can occur following the ingestion of wheat. In celiac disease, an allergy to gliadin plays an important role in the pathogenesis. After exposure to gluten infiltration of eosinophils and neutrophils, edema and an increase in vascular permeability of the mucosa of the small intestine can be observed. If the allergic reaction is chronic, the infiltration consists mainly of lymphocytes and plasma cells. Further, flattening of the mucosal surface is found. The disorder manifests itself typically 6 to 12 months after introduction of gluten into the diet. It is characterized initially by intermittent symptoms such as abdominal pain, irritability, and diarrhea. If not treated, anemia, various deficiencies, and growth failure may occur as a result of malabsorption. Improvement is seen about 2 weeks after elimination of gluten from the diet. In addition to the immunological reaction to gluten, a direct toxic effect may also play a role in causing the disease.

14.2.4.2 Additives

Food intolerance reactions can be caused by a variety of substances. The occurrence of metabolic or idiosyncratic reactions depends on the underlying disorder in the host. The different foods that may cause metabolic reactions have already been mentioned in Section 14.2.3. The additives that are most frequently involved in idiosyncratic food intolerance reactions will be briefly discussed.

14.2.4.2.1 Azo dyes. Tartrazine is a yellow dye which is, of all azo dyes, most frequently associated with certain symptoms. In Europe, it is admitted in lemonades, puddings, ice cream, mayonaise, sweets, and preservatives. Some authors claim that it can

cause hyperreactivity in children. However, this remains controversial. Asthma has also been related to tartrazine intake, although recent studies have failed to identify sensitive patients in double-blind challenges. Other symptoms which are attributed to tartrazine are urticaria and angioedema, but these are extremely rare.

14.2.4.2.2 Sodium benzoate. This preservative is used in foods such as lemonades, margarine, jam, ice cream, fish, sausages, and dressings. Sometimes it is also added to flavorings. Benzoates can elicit asthmatic attacks in asthmatic patients. Further, benzoates may play a role in patients with urticaria.

14.2.4.2.3 Sulfites. Sodium and potassium bisulfite and metabisulfite are used in food products to prevent spoilage by microorganisms as well as oxidative discoloration. They are added to among others, salads, wine, dehydrated fruits, potatoes, seafood, baked goods, tea mixtures, and sugar products. Symptoms that may occur in sulfite-intolerant persons are airways constriction, flushing, itching, urticaria, angioedema, nausea, and in extreme cases hypotension. Different underlying mechanisms have been postulated. A conclusive explanation of the intolerance of sulfites has not been given.

14.2.4.2.4 Monosodium glutamate (ve-tsin). Salts of glutamic acid are used as flavorings, for instance in Chinese food, soup, meat products, and heavily spiced foods. The well-known "Chinese restaurant syndrome" was first described for a person who had consumed a Chinese meal. Symptoms such as tightness in the chest, headache, nausea, vomiting, abdominal cramps, and even shock, may show themselves. In asthmatic patients, ve-tsin may cause bronchoconstriction. The first symptoms may appear after 15 minutes, while an interval of 24 hours has also been described. The mechanism underlying this syndrome is not known.

If a person complains of dizziness, shortness of breath, nausea and vomiting shortly after consumption of a Chinese meal, this may have been brought about by a number of substances. The symptoms could be related to an allergic reaction, but also to an intolerance reaction. A Chinese meal often contains additives such as sodium glutamate, as well as many proteins and vegetables. For example, koriander (also a component of curry) and garlic are spices which may be responsible for this reaction, or also vegetables such as bean sprouts and cabbage. It should also be borne in mind that fish or fish products or peanut sauce could have been added to the meal. Only if a complete dietary recording and a medical examination have been carried out can the possible cause be identified.

14.2.4.2.5 Annatto. This is a coloring agent of natural origin that is added to cheese products, butter, dressings, syrups, and some types of oil. Some investigators have demonstrated that symptoms may worsen in patients with urticaria and/or angioedema, after ingestion of annatto.

