Food Allergies and Sensitivities

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Introduction

Eating is necessary to sustain life. For most people, given the variety and abundance of food available to them, eating is an enjoyable experience. For individuals with food allergies and sensitivities, however, consuming certain foods can be a debilitating and possibly even life-threatening experience. For such people, the joy of eating is diminished by the ever-present concern that they might consume a food or food component that will cause an adverse reaction. The standard treatment for food allergies and sensitivities is the removal of the offending food from the diet. For such consumers, food selection often becomes a tedious task requiring meticulous reading of ingredient lists on labels, dependence on food manufacturers to maintain accurate labels, and a continual search for more knowledge about food composition. Food preparation for them requires, in many cases, careful attention to detail, cooking “from scratch,” and seeking alternative recipes for many dishes. These consumers live in constant fear that trace amounts of the offending food, sufficient to elicit an adverse reaction, might still exist in the foods that they consume.

Food allergies and sensitivities can be collectively referred to as “individualistic adverse reactions” to foods. These food-related illnesses are individualistic because they affect only a few people in the population. Often, these diseases are grouped together under the general designation of “food allergies,” but it must be recognized that this term covers a host of different diseases. In fact, true food allergies represent only some of the individualistic adverse reactions to foods. Table 1.1 provides a classification scheme for the various illnesses that are known to occur as individualistic adverse reactions to foods. Knowing the difference between immunological food allergies and nonimmunological food intolerances is critical. Intolerances are often controlled by limiting the amount of food eaten; with allergies, total avoidance is essential.

Food allergy is an abnormal immunological response to a food or food component (almost always a protein). Examples are allergic reactions to common foods such as peanuts and milk. Within this category are immediate hypersensitivity reactions (IgE-mediated allergies) and delayed hypersensitivity reactions (cell-mediated allergies).

Immediate hypersensitivities are IgE-mediated and occur within a few minutes to several hours after consumption of the offending food. Exercise-induced food allergies are a subset of food allergies that involve immediate reactions that occur only when the specific food is ingested just before or after
exercise, although many cases of exercise-induced allergies are not related to foods. Delayed hypersensitivities are cell-mediated involving the response of sensitized cells, usually lymphocytes, to the specific foreign substance that triggers the reaction. The ultimate result is tissue inflammation often restricted to certain sites in the body. Symptoms appear from 6 to 24 h after consumption of the offending food.

Nonimmunological food reactions or food intolerances, in contrast to true food allergies, and as the name implies, do not involve abnormal responses of the immune system. Anaphylactoid reactions are a non-IgE-mediated release of the chemical mediators (mostly histamine) of allergic reactions in the body. Foods such as strawberries, shellfish, and chocolate can allegedly induce such reactions, but proof for this type of food intolerance does not exist. Metabolic food disorders are genetically determined metabolic deficiencies that result in adverse reactions to a food component. An example would be lactose intolerance, which is due to a deficiency of the intestinal enzyme, lactase, that is essential for the metabolism of the lactose in milk. Food idiosyncrasies are adverse reactions to foods or a food component that occurs through unknown mechanisms. Psychosomatic illnesses are included in this category and, frequently, the cause-and-effect relationship between the food or food component and the particular adverse reaction remains to be well proven. Examples include sulfite-induced asthma, tartrazine-induced asthma, food-associated migraine headache, and a variety of other illnesses. An allergy-like food intoxication is not an individualistic adverse reaction as everyone in the population is probably susceptible. However, such illnesses are often misdiagnosed as a food allergy. This reaction occurs

TABLE 1.1
A Classification Scheme for Food Allergies and Sensitivities

<table>
<thead>
<tr>
<th>Food Sensitivity</th>
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<tbody>
<tr>
<td><strong>Primary Food Sensitivity</strong></td>
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<tr>
<td>Immunological (food allergies)</td>
</tr>
<tr>
<td>IgE-mediated</td>
</tr>
<tr>
<td>Typical food allergies</td>
</tr>
<tr>
<td>Immediate allergic reactions</td>
</tr>
<tr>
<td>Delayed allergic reactions</td>
</tr>
<tr>
<td>Exercise induced</td>
</tr>
<tr>
<td>Non-IgE-mediated</td>
</tr>
<tr>
<td>Celiac disease (not proven)</td>
</tr>
<tr>
<td>Nonimmunological</td>
</tr>
<tr>
<td>Allergy-like intoxications</td>
</tr>
<tr>
<td>Anaphylactoid reactions</td>
</tr>
<tr>
<td>Metabolic reactions</td>
</tr>
<tr>
<td>Food idiosyncrasies</td>
</tr>
<tr>
<td><strong>Secondary Food Sensitivity</strong></td>
</tr>
<tr>
<td>Secondary to another event like illness or drug therapy</td>
</tr>
</tbody>
</table>
as a result of the ingestion of chemical mediators of allergic disease. The only example is histamine poisoning (also known as scombroid fish poisoning) which is commonly associated with the ingestion of spoiled tuna, mackerel, mahi-mahi, and other fish and also occasionally with cheese.\textsuperscript{7}

Avoidance diets are the only reliable means of prevention for food allergies.\textsuperscript{8} Pharmacologic and other therapeutic methods of prevention of food allergies do not exist, although certain drugs, such as epinephrine (adrenaline) and antihistamine, can be used to treat the symptoms that develop during an allergic reaction. Thus, food-allergic individuals are forced to become avid label readers in an attempt to avoid offending foods and certain ingredients derived from these foods. Their efforts are fraught with difficulty because individuals with true, immunologically mediated food allergies, can react to mere traces of the offending food in their diet.\textsuperscript{8,9}

### Immunological Food Hypersensitivities

**True Food Allergies**

The main function of the gastrointestinal tract is to process ingested food into a form that can be absorbed and used by the body for energy and cell growth. The “gut associated lymphoid tissue” must remain unresponsive to a wide variety of nutrient materials, and yet stand ready to mount a rapid and potent response against pathogenic viruses, bacteria, parasites, and other foreign substances. The human immune system is very effective in reacting with unwanted and potentially harmful foreign substances in our bodies, often by mounting humoral (antibody-based) or cellular immune responses against specific proteins present in the foreign material. But, at the same time, the immune system must develop tolerance to the hundreds of thousands of different proteins that are ingested with the typical human diet, lest we become sensitized to many foods. The small portion of the population (approximately 5\% of infants and 2 to 2.5\% of adults) with true food allergies has a genetically based predisposition to develop abnormal immunological responses to substances, usually naturally occurring proteins, in their environment. These responses may take the form of environmental allergies to pollens, mold spores, animal danders, bee venom, etc. or they may take the form of allergic responses to specific foods. As noted earlier, a food allergy is defined as an abnormal immunological reaction in which the body’s immune system overreacts to ordinarily harmless substances in foods.

### Mechanisms

Allergic reactions (or hypersensitivity reactions) are based on four different immunological mechanisms (Type I, II, III, IV) as first classified by Coombs.
These same mechanisms apply for food allergies and for allergic reactions to pollens, mold spores, animal danders, insect venoms, and drugs. The Type I mechanism also is called “immediate hypersensitivity,” and involves the formation of IgE. IgE-mediated reactions are the most important type of food allergy. Type II reactions are not associated with food hypersensitivities. Type III, or immune complex responses, may be involved in food allergies but evidence is rather limited. Type IV reactions, also known as cell-mediated reactions or delayed hypersensitivities, probably play an important, although as yet undefined, role in food hypersensitivity. Celiac disease, which will be discussed later, may be a form of cell-mediated delayed hypersensitivity.

**IgE-Mediated Allergic Reaction (Immediate Hypersensitivity)**

Hippocrates was the first to document the occurrence of food allergies. The beginnings of allergy as a clinical science may be traced to the experiments of Prausnitz and Kustner who subcutaneously injected a nonallergic individual with a fish extract and noted no adverse reaction. However, when the normal individual was first inoculated under the skin with serum from a fish-allergic person and then injected with the fish extract, there was an inflammatory skin reaction at the sensitized site. This experiment provided the first evidence that the blood contained some substance that sensitized the allergic individual to the fish. In 1966, Ishizaka et al. demonstrated that this reaginic activity was associated with a unique immunoglobulin and tentatively called this protein E. The protein was officially named immunoglobulin E or IgE by the World Health Organization (WHO) in 1968. Identification of IgE as a reaginic antibody provided immunochemical approaches to analyze the mechanisms involved in hypersensitivity reactions. Immunoglobulin E (IgE) is one of five classes of antibody that are present in the human immune system.

In IgE-mediated food allergies, the allergen-specific antibodies are produced in response to stimulus of the antibody-forming B cells by a food allergen, usually a naturally occurring protein present in the food. The IgE antibodies bind to the surfaces of mast cells in the tissues or basophils in the blood. When the same food allergen is encountered on a subsequent occasion, the allergen associates with the mast cell- or basophil-bound IgE, and cross-links two of the IgE molecules. This precipitates a cascade of biochemical events which causes cell membrane disruption and the release of a variety of mediators contained within granules existing in the mast cells and basophils. The granules in mast cells and basophils contain most of the important mediators of the allergic reaction. While more than 60 substances have been identified as chemical mediators eminating from mast cell and basophils, histamine is responsible for most of the immediate effects of allergic reactions. The histamine-related effects include inflammation, pruritis, and contraction of the smooth muscles in the blood vessels, gastrointestinal tract, and respiratory tract. Other important mediators include a variety of
prostaglandins and leukotrienes; these particular mediators are associated with some of the slower-developing responses observed in some cases of food allergy (e.g., late-phase asthmatic reactions).

A nonallergic individual will not respond to an exposure of a food protein with the production of an allergen-specific IgE. Even among individuals predisposed to allergies, exposure to food proteins does not usually result in formation of allergen-specific IgE. In normal individuals, exposure to a food protein results in oral tolerance through the formation of protein-specific IgG, IgM, or IgA antibodies. The true prevalence of food allergies is unknown, although it has been estimated that approximately 5% of infants and perhaps 1% of adults have food allergies. Heredity and other physiological factors are significant in predisposing individuals to the development of allergies, including food allergies. Approximately 65% of patients with clinically documented allergy have first-degree relatives with allergic disease. Conditions that increase the permeability of the intestine to macromolecules such as viral gastroenteritis, premature birth, and cystic fibrosis, may increase the risk of development of food allergy. Although food allergies also may involve other types of immunological mechanisms, the IgE-mediated mechanism is, by far, the most well documented and understood.

Allergic reactions involve numerous symptoms ranging from mild to life-threatening (Table 1.2). The symptoms experienced by individuals with food allergies are quite varied, and no one likely suffers from all of the symptoms mentioned in Table 1.2. The nature and severity of the symptoms also may vary from one occasion to another in the same individual as a result of the amount of the offending food ingested and the length of time since the last previous exposure.

Among the many symptoms involved in food allergies, systemic anaphylaxis is the most severe manifestation. Systemic anaphylaxis, sometimes referred to as anaphylactic shock, involves many organ systems and numerous symptoms. Symptoms may include tongue swelling and itching, palatal itching, throat itching and tightness, nausea, abdominal pain, vomiting, diarrhea, dyspnea, wheezing, cyanosis, chest pain, urticaria, angioedema, hypotension, and shock. Anaphylactic shock is the most common cause of death in the occasional fatalities associated with true food allergies.23,24

<table>
<thead>
<tr>
<th>TABLE 1.2</th>
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</thead>
<tbody>
<tr>
<td>Symptoms of IgE-Mediated Food Allergies</td>
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<tr>
<td>---</td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
</tr>
<tr>
<td>Nausea, vomiting, diarrhea, abdominal cramps</td>
</tr>
<tr>
<td><strong>Respiratory</strong></td>
</tr>
<tr>
<td>Asthma, wheezing, rhinitis, bronchospasm</td>
</tr>
<tr>
<td><strong>Cutaneous</strong></td>
</tr>
<tr>
<td>Urticaria (hives), eczema or atopic dermatitis, pruritis, rash, angioedema</td>
</tr>
<tr>
<td><strong>Other</strong></td>
</tr>
<tr>
<td>Anaphylactic shock (systemic shock), headache, hypotension, palatal itching, swelling including tongue and larynx</td>
</tr>
</tbody>
</table>
**Exercise-Induced Allergic Reactions**

Little is known about the natural history of exercise-induced anaphylaxis (EIA). A syndrome characterized by exertion-related development of allergy-like symptoms was first described in 1936. Increasingly, there has been recognition that in certain individuals experiencing EIA, the exercise must be preceded or followed by the ingestion of specific foods in order to elicit an allergic reaction. Shellfish, peach, wheat, and celery are among the foods that have been incriminated in food-dependent EIA. While the mechanism for food-dependent, exercise-induced anaphylaxis is unknown, enhanced mast cell responsiveness to physical stimuli may be involved. The symptoms in this type of food allergy are individualistic and similar to those involved in other food allergies. With awareness of the existence of this syndrome, and the recent national emphasis on physical activity, reports of this condition may continue to increase.

**Cell-Mediated Reactions (Delayed Hypersensitivity)**

As noted earlier, cell-mediated allergic reactions also are known as delayed hypersensitivity or Type IV reactions because the symptoms of these reactions usually begin to appear 6 to 24 h after ingestion of the offending food. These reactions develop slowly, reaching a peak at approximately 48 h and subsiding after 72 to 96 h. Cell-mediated food allergies involve interaction between specific antigens or allergens from the food and sensitized T lymphocytes. The stimulation of lymphocytes, which release cytokines and lymphokines, produces a localized inflammatory response. In contrast to the Type I mechanism, these reactions occur without the involvement of allergen-specific antibodies.

T lymphocytes are a major component of the gut-associated lymphoid tissue. Evidence for the involvement of cell-mediated immune reactions in food allergies is sparse with the possible exception of celiac disease (discussed below). However, some reasonably compelling information exists on the possible role of cell-mediated reactions in some cases of cows’ milk allergy. Both immediate and delayed reactions have been observed in cows’ milk-allergic infants. Increased numbers of intestinal intraepithelial lymphocytes have been observed in cows’ milk allergy. These reactions may be involved in the development of enteropathy in some cows’ milk allergic individuals, but further evidence is needed. No estimates of the prevalence of cell-mediated food allergies have been made.

**Nature and Chemistry of Food Allergens**

Allergens are almost always naturally occurring proteins found in food. Any food that contains protein has the theoretical potential to elicit allergic sensitization and, upon subsequent exposure, to cause an allergic reaction in the sensitive individual. However, only a few foods are most commonly...
associated with food allergy (Table 1.3). These eight foods or food groups are thought to be responsible for at least 90% of all food allergies. Foods frequently and falsely implicated by consumers as causes of food allergies such as chocolate, strawberries, and citrus fruits do not give positive results in double-blind food challenges in children with atopic dermatitis. In infants and young children, cows’ milk allergy is the most common food allergy but it is usually short-lived. Other common food allergies in this age group are allergies to peanuts, eggs, and soybeans. These foods are commonly allergenic in infants and young children in part because they are very frequently consumed foods for this age group. In contrast, peanuts and crustacea are likely to be the most common allergenic foods among adults in the U.S.

While frequency of exposure may have something to do with why these foods are among those most commonly associated with IgE-mediated food allergy, the inherent immunogenicity of the protein also must play an important role. Some commonly eaten, proteinaceous foods such as beef, pork, and chicken are rarely implicated in true food allergies. Because of differences in the diet in other countries, the prevalence of true food allergies to other foods may be higher. For example, soybeans in Japan, codfish in Scandinavian countries, and buckwheat in South Korea are commonly allergenic and comparatively popular foods in those countries.

Relatively few food allergens have been purified and characterized (Table 1.4). Some commonly allergenic foods contain multiple allergenic proteins including cows’ milk, eggs, and peanuts. Foods may contain both major and minor allergens. Major allergens are defined as allergens that bind to serum IgE antibodies from more than 50% of patients with that specific food allergy.

Cows’ milk contains several major allergens. The major proteins in cows’ milk — casein, β-lactoglobulin, and α-lactalbumin — are major allergens. Several other cows’ milk proteins are minor allergens that affect only a small percentage of cows’ milk-allergic individuals. The major cow’s milk allergens retain their allergenicity even when subjected to severe heat treatments. Cows’ milk appears to retain its allergenicity after such common heat-processing treatments as pasteurization, condensation, evaporation, and drying.