14.3 Clinical aspects of food allergy and food intolerance

14.3.1 Symptoms

In the case of *food allergy*, late reactions seldom occur. The clinical symptoms of allergic food reactions are listed in Table 14.2. The oropharynx and gastrointestinal tract are the initial sites of exposure to food antigens. Symptoms such as edema and itching of the mouth often occur. However, these reactions may be transient and are not necessarily followed by other symptoms. In some people, certain fruits, nuts, and vegetables cause oral symptoms only, while in others a more extensive reaction is seen. The quantity of the offending food also plays a role in the gravity and extent of the reaction, although in

Table 14.2 Symptoms of food allergy

Skin symptoms	Itching, erythema
	Angioedema
	Urticaria
	Increase of eczema
Respiratory symptoms	Itching of (eyes,) nose, throat
	(Tearing, redness of the eyes)
	Sneezing, nasal obstruction
	Swelling of the throat
	Shortness of breath, cough
Gastro-intestinal symptoms	Nausea, vomiting
	Abdominal cramps
	Diarrhea
Systemic symptoms	Hypotension, shock
Controversial symptoms	Arthritis
	Migraine
	Glue ear
	Irritable bowel syndrome

principle a small amount of a certain food can readily cause a response. Sometimes the allergic reaction only develops if the food intake is followed by exercise. This is referred to as exercise-induced food allergy. Hypotension and shock are life-threatening consequences of a food-allergic reaction. Generally, the reaction is accompanied by other anaphylactic symptoms such as abdominal cramps, nausea, vomiting, diarrhea, dyspnea, urticaria, and angioedema.

Table 14.1 shows that *food intolerance* comprises many different clinical disease entities, with different symptoms. Often, the clinical picture is difficult to distinguish from an allergic reaction. The distinction intolerance/allergic cannot always be made on the basis of history alone.

14.3.2 Diagnosis

The manifestation of food allergy and food intolerance can vary from innocent symptoms, like rhinorhea, to life-threatening symptoms, such as shock. The diagnosis is made on the basis of clinical as well as laboratory data, according to the following procedure:

1. History of the patient (complaints, possible associations with food intake, family history, atopic manifestations);
2. Overview of food intake, recorded by a dietician. Often, people have already excluded food products of their own accord;
3. Physical examination (signs of eczema, asthma, rhinitis, abdominal disorders, and nutritional state);
4. Blood examination (eosinophils, total and specific IgE);
5. Skin tests (food allergens, inhalant allergens);
6. Exclusion of all potentially suspected foods (trial diet);
7. Challenge test, for one or a few food products or additives;
8. Gradual reintroduction of food products.

Some of the diagnostic tests are rather time consuming and costly. Also, they cause some risk or discomfort to the patient. The approach is modified depending on type of reaction involved, age, and other characteristics of the patient. Skin test results and specific IgE determinations may be unreliable. For many foods, the identity of the allergenic

moieties is unknown and information about their stability is lacking. Examples include the allergens of some fruits and vegetables. It is known that most people allergic to apples can eat apple pie without any problems. The allergen in apple is not heat-stable, and is destroyed by baking. The question is how reliable the skin tests for apple are. Negative results do not rule out a possible allergy for the tested allergen. Positive results do not automatically imply that the particular food does indeed cause the symptoms. The golden standard for the diagnosis of food allergy remains reintroduction or challenge after a period of exclusion. If the diagnosis is correct and compliance is maintained, exclusion of the suspicious food(s) should result in improvement of the patient's condition, and challenge or reintroduction should lead to relapse of the symptoms. It should be realized that food intolerance is not IgE-mediated, and cannot be detected by skin tests and specific IgE determinations. Food intolerance can only be demonstrated by exclusion and challenge. Challenge tests should be carried out in a double-blind placebo-controlled way to prevent subjective interpretation of the results. However, it may be difficult to determine which food component is responsible for the patient's symptoms. An open food challenge with the natural product is then preferable. In addition, challenges with encapsulated foods also have disadvantages. The food is digested in a different way which may result in different symptoms. Further, the food must be pulverized before encapsuling, which may change its allergenicity. If the test results cannot give a conclusive answer about food allergy or food intolerance, other causes must be considered. There is an extensive differential diagnosis. For example, diseases of the stomach or gall bladder cannot be detected by these examinations. Further investigations, such as endoscopy of the stomach and X-ray have to be carried out. It is beyond the scope of this book to go more deeply into this matter.