In most published studies of egg allergies, the egg white has been shown to be more allergenic than the egg yolk. The major allergens have been
identified as \textit{Gal d} 1 (ovomucoid), \textit{Gal d} 2 (ovalbumin), and \textit{Gal d} 3 (conalbumin).\textsuperscript{34} It should be noted, however, that IgE antibodies also can be directed to egg yolk proteins,\textsuperscript{44} and cross-reactivity may exist between egg yolk and egg white proteins, and between eggs of various birds.\textsuperscript{45} Bernhisel-Broadbent et al.\textsuperscript{46} determined that ovomucoid is the major antigenic and allergenic egg white protein for humans. The allergenicity of ovalbumin was due primarily to the presence of small amounts of ovomucoid as a contaminant of commercial ovalbumin.\textsuperscript{46} Ovomucoid or \textit{Gal d} 1 has a molecular weight of 28 kDa, comprises 11\% of protein in egg white, is noncoagulable by heat, and is not denatured by 8 M urea.\textsuperscript{47} Ovalbumin or \textit{Gal d} 2 has a molecular weight of 45 kDa, compromises 54\% of egg white protein, and is easily denatured by urea and guanidinium salts. Some egg allergens, ovomucoid in particular, are considerably heat stable. Allergic individuals may react to foods containing cooked eggs as well as raw eggs.\textsuperscript{41}

The most extensively characterized food allergen is \textit{Gal c} 1 (allergen M), a parvalbumin from codfish.\textsuperscript{34} \textit{Gal c} 1 contains 113 amino acid residues and 1 glucose moiety, has a molecular weight of 12,328 and an isoelectric point (pl) of 4.75.\textsuperscript{40} The three-dimensional structure is known, and \textit{Gal c} 1 apparently contains several IgE-binding sites.\textsuperscript{49,50} Synthetic polypeptides of the sequence of the domains of the \textit{Gal c} 1 molecule have the ability to bind IgE from the sera of cod-allergic individuals.\textsuperscript{49,50} \textit{Gal c} 1 is extremely resistant to physical destruction\textsuperscript{41,51} and would, therefore, be expected to retain its allergenic activity through most processing and cooking treatments.

The major shrimp allergen has been shown to be tropomyosin.\textsuperscript{52-54} This protein contains approximately 300 amino residues with a pl range of 4.8 to 5.4.\textsuperscript{52} Extensive cross-reactivity between different members of crustacea among crustacea-allergic individuals may be due to homology between tropomyosin from these sources.\textsuperscript{52-55} The allergenic activity of tropomyosin is heat-stable, and this shrimp allergen has been isolated from shrimp cooking water.\textsuperscript{56,57}
Multiple IgE-binding proteins have been identified in peanuts. Barnett et al. identified 16 IgE-binding protein bands in raw peanuts and 7 IgE-binding protein bands in roasted peanuts. While many of these peanut allergens remain to be purified and characterized, several of the major peanut allergens are relatively well defined. Barnett and Howden purified a 65 kDa concanavalin A-reactive glycoprotein that they documented as a major allergen. Burks et al. purified a major peanut allergen, Ara h 1, with a molecular weight of 63.5 kDa and a pI of 4.55. Although it appears as though Ara h 1 and the concavalin A-reactive glycoprotein may be the same based upon the similarity in molecular weight, Ara h 1 does not bind to concanavalin A. These same investigators also identified and characterized a second peanut allergen, Ara h 2, with a molecular weight of 17 kDa and pI of 5.2. More recently, yet a third major peanut allergen, Ara h 3, has been purified and characterized. The IgE-binding capabilities of a crude peanut extract and two of the major peanut allergens, Ara h 1 and Ara h 2, were unaffected by heating at 37°C for 60 min, 56°C for 60 min, 100°C for 5 min, 100°C for 20 min, or 100°C for 60 min. Processed peanut products containing detectable peanut proteins appear to retain their allergenicity through typical processing practices.

Soybeans also seem to contain multiple allergens. Soybeans have two major protein fractions, the globulin and the whey. The major globulins are glycinin or the 11S fraction and β-conglycinin or the 7S fraction. A minor fraction, the 2S fraction, contains several trypsin inhibitors. Allergenic activity has been found in the 2S, 7S, and 11S fractions by radioallergosorbent test (RAST), RAST inhibition, and Western blotting. The soybean allergenic protein, Gly m 1, which is most strongly and frequently recognized by the IgE antibodies in sera of soybean-sensitive patients, has been identified as an oleosin or oil body-associated protein with a molecular weight of 34 kDa. Certain components of the glycinin fraction also appear to be significant soybean allergens. As with peanuts, the soybean allergens are remarkably heat stable. Processed soybean products containing detectable and nonhydrolyzed soybean proteins possess allergenic activity.

The allergens in green peas are localized in the albumin fraction. These pea allergens are also heat stable. However, the allergens from green pea were not completely purified, identified, or characterized.

Comparatively less information is available regarding the allergens in tree nuts. A study by Bargman et al. determined that almond may have two major IgE-binding proteins of 20 kDa and 40 to 50 kDa. The immunoreactivity of the larger one was reduced by heat processing, while the smaller one was stable and maintained IgE binding after roasting and blanching. The Brazil nut is a common cause of allergic reactions in tree-nut sensitive individuals. Studies have shown that several proteins with potent antigenic properties are found in Brazil nuts, the most prominent being a methionine-rich 2S protein. The 2S protein found in Brazil nuts contains 18% methionine residues making it an excellent candidate to supplement sulfur amino acid-poor crops, such as soybeans. A recent study by Nordlee et al. demonstrated
that a chimeric gene encoding the 2S Brazil nut protein transferred to soybeans resulted in the protein being expressed in the transgenic seed. This protein was then found to bind human IgE, making it a probable allergen. More recently, the major allergen has been isolated from walnuts and also is a small molecular-weight storage protein.75

Matsuda et al.76 have demonstrated that the proteins responsible for rice allergy are major components of the rice albumin proteins. These proteins have molecular masses of about 14 to 16 kDa and a pI of about 6 to 8. The ability to bind IgE was decreased when the fractions were heated.

Adverse reactions to buckwheat have been reported and, though rare, can be rather severe in some cases.77,78 Immunoblotting with the sera of one patient who had multiple episodes of buckwheat-associated anaphylaxis revealed four IgE-binding bands in the molecular weight range of 9 to 40 kDa.79 Other investigators also using sera from buckwheat-allergic patients identified three proteins, including one trypsin inhibitor, in the molecular weight range of 8 to 9 kDa that bound to IgE.80

Sesame seed is a food of increasing allergenic significance,81 and sesame seed allergy occurs comparatively commonly in some countries.82 Recently, the major allergens from sesame seed have been identified.83

Adverse reactions to mustard have been documented by several studies.84,85 Mustard is made from the seed flour of mustard plants, namely *Brassica nigra* (black mustard), *Brassica alba* (white mustard), *Sinapis alba* L. (yellow mustard), and *Brassica juncea* L. (oriental mustard). Table mustard is usually made from yellow mustard and oriental mustard. The relative amount in the commercial product may be different depending on the manufacturer, with yellow most common in Europe, and oriental being most abundant in mustard extracts in the U.S. and Japan. Menendez-Arias et al.86 describe the major allergen from yellow mustard seeds as a 2S albumin, designated *Sin a* 1. This protein is composed of two disulfide-linked polypeptide chains of 39 and 88 amino acids. The *Sin a* 1 allergen is found to be related to other low-molecular-mass albumins, such as those isolated from rapeseed, castor bean, and Brazil nut. Gonzalez de la Pena et al.87 isolated and characterized a 2S albumin from oriental mustard seeds. This protein, *Bra j* 1, was found to be closely related to *Sin a* 1.

**Avoidance of True Food Allergies**

The only treatment for all food allergies and sensitivities is the specific avoidance diet. Individuals with peanut allergy must avoid peanuts, for example. While such diets can be quite successful, adherence can be quite challenging. The construction of safe and effective avoidance diets and the difficulties faced by consumers who must adhere to such diets have been extensively reviewed elsewhere.9,88

Patients with true food allergies are faced with three serious issues as they attempt to implement a safe and effective avoidance diet:
1. Will trace levels of the food elicit reactions or increase sensitization?
2. Do all foods and food ingredients made from the offending food contain the allergens?
3. Are cross-reactions likely to occur between closely related species?

First, trace levels of the offending food can elicit adverse reactions. Many experiences have been anecdotally related, such as reactions from touching utensils or bottles contaminated with the offending food, kissing the lips of someone who has recently eaten the offending food, opening packages of the offending food, inhalation of vapors from cooking the offending food, and the transfer of food allergens from lactating mothers to breast-feeding infants. In such situations, the amount of the offending allergen that is ingested must be rather low. However, several episodes have been well investigated and lend credibility to the anecdotal reports. While, for all practical purposes, complete avoidance must be maintained, threshold doses do exist below which allergic individuals will not experience adverse reactions. The threshold doses are likely to be very low and variable from one allergic individual to another. In a recent clinical study of threshold doses for peanuts, the most sensitive peanut-allergic individual among a group of 12 began to experience subjective symptoms when exposed to 100 µg of peanut protein and experienced objective symptoms when exposed to 2 mg of peanut protein. However, four other peanut-allergic individuals in this study with equally impressive histories of allergic reactions to peanuts had no reaction when exposed to the highest dose used in the trial, 50 mg of peanut protein.

Foods may become contaminated with trace amounts of other foods through various means. For food processors, the major concerns are the use of rework and the use of shared equipment. Contamination of food products with trace, unlabeled residues of allergenic foods is especially important to individuals who are exquisitely sensitive to the offending food and who experience life-threatening symptoms. No avoidance diet provides absolute safety, but careful adherence to an effective avoidance diet will minimize the chance of a reaction.

When considering foods derived from an allergenic food source, the presence of the allergenic protein is important. In a study by Nordlee et al., the allergenicity of peanut products was determined by RAST-inhibition using blood sera from peanut-allergic individuals. Most processed peanut products retained their ability to bind specific IgE from the sera indicating that peanut allergens are highly heat stable and survive typical food processes, such as roasting. The allergic reactivity of soybean products was determined, also using RAST inhibition, by Herian et al. Some soy products, such as soy oil and soy lecithin, which do not normally contain soy protein may be safe for consumption by soy-allergic individuals. Soy products, such as hydrolyzed vegetable protein (HVP) and soy sauce, which are subjected to considerable proteolysis during processing and which, therefore, may not contain intact
allergenic proteins, remain unsafe for soy-allergic consumers in many cases as the samples evaluated in this study were able to bind serum IgE. Edible oils, if processed by the typical hot-solvent extraction process, do not contain sufficient levels of protein to elicit allergic reactions in sensitive individuals. Extremely low levels of protein (<1.0 ppm) can be detected in these oils. However, double-blind challenge tests have been conducted with allergic individuals using peanut, soybean, and sunflower seed oils and all have been documented to be safe for ingestion.92-94 If foods derived from allergenic sources contain detectable protein residues, the safety of these foods must be established by clinical trials in sensitive individuals. Alternatively, the foods should be labeled to declare the source of the ingredient.

No ubiquitous statement can be made about cross-reactions between closely related foods because only limited studies have been conducted. Cross-reactivity to closely related foods seem to occur among some food-allergic patients, but not others. For example, individuals with a shrimp allergy may be told to avoid all seafood including both crustacean and molluscan shellfish and fish. Considering the distant taxonomic relationships between edible seafood, it is unlikely that shrimp would cross-react with fish or molluscan shellfish.95 However, patients with shrimp allergy will usually experience adverse reactions after ingestion of other crustacean species such as lobster, prawn, crab, and crayfish,96 suggesting appreciable similarity in the IgE-binding epitopes of the offending allergens from these sources.52 A study by Bernhisel-Broadbent et al.97 indicates that patients allergic to one or more fish species can often consume other fish species without adverse reactions. Some peanut-allergic individuals are allergic to other legumes, such as soybeans, although this is not a frequent occurrence. Clinical hypersensitivity to one legume, such as peanuts or soybeans, does not warrant dietary elimination of the entire legume food family unless allergy to each legume is individually confirmed by double-blind, placebo-controlled food challenges (DBPCFC).98 In contrast, cross-reactions are known to commonly occur between different species of avian eggs45 and between cows’ milk and goats’ milk.99

Cross-reactions also are known to occur between some types of pollens and certain foods. These include ragweed pollen and melons (watermelon, cantaloupe, honeydew); mugwort pollen and celery; mugwort pollen and hazelnuts; and birch pollen and various foods such as carrots, apples, hazelnuts, and potatoes.34 Another allergic cross-reaction is that between latex and fruit, particularly banana, chestnut, and avocado.34,100 Patients with a history of allergic reactions to latex should be aware of the potential for allergic reactions to certain fruits.

Clinical observation of cross-reacting IgE antibodies are occasionally unexpected and confusing, but they don’t always imply the existence of an allergy to each food. For the interpretation of IgE antibody assays, it is important to appreciate that finding IgE antibodies to an allergen does not imply that the patient has ever been exposed to that allergen or that they will react after ingestion of that food.101
Allergen Cross-Contact and Its Control

The issue of cross-contact of allergenic foods with other foods from the use of shared facilities and equipment came to the attention of manufacturers in the early 1990s as more incidents occurred where allergic individuals became ill from the consumption of products containing low levels of undeclared allergenic foods. To help prevent costly recalls and serious reactions in consumers, there are steps the food industry can take to minimize the opportunity for cross-contamination or mislabeling (Table 1.5). Manufacturers need to be aware that inadvertent transfer of allergenic food residues from one product to another and accidental mislabeling may result in serious, life-threatening reactions among allergic consumers. The amount of allergen that can set off a serious allergic response is extremely small and well below visual detection, although visual detection is sometimes the only method for inspection. Processors should approach all of the commonly allergenic foods listed in Table 1.3 with extreme caution with respect to cross-contact. Since these allergenic foods comprise 90% or more of the problem, the focus should be placed primarily on these particular commonly allergenic foods or food groups. It appears that the potential for peanut and tree nut allergies to elicit more severe manifestations is greater than those for most other food allergies. There is also an increasingly widespread use of peanuts in the food sector. This is a risk especially with the use of peanuts in products where it would not be expected and where they might not be visible or apparent (e.g., peanut shavings garnishing a lemon meringue pie). It appears that there are no adverse reactions to fully refined peanut oils. However, sometimes a “cold-pressed” peanut oil is utilized in gourmet and ethnic food production which could contain allergenic protein residues. Also, some ethnic food products containing peanuts are fried in peanut oil; in such cases, cross-contamination of the oil is probable. So although refined peanut oils are unlikely to trigger adverse reactions, it would be appropriate for allergic individuals to be cautious.

TABLE 1.5
Steps to Minimize Cross-Contamination and Mislabeling

1. Never substitute for listed ingredients without changing label accordingly.
2. Package label should accurately reflect product contents.
3. Check supplies to ensure all necessary precautions have been taken in-house.
4. Inspect incoming ingredients upon receipt.
5. Throw away unused supplies of outdated labels.
6. Ensure that limited opportunities exist for cross-contaminants to transfer from adjacent lines and that the production process and equipment are designed for avoidance of cross-contamination.
7. Inspect cleanup of equipment used for allergen-containing ingredients.
8. If reworked product is included in the formulation, adopt a “like-into-like” policy.
9. Schedule known allergenic foods and ingredients near the end of a run and prior to a full cleanup, shutdown, and inspection.
10. Institute an in-house education program in food allergies and anaphylaxis.

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Accurate labeling is the best approach to the prevention of severe allergic reactions to packaged food products. However, in most of the reported cases, the victim had no access to the label (e.g., food consumed from food service outlets). Restaurants, catering businesses, and similar establishments should consider including allergen training in their food safety training courses and placement of nonprescription antihistamine drugs in their first aid kits.

In Canada, with the cooperation of government agencies and industry, the Allergy Beware Program was launched in 1993. The program includes a videotape, instructor’s manual, employee summary, and cross-contact audit checklists. Through the program, manufacturers can learn to be aware of the program, how to be more accurate in food labeling, how to avoid the problem, and action to take if, despite all efforts, an allergen goes undetected. Programs like this one protect the consumer, the customer, the branch franchises, and the company.

### Celiac Disease (Gluten-Sensitive Enteropathy)

Celiac disease, also known as celiac sprue or gluten-sensitive enteropathy, is a malabsorption syndrome occurring in sensitive individuals following the ingestion of wheat, rye, barley, and, in some instances, oats. Following the ingestion of these grains, the absorptive epithelial cells in the small intestine are damaged resulting in a decreased number of epithelial cells that are critical for digestion and absorption. The activity of the mucosal enzymes necessary for digestion and absorption also are decreased in the damaged cells. This damage to the absorptive function of the small intestine results in a severe malabsorption syndrome characterized by diarrhea, bloating, weight loss, anemia, bone pain, chronic fatigue, weakness, muscle cramps, and in children, failure to gain weight and growth retardation.