14.3.3 Treatment

The preferred approach to the management of food allergy (as with any disease) is prevention. Prevention starts in the newborn. IgE synthesis begins before birth, during the 11th week of gestation. There is little evidence that the maternal diet during the last 3 months of pregnancy has any determining effect on the development of a food allergy in the child. If a child has atopic parents, the child has a greater chance of becoming atopic. If both parents have one of the above manifestations of allergy, the chance is about 70%; if only one parent is atopic, the chance is reduced to 30 to 40%, and if neither parent is atopic, the chance is 5 to 10%. For children carrying the risk of atopy, it might be advisable to recommend a special diet. As mentioned before, a dietary regimen in the first months of life can decrease the incidence of food allergy in early infancy. In view of the gut maturity, the introduction of solid foods should be postponed by 6 months. Breast feeding is preferred, as this has several advantages. First, the allergenic burden is less, although some allergens may be found in breastmilk. Secondly, breast milk contains IgA, to which bacteria, viruses, toxins, and also antigens are bound. The binding of antigens which are ingested by the mother herself and are excreted in the breast milk, to IgA is of particular importance. Binding of microorganisms to IgA probably diminishes the incidence of gastrointestinal infections in the infant, resulting in a reduction of the absorption of food allergens and a decrease of the chance of being sensitized. Substances have been found in breast milk which might promote the maturation of the gut. It should be noted that with regard to food allergy, breast milk is superior to current milk formulas, especially if eggs and milk are excluded from the maternal diet. Other alternatives to cow's milk have already been mentioned in Section 14.2.4. Preparations may be considered hypo-allergenic only if it has been proven that they rarely evoke allergic reactions in food-allergic subjects. Formulations based on amino acid solutions are the most hypo-allergenic. The disadvantages are high cost and bad taste. Recent formulations have almost solved these problems.

Once treatment has been started, strict avoidance of all offending foods is needed. It is the task of the dietician to provide a diet that guarantees optimal nutrition and at the same time excludes all hidden sources of offending substances. In the case of food often used as raw material for food products, e.g., milk, egg, and wheat, this can be very difficult. Even the most careful patient may ingest clinically significant amounts of the food to which he is sensitive. With every diet, the degree of sensitivity and the seriousness of symptoms should be taken into account. Some foods (e.g., certain vegetables and fruits) which are not tolerated raw, may lose their allergenicity upon cooking, and may be ingested without any problem if completely cooked. In case of food intolerance, a large number of food products often has to be excluded. For the patient, it is often difficult to know which foods contain additives. Since January 1990, however, this problem no longer exists since by law, all additives have to be listed on the food packaging. However, there are shortcomings to this requirement. One of these is that additives, which make up less than 25% of the end product, are not required to be listed on the packaging material. A second shortcoming is that additives which have no function in the end product also do not need to be listed. It can be concluded, therefore, that information on the composition of food products as given in Part 1 of this book is very important. In case of an intolerance of substances of natural origin, like histamine, avoidance of food products with high contents of such particular substances is often sufficient.

14.4 Summary

It is very important when dealing with adverse food reactions to use generally accepted terminology; this will avoid misunderstandings. As this chapter illustrates, many mechanisms underlying food allergy and food intolerance still have to be elucidated. It is often difficult to give an accurate diagnosis of food allergy. This is largely due to the limited reliability of the diagnostic means. Good therapy can only be started if the diagnosis is clear; herein lies an important problem.

If treatment is prescribed, the help of a dietician is essential, and good patient compliance is important. Some diets require considerable self-discipline on the part of patients. In the other extreme, patients may exclude many foods from their diet on their own accord, thus resulting in nutritional deficiencies. Other problems include the immense assortment of food products that are available, and the lack of knowledge of possible components, as well as the cost of specific diets, which may be quite considerable.

Reference and reading list

Allen, D.H., Delohery and G.J. Baker, Monosodium L-glutamate-induced asthma, in: *J. Allergy Clin. Immunol.* 80, 530–537, 1987.

Hattevig, G., Kjellman, N.I.M., and N. Sigurs B. Bjorksten, and N.I.M. Kjellman, Effect of maternal avoidance of egg's, cow's milk and fish during lactation upon allergic manifestations in infants, in: *Clin. Exp. Allergy* 19, 27–32, 1989.

James, J.M., A.W. Burks, Food hypersensitivity in children. *Curr. Opin. Pediatr.* 6, 661–667, 1994.

Kagnoff, M.F., Immunology of the digestive system, in: Johnson, L.R., (Ed.), *Physiology of the Gastro-Intestinal Tract.* Raven Press, 1987.

Metcalfe, D.D., Food allergens, in: *Clin. Rev. Allergy* 3, 331–349, 1985.

Sampson, H.A., Mechanisms in adverse reactions to food. The Skin. *Allergy* 50 (20 Suppl.), 46–51, 1995.

Simon, R.A. and D.D. Stevenson, Adverse reactions to sulfites, in: *Allergy, Principles and Practice,* Middleton *et al.*, (Eds.), St. Louis, C.V. Mosby Company, 1988.

Stevenson, D.D., R.A. Simon, W.R. Lumry and D.A. Mathison, Adverse reactions to tartrazine, in: *J. Allergy Clin. Immunol.* 78, 182–191, 1986.