While the mechanism for producing this damage is not known, several theories have been promulgated:

1. Sensitive individuals lack some enzyme necessary for the digestion of the wheat protein fraction, gliadin.
2. Gliadin acts like a lectin and binds to abnormal glycoprotein receptors on the surfaces of the epithelial cells of sensitive individuals and this interaction results in a cytotoxic effect.
3. Sensitive individuals mount an abnormal immunologic response to a fraction of the gliadin protein.

Strober suggested that the mechanism of celiac disease might be a Type IV allergic mechanism, an immunocytotoxic reaction mediated by intestinal lymphocytes. Researchers have found that immunoglobulins synthesized by celiac mucosa have antigluten specificity, but this response may occur secondary to the intestinal damage.
Celiac disease is an inherited trait; however, its inheritance is complex and poorly understood. Celiac disease occurs in about 1 of every 3000 individuals in the U.S.\textsuperscript{104,108} The disease occurs with differing frequencies in other parts of the world. The highest incidence of celiac disease is in County Galway, Ireland, affecting 1 in every 300 individuals.\textsuperscript{108} Celiac disease occurs more frequently among Europeans than among Americans of European descent for unexplained reasons. Celiac disease rarely, if ever, occurs in those of Chinese or African descent.\textsuperscript{105}

The intestinal damage that occurs in celiac disease is associated with the abnormal immunological response to the prolamin protein fractions of wheat, rye, barley, and perhaps oats. Specifically, in wheat, this fraction is called gliadin, but related prolamin proteins also occur in barley, rye, and oats.\textsuperscript{106} It is likely that the cross-reactivity is due to the conservation of reactive peptide sequences in these complex protein fractions among these closely related grains. The role of oats in celiac remains somewhat uncertain. A recent Finnish study documented that celiac sufferers can safely ingest oats.\textsuperscript{109} However, in commerce in much of the world, oats would often be contaminated with wheat so the avoidance of oats may still be a wise idea for those with severe celiac sensitivity.

The treatment of celiac disease typically involves the total avoidance of wheat, rye, barley, and probably oats and their products.\textsuperscript{104} While the tolerance for wheat, rye, and barley protein in celiac sufferers is not precisely known, the symptoms of celiac disease can be triggered by ingestion of rather small quantities of these grains. Treatment with a gluten-free diet results in resolution of the damage to the intestinal mucosa and its absorptive function. Since a safe tolerance level cannot yet be estimated, complete avoidance is usually practiced by celiac sufferers. However, adherence to strict avoidance diets can be quite difficult since wheat and wheat products are so commonly used in food formulations. Questions remain about the necessity of excluding ingredients prepared from wheat, rye, barley, and oats if the ingredients contain no intact proteins. Examples might include wheat starch, rye whiskey, malt extract, and hydrolyzed vegetable protein. In the absence of data demonstrating the safety of these ingredients for celiac patients, most celiac sufferers will likely continue to avoid these products.

Nonimmunological Food Sensitivities

In contrast to true food allergies, many of the individualistic adverse reactions to food do not involve the immune system. The prevalence of these reactions is unknown. Most of the nonimmunological food sensitivities are associated with foodborne substances other than proteins. While true food allergies can be attributed to proteins, nonimmunological food sensitivities are associated with both naturally occurring and additive substances (Table 1.6).
Anaphylactoid reactions result from substances in food that cause mast cells and basophils to spontaneously release histamine and other mediators of allergic reactions. However, unlike true food allergies, there appears to be no involvement of IgE or other immunoglobulins, and prior exposure is not a prerequisite.\textsuperscript{1,107}

Metabolic food disorders are adverse reactions to a food or food additive that occur through some effect of the substance on the metabolism of the individual.\textsuperscript{1,107} Two of the most common examples of metabolic food disorders are lactose intolerance and favism.

Idiosyncratic reaction is the term used to describe a variety of individual food sensitivities thought to occur through nonimmunological, but unknown, mechanisms.\textsuperscript{1,107} Many of the reported adverse reactions to food additives are placed in this category because of the lack of understanding of their modes of action. The cause-and-effect relationship between the food additives allegedly involved in idiosyncratic reactions and the adverse reactions is not yet clearly established. In a few cases, the cause-and-effect relationship is very well established. For example, the involvement of sulfites in asthma is well documented.\textsuperscript{110,111} However, the extent to which chocolate causes migraine headaches,\textsuperscript{112} food coloring agents and sugar cause hyperkinesis,\textsuperscript{6,113,114} tartrazine (FD&C yellow #5), butylated hydroxyanisole (BHA), and butylated hydroxytoluene (BHT) cause hives,\textsuperscript{6} and monosodium glutamate causes the headache, facial flush, and chest pain termed “monosodium glutamate (MSG) symptom complex” in sensitive individuals\textsuperscript{115} is unproven.

\begin{table}
\centering
\caption{Substances Associated with Nonimmunological Food Sensitivities}
\begin{tabular}{|l|l|l|}
\hline
\textbf{Type of Reaction} & \textbf{Specific Illness} & \textbf{Known, Suspected, or Alleged Causative Substance} \\
\hline
\textit{Naturally Occurring Substances} & & \\
Anaphylactoid & — & Unknown substances in strawberries, shellfish \\
Metabolic food disorder & Lactose intolerance & Lactose \\
& Favism & Vincine and convicine \\
Idiosyncratic & Migraine headache & Chocolate, cheese \\
\hline
\textit{Additive Substances} & & \\
Anaphylactoid & — & None known or suspected \\
Metabolic food disorder & — & None known or suspected \\
Idiosyncratic & Asthma & Sulfites, tartrazine, MSG, BHA, BHT, benzoates, sunset yellow \\
& Chronic urticaria & Tartrazine, BHA, BHT, benzoates, parabens, sunset yellow, aspartame \\
& Migraine headache & Aspartame \\
& Behavioral disorders & Food colorants, sugar \\
& MSG symptom complex & MSG \\
\hline
\end{tabular}
\end{table}
Anaphylactoid Reactions

In true food allergies, the release of histamine and other mediators of the allergic response from the mast cells and basophils is mediated by IgE, as discussed earlier. In contrast, anaphylactoid reactions are caused by substances that bring about the nonimmunologic release of these same mediators from mast cells without the involvement of IgE.\(^1,107\)

Occasionally, histamine poisoning (also known as scombroid fish poisoning) is included as an example of an anaphylactoid reaction.\(^1\) However, histamine poisoning is actually a foodborne intoxication associated with the ingestion of foods containing unusually high levels of histamine.\(^116\) The histamine is formed during bacterial spoilage.\(^117\) All consumers are susceptible to histamine poisoning, so it does not truly fit into the category of food allergies and sensitivities, the so-called individualistic adverse reactions to foods. Histamine poisoning is clearly an illness that is distinct from food allergies as it involves the ingestion of exogenous histamine rather than the release of histamine from mast cells and basophils \textit{in vivo}. It is frequently included because the symptoms resemble those encountered with food allergies. Histamine poisoning has been described in several reviews.\(^116,118\)

In anaphylactoid reactions, some substance in the implicated food is presumed to destabilize the mast cell membranes allowing the spontaneous release of the histamine and other mediators. Actually, no such histamine-releasing substances has ever been isolated or identified in foods. However, this mechanism is well-established with certain drugs. Therefore, the best evidence for the existence of anaphylactoid reactions is actually the lack of evidence for an IgE-mediated mechanism in a few types of food allergy, such as strawberry allergy. Strawberries are known to cause adverse reactions (frequently urticaria) in some individuals. Yet, strawberries contain little protein, and no evidence of a strawberry allergen has ever been found. Additionally, no evidence has been obtained for the existence of strawberry-specific IgE in the sera of strawberry-sensitive individuals. The symptoms of strawberry “allergy” are very similar to those occurring in IgE-mediated food allergy, so \textit{in vivo} release of histamine and other mediators is a possible mechanism. Also, histamine poisoning is not a likely explanation since strawberries also contain only traces of histamine. Thus, by a process of elimination, non-immunological release of the mast cell and basophil mediators seems a plausible, if unproven, explanation.

Metabolic Food Disorders

Metabolic food disorders involve genetically determined deficiencies that either (1) affect the host’s ability to metabolize a food component or (2) enhance the sensitivity of the host to some foodborne chemical via an altered metabolic pattern.\(^1\) Lactose intolerance is an example of an illness that occurs when a genetic deficiency affects the host’s ability to metabolize a food component. In lactose intolerance, a deficiency in the enzyme, β-galactosidase,
leads to an impaired ability to digest lactose. Favism is an example of a genetic deficiency that enhances the sensitivity to a foodborne chemical. In favism, a genetic deficiency in erythrocyte glucose-6-phosphate dehydrogenase causes an increased sensitivity to several hemolytic factors in fava beans. These two metabolic food disorders are certainly the most common and best understood within this category of food sensitivities.

**Lactose Intolerance**

Lactose, a disaccharide and the principal naturally occurring sugar in milk, is hydrolyzed into its constituent monosaccharides, galactose and glucose, in the intestinal mucosa in normal digestive processes. The galactose and glucose can then be absorbed and used metabolically as energy sources. In lactose intolerance, the activity levels of the key intestinal hydrolytic enzyme, known as β-galactosidase or lactase, are diminished.\(^4,119\)

Lactose cannot be absorbed in the small intestine unless it is hydrolyzed to galactose and glucose. In case of the lactose intolerance, the undigested lactose passes into the colon where it encounters large numbers of bacteria. The bacteria present in the colon metabolize the lactose to CO\(_2\), H\(_2\), and H\(_2\)O.\(^1\) The symptoms of lactose intolerance (abdominal cramping, flatulence, and frothy diarrhea)\(^120\) are the result of this bacterial action. The symptoms vary in intensity depending upon the individual’s level of intestinal β-galactosidase activity and the amount of lactose ingested.

Lactose intolerance affects many people on a worldwide basis. While only about 6 to 12% of Caucasians are affected,\(^4\) lactose intolerance is much more prevalent in other ethnic groups and races, affecting as many as 60 to 90% of Greeks, Arabs, Jews, African-Americans, Hispanics, Japanese, and other Asians.\(^4,119\) Although lactose intolerance tends to worsen with advancing age and is often more common and more severe among the elderly, it can have its onset at any age, occurring as early as the age of three.\(^119,121\) The level of intestinal β-galactosidase activity is usually sufficient at birth to allow the digestion of lactose in mother’s milk.\(^1\) However, individuals born with an inherited deficiency of intestinal β-galactosidase suffer a decline in the activity of the enzyme as they age. At some point, symptoms may begin to develop following the consumption of dairy products containing lactose at levels that exceed the saturation point of the enzyme activity.

Lactose intolerance also can occur secondary to another intestinal illness or infection, such as a bout with viral gastroenteritis.\(^122\) Secondary lactose intolerance is often a short-term illness because enzymatic activity levels can recover after the original illness subsides.\(^1\)

The lactose tolerance test (LTT) is usually used as the basis for a clinical diagnosis of lactose intolerance.\(^1,14\) The LTT involves the oral administration of 50 g of lactose to a fasting individual with monitoring for blood glucose or breath hydrogen levels after challenge to determine whether lactose is being absorbed. Gastrointestinal symptoms are also monitored. While the LTT definitely establishes lactose intolerance, the dose is sufficiently high in the LTT...
that the test does not establish the degree of lactose intolerance. Few individuals would ever ingest 50 g of lactose in a single meal. Newcomer\textsuperscript{123} concluded that only 19\% of lactase-deficient individuals were intolerant to ingestion of 8 oz of milk containing 12 g of lactose. As a result of such concerns, some physicians have advocated the use of lower doses of lactose in the diagnosis of lactose intolerance.\textsuperscript{1} The use of sequentially increasing doses of lactose, while perhaps a tedious diagnostic procedure, would help to clarify the degree of intolerance to various doses of lactose and the extent to which lactose intolerance worsens with age in affected individuals.

Careful differential diagnosis is important in the assessment of possible cases of milk intolerance. Lactose may not be responsible for all cases of milk intolerance. True cows’ milk allergy is another possibility that has already been discussed. Additionally, investigators have identified individuals with normal capacities for lactose ingestion, as indicated by the LTT, who experience the same symptoms as lactose-intolerant individuals when challenged with 8 to 12 oz of milk.\textsuperscript{124} These investigators speculated that substances other than lactose in milk may be responsible for some cases of milk intolerance. Milk protein intolerance, an illness distinct with IgE-mediated cows’ milk allergy, might be one possibility, although the symptoms often display a delayed onset of several hours in this form of milk intolerance.\textsuperscript{32,125}

Individuals with lactose intolerance are able to control their symptoms through the avoidance of dairy products containing lactose. However, the extent to which lactose avoidance must be practiced depends upon the lactose-intolerant individuals and their individual degree of tolerance for lactose. As noted above, some lactose-intolerant individuals may be able to tolerate some dairy products and some lactose. Individuals identified as intolerant to 50 g oral challenges in the LTT may, in some cases, be able to tolerate the lower amounts of lactose present in most dairy products. Dietary alternatives also exist for individuals with greater degrees of lactose intolerance who would experience symptoms from ingestion of typical amounts of many dairy products. Some of these individuals will be able to tolerate small, divided doses of milk. Lactose-hydrolyzed milk is also available in the marketplace.\textsuperscript{126} This product is effective, but its sweet taste limits acceptance. The addition of $\beta$-galactosidase to milk just before consumption also seems to be effective.\textsuperscript{127} Presumably, the enzyme retains its activity and hydrolyzes the ingested lactose in the gut. Martini and Savaiano have demonstrated that the tolerance for lactose increases when the lactose is consumed with a meal.\textsuperscript{128} Because yogurt and acidophilus milk contain active cultures of bacteria with $\beta$-galactosidase activity, lactose-intolerant individuals appear to be more susceptible to these dairy products than others.\textsuperscript{129,130} The level of lactase activity varies from one brand of yogurt to another, so some brands are more easily tolerated than others.\textsuperscript{131} Since dairy products are excellent sources of calcium and also have other important nutritional attributes, the incorporation of maximal, tolerated levels of dairy products into the diets of lactose-intolerant individuals is important.\textsuperscript{3} Birge et al. suggested that osteoporosis may result from the inadequate calcium intakes
associated with dairy product-avoidance diets among lactose-intolerant individuals. The main objective should be to determine the tolerance level for each sensitive individual and construct an avoidance diet that allows the maximum benefit and enjoyment of dairy products.

**Favism**

Favism occurs as the result of an intolerance to the consumption of fava beans or the inhalation of pollen from the *Vicia faba* plant. As a result, the individual suffers from acute hemolytic anemia with symptoms including pallor, fatigue, dyspea, nausea, abdominal and/or back pain, fever, and chills. In rare and severe cases, hemoglobinuria, jaundice, and renal failure can occur. The onset time ranges from 5 to 24 h after ingestion. The disease is usually self-limited with symptoms resolving promptly and spontaneously following avoidance of any further exposure. Favism is most prevalent when the *V. faba* plant is blooming, causing elevated levels of airborne pollen.

Individuals with an inherited deficiency of the enzyme, glucose-6-phosphate dehydrogenase (G6PDH), in their red blood cells are susceptible to favism. G6PDH is a critical enzyme in erythrocytes because it helps maintain adequate levels of the reduced form of glutathione (GSH) and nicotinamide adenine dinucleotide phosphate (NADPH). GSH and NADPH help prevent oxidative damage to erythrocytes.

Fava beans contain naturally occurring oxidants, including vicine and convicine (Figure 1.1), that are able to damage the red blood cell membranes of G6PDH-deficient individuals causing hemolysis of the erythrocytes and the symptoms of hemolytic anemia. While both lactose intolerance and favism are metabolic food disorders, the mechanism of favism is quite distinct from that of lactose intolerance. With favism, the genetic deficiency causes an increased susceptibility to the oxidative toxins present in fava beans.

G6PDH deficiency occurs very frequently affecting about 100 million people. Prevalence is highest among Asian Jewish communities in Israel, among Sardinians, Cypriot Greeks, African-Americans, and certain African populations. G6PDH deficiency is virtually absent among Caucasians and Native Americans. Despite the high prevalence of G6PDH deficiency, the incidence of favism is low. Favism occurs primarily in the Mediterranean area, the Middle East, China, and Bulgaria where G6PDH deficiency is fairly

**FIGURE 1.1**

Structures of vicine and convicine.

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common and where fava beans are grown and are frequently consumed. The treatment for favism is the avoidance of fava beans both in the diet and from the inhalation of the plant pollen.

Idiosyncratic Reactions

The mechanisms are unknown for some adverse reactions to foods experienced by certain individuals in the population. Conceivably, a large number of different mechanisms could be involved in these idiosyncratic reactions. As expected, the symptoms associated with this wide variety of illnesses range from the trivial to severe life-threatening reactions.

Some foodborne idiosyncratic reactions are rather well documented and the relationship with specific foods and/or food ingredients is firmly established. Sulfite-induced asthma would be a good example. For many other idiosyncratic reactions to foods, the association with specific foods and/or food ingredients has not been clinically established. Examples would include the role of chocolate or aspartame in migraine headache; the roles of BHA, BHT, or tartrazine in chronic urticaria; the role of tartrazine in asthma; the role of MSG in asthma or MSG symptom complex; and the role of sugar in aggressive behavior. The role of psychological disorders in perceived reactions to foods has been the subject of several notable studies. In some cases, the symptoms are so subjective that the confirmation of the responses is difficult. In a few cases, the role of specific foods or food ingredients in idiosyncratic reactions has been disproven by careful clinical investigations. However, consumers may persist in the belief that these relationships are real. The outstanding example of such a reaction is the role of artificial food colors in hyperkinetic behavior in children. Food colorants were first implicated as causative factors in hyperkinesis by Dr. Benjamin Feingold on the basis of poorly controlled trials and anecdotal experiences. The Feingold hypothesis received considerable publicity, and many consumers became convinced of the relationship between ingestion of artificial food colors and hyperkinetic behavior in children. Subsequently, several well-controlled, double-blind challenge trials revealed that few, if any, hyperkinetic children were adversely affected by ingestion of these food colorants. Despite this evidence, some consumers continue to believe that artificial food colorants are involved in hyperkinetic behavior in children. Table 1 contains a partial list of food-related idiosyncrasies in each of these categories (proven, unproven, and disproven).

As noted above, the role of specific foods or food ingredients in many of these idiosyncratic reactions remains to be established. The cause-and-effect relationships can only be established through carefully controlled DBPCFC (double-blind, placebo controlled food challenges). A positive DBPCFC confirms that the specific food or food ingredient is involved in the particular adverse reactions. Conversely, a negative DBPCFC may indicate either that...
foods are not involved in the reaction or at least that the specific food or ingredient was wrongly incriminated.

A complete discussion of all of the many alleged food-associated idiosyncratic reactions is beyond the scope of this chapter. Instead, several idiosyncratic reactions will be highlighted as examples.

**Sulfite-Induced Asthma**

Sulfiting agents including sulfur dioxide (SO$_2$), potassium metabisulfite (K$_2$S$_2$O$_5$), potassium bisulfite (KHSO$_3$), sodium bisulfite (NaHSO$_3$), and sodium metabisulfite (Na$_2$S$_2$O$_5$) have been widely used in foods for many years. Sulfites are used as food additives for several important commercial purposes: to prevent enzymatic and nonenzymatic browning, as broad spectrum antimicrobial agents, as dough conditioning agents, to provide antioxidant protection, and as bleaching agents in the processing of maraschino cherries and hominy. As a result, residues of sulfite can occur in a variety of foods at levels ranging from a few ppm to >1000 ppm in dried fruits. Among the foods and beverages with the highest sulfite levels as consumed are dried fruits other than dark raisins or prunes, nonfrozen lemon and lime juices, wines, molasses, dehydrated potatoes, refrigerated or fresh hash brown potatoes, shrimp, white and pink grape juices, and sauerkraut juice. Sulfites also occur naturally in some foods, especially fermented foods, but the residues from naturally occurring sulfites are usually low.

Sulfites added to foods can react with other food components such as reducing sugars, proteins, amino acids, aldehydes, and ketones. Consequently, very little free, unreacted sulfite remains in most foods. Instead, residual sulfites are typically bound to other organic constituents either reversibly or irreversibly. Sulfites also are oxidized to sulfate in some food systems. Sulfites also can be volatilized as SO$_2$, especially from acidic food and beverages. Thus, the residual sulfite levels in foods, measured as SO$_2$ equivalents, decreases with processing and storage in most food matrices.
Although sulfites were used for centuries with little evidence of harm to consumers, in recent years, sulfites have been implicated as triggers for asthmatic reactions in some sensitive individuals.\textsuperscript{110,111} The reactions usually occur within a few minutes after ingestion of a provoking dose of sulfite. The reactions can be quite severe on occasion, and deaths have been attributed to sulfite-induced asthma.\textsuperscript{111}

Asthma is the only well-documented symptom involved in sulfite sensitivity. The role of sulfites in asthma has been verified by numerous investigators through the use of DBPCFCs.\textsuperscript{110,111,139,140} Other symptoms have been reported as associated with sulfite sensitivity, but these reports are largely anecdotal and unverified by DBPCFC.\textsuperscript{139} Double-blind challenges have been conducted with sulfite in capsules and in acidic beverages. Volatilization of SO\textsubscript{2} occurs in acidic beverages, and sulfite-sensitive asthmatics are more likely to respond to sulfited, acidic beverages than to capsules.\textsuperscript{141} In acidic beverage challenges, the increased sensitivity seems to be due to the inhalation of SO\textsubscript{2} vapors while swallowing.\textsuperscript{141}

Sulfite sensitivity occurs rather infrequently among asthmatic individuals. From challenges conducted on over 200 asthmatics, Bush et al. concluded that severe asthmatics, defined as those requiring steroid-based drugs for control of their asthmatic conditions, are most likely to be sulfite-sensitive.\textsuperscript{140} The prevalence among steroid-dependent asthmatics is estimated at 4 to 7\%.\textsuperscript{140} However, steroid-dependent asthmatics comprise only about 20\% of the entire asthmatic population. Thus, the overall prevalence of sulfite sensitivity among asthmatics can be estimated at 1 to 1.5\%. None of the mild asthmatics in the large clinical trial conducted by Bush et al. were confirmed to be sulfite sensitive.\textsuperscript{140} Other investigators have estimated a higher prevalence of sulfite sensitivity among asthmatics,\textsuperscript{142,143} but these estimates may have been based mostly on challenges of steroid-dependent asthmatics rather than a representative cross section of the entire asthmatic population.\textsuperscript{139}

The mechanism involved in sulfite-induced asthma is now known. Hence, despite the well proven existence of sulfite sensitivity, it remains an idiosyncratic reaction. Multiple mechanisms have been proposed including IgE-mediated reactions, hyperreactivity to inhaled SO\textsubscript{2}, and sulfite oxidase deficiency.\textsuperscript{6} The hyperreactivity to inhalation of SO\textsubscript{2} while swallowing seems to explain the sensitivity to ingestion of acidic beverages.\textsuperscript{141} However, this mechanism cannot explain adverse reactions to ingestion of sulfite in capsules.

Sulfite-sensitive asthmatics display thresholds for sulfites.\textsuperscript{111} However, sulfite-sensitive asthmatics must avoid highly sulfited foods and beverages, as the reaction may be serious or even fatal. The threshold for sulfites varies among sulfite-sensitive asthmatics. In controlled challenges with capsules and/or acidic beverages, the threshold level of sulfite ranges from 3 to 130 mg of SO\textsubscript{2} equivalents.\textsuperscript{5} Sulfite-sensitive asthmatics are even more tolerant of sulfites in foods.\textsuperscript{144} Perhaps the increased tolerance occurs because sulfite-sensitive asthmatics are more tolerant of bound sulfite than they are to free sulfite.\textsuperscript{144} Sulfite-sensitive asthmatics are especially sensitive to sulfited
Lettuce contains a preponderance of free, unbound sulfite\(^{146}\) and may represent an especially hazardous food for sulfite-sensitive asthmatics. As a result of growing concerns over reactions to sulfites among consumers, the U.S. Food and Drug Administration (FDA) has instituted several regulations for the protection of sulfite-sensitive asthmatics\(^{111}\). Since 1986, the FDA has banned the use of sulfiting agents on raw fruit and vegetables. This ban prohibits the use of sulfite on fresh lettuce and other vegetables and fruits in restaurant salad bars. This unlabeled use of sulfites was associated with many of the consumer reactions. Use of sulfites in shrimp has been limited to levels that will result in sulfite residues not exceeding 100 ppm total SO\(_2\). Packaged food containing greater than 10 ppm of SO\(_2\) equivalents must identify the presence of the specific sulfite on the ingredient declaration. Because of these public health interventions, the risk of sulfite reactions in sensitive asthmatics appears to be greatly reduced.

**Role of MSG in Idiosyncratic Reactions**

The involvement of monosodium glutamate (MSG) in idiosyncratic reactions remains to be proved. MSG has been linked to the so-called MSG symptom complex (headache, chest tightness, burning sensation along the back of the neck, nausea, and diaphoresis occurring within minutes after the ingestion of high levels of MSG in foods) and asthma. Recently, an extensive review of MSG reactions was conducted by a group of independent scientists under the auspices of the Federation of American Societies for Experimental Biology (FASEB).\(^{115}\) This review helped to put these safety concerns into perspective and reaffirmed the FDA’s belief that MSG and related substances are safe ingredients for most people when eaten at customary levels. The FASEB review panel concluded that some evidence exists to suggest that certain people may develop short-term reactions (the MSG symptom complex) when they consume large doses (3 g or more) of MSG.\(^{115}\) No evidence was found linking the MSG symptom complex to consumption of lower levels (<3 g) of MSG.\(^{115}\) Few meals would contain more than 3 g of MSG. Also, the FASEB review panel failed to find convincing evidence for a role for MSG in more serious alleged reactions with the possible exception of asthma. The panel noted that there may be a small subgroup of people with severe asthma who may respond to ingestion of large doses of MSG (>3 g).\(^{115}\) However, scientific and clinical consensus on a role of MSG in the provocation of asthma has certainly not been achieved. Several clinical investigations have linked MSG exposure to asthma in a few severe asthmatics.\(^{147-149}\) However, some questions remain about the validity of the diagnosis in some of these cases because delayed (10 to 14 h) reactions occurred with some patients and very large doses of MSG (>3 g) were required in the majority of cases.\(^{107}\) Moreover, other clinical investigators have failed to identify any MSG-sensitive asthmatics in clinical trials.\(^{150-153}\) However, the selection of patients in these trials may have diminished the likelihood of finding reactors, since mild
asthmatics were used for the most part. Thus, further clinical studies will be
needed to confirm or refute the role of MSG in the provocation of asthma.
However, it can certainly be concluded at this point that MSG-induced
asthma, if it exists, is an extremely rare condition.

Tartrazine-Induced Asthma and Urticaria

Tartrazine, also known as FD&C Yellow #5, is a certified, artificial colorant
used in foods, drugs, and cosmetics in the U.S. and other countries. In 1959,
Lockey154 presented the first anecdotal evidence of tartrazine-induced urti-
caria (hives) after the ingestion of yellow-colored drugs. Later, clinical evi-
dence was presented that seemed to link asthma in a small percentage of
aspirin-intolerant asthmatics with provocation by tartrazine as well.155
Mounting evidence, mostly from anecdotal reports or non-blinded or open
challenges with tartrazine, led the FDA to require the specific labeling of
FD&C Yellow #5 on food products in 1979.156 Today, the failure to properly
declare FD&C Yellow #5 on food labels is one of the most frequent causes of
food recalls in the U.S.

Since the FDA action in 1979, many additional clinical trials have been con-
ducted on tartrazine-induced asthma and urticaria; these trials have recently
been critically reviewed.6 Many of these trials were flawed in one respect or
another, such as the failure to use double-blind, placebo-controlled trial
designs or the withdrawal of key medications just before initiation of the
trial.6 The trials that were conducted in double-blind, placebo-controlled
fashion represent a strong test of the hypothesis that tartrazine is involved in
the causation of asthma and urticaria. The results of the double-blind oral
challenges with tartrazine have indicated that tartrazine plays virually no
role in either asthma or urticaria.6,157,158 With respect to asthma, the most care-
fully controlled double-blind, placebo-controlled trials with tartrazine have
failed to identify any tartrazine-sensitive subjects even when the patient pop-
ulation was comprised of aspirin-intolerant asthmatics.157,158 The clinical
studies that have implicated tartrazine in the causation of asthma have often
been complicated by withholding bronchodilator drugs from patients with
unstable, chronic airway disease.6,157,158 Stevenson et al.157 concluded that tar-
trazine does not induce asthma and that the early reports were simply the
exacerbations of asthma in patients with unstable airways who had been
deprived of their bronchodilators.

With regard to urticaria, a very small number of tartazine-sensitive indi-
viduals have been identified in double-blind, placebo-controlled trials.6,157
As was the case with the studies on the role of tartrazine in asthma, most of
the clinical studies of tartrazine on urticarial patients are complicated by
the failure to blind the challenge, a lack of placebo controls, and/or the
withholding of antihistamines. The withholding of antihistamines is an
especially significant clinical design element because such drugs are essen-
tial for the control of symptoms in patients with chronic urticaria.6,157
Tartrazine is, at worst, a cause of urticaria in only a few of the many individuals with this symptom.\textsuperscript{1,6,157}

**Other Food Additives in Chronic Urticaria and Asthma**

Chronic urticaria is a disease with few known causes. Most chronic urticaria patients must take antihistamines on a daily basis to control the urticarial lesions. The clinical study of causative factors in chronic urticaria is complicated by the chronic and episodic nature of the illness. Since the hives appear on an episodic basis, careful placebo control of clinical studies is essential to document that any lesions are the result of the challenge material and not occurring on the basis of chance. As noted above in the discussion on tartrazine, the withdrawal of antihistamines can really complicate the interpretation of these clinical challenge studies. When a chronic medication such as the antihistamines are removed before challenge, any urticarial lesions could be the result of the challenge material or breakthrough urticaria from the withdrawal of the medication. However, if the patient is maintained on the antihistamines, it can be argued that a much higher dose of the challenge material would be needed to elicit urticarial lesions because the challenge material would have to overwhelm the antihistamine in the system. Few clinical trials conducted on food additives have succeeded in controlling these important design elements. Thus, the results of these trials can be questioned.\textsuperscript{6}

In the search for causative agents in chronic urticaria, considerable attention has been focused on food additives: tartrazine, sunset yellow (FD&C Yellow #6), sodium benzoate, benzoic acid, and the parabens, and BHA, and BHT. Numerous clinicians have concluded that these additives play a causative role in chronic urticaria,\textsuperscript{6} but as noted above, the study designs have been flawed in most cases.

Asthma is also a chronic, episodic illness. Asthmatic individuals must take medications on a daily basis to control the illness and maintain good respiratory function. Several ingested substances, such as aspirin and many of the common allergic foods, are well documented to provoke asthmatic reactions in certain individuals within the overall asthmatic population. However, the role of food additives in asthma is far less clear. As noted above for tartrazine and MSG, many of the studies that have been conducted on food additives and their role in asthma did not employ proper placebo controls, were not done in double-blind fashion, and/or did not allow the patients to maintain critical medications. Because asthma is a chronic condition, withdrawal of medication could easily lead to false-positive results. Although asthma also has been linked to certain other food additives beyond tartrazine and MSG, the relationship of these additives to exacerbation of asthma is not well proved.\textsuperscript{6}

The evidence implicating various food additives in chronic urticaria and asthma is suspect. Changes in the use and regulation of any of these food additives on the basis of this type of evidence are unwarranted.\textsuperscript{1}
Summary

Food allergies and intolerances are adverse reactions that plague a large number of people. Although the symptoms of these allergies and intolerances are manifested in only a small segment of the total population, the public can view such illnesses as a major health concern. The public and even some healthcare professionals fail to distinguish between the different types of illnesses that fall within this general category. Food allergies and intolerances are an increasingly important concern to consumers and food manufacturers alike. Allergic individuals must alter their lifestyles on a continuing basis to avoid the offending food, and the food industry must continue to be alert to the needs of these consumers by providing accurate and complete labeling. Manufacturers also must be aware that cross-contact between allergenic foods and other foods within the manufacturing environment may cause residues of the allergenic food to be present in the other food but not declared on the ingredient statement. Cross-contact, improper use of rework, and accidental mislabeling can result in serious, life-threatening allergic reactions among sensitive consumers.

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