

Allergic Reactions to Foods

27431

John A. Anderson

Division of Allergy and Clinical Immunology, Departments of Pediatrics and Medicine, Henry Ford Health System, Detroit, Michigan

I. INTRODUCTION

The term *food allergy* is often overused by the public, as well as by some physicians and scientists, to describe any undesired or bothersome problem related to diet. To discuss allergic reactions to foods, it is important to establish a set of definitions to describe these types of reactions. Table 1 provides such a glossary of terms¹ that has evolved over the years from an earlier classification.¹ In this set of definitions, *food intolerance* is used to describe nontoxic, nonimmune-mediated reactions and *food allergy* relates to immunologic reactions (usually immunoglobulin E [IgE mediated]).

II. PREVALENCE OF ADVERSE FOOD REACTIONS

Although the best estimates suggest that less than 1 to 2% of the general population suffer from food allergies, the prevalence of adverse reactions to foods is unknown.^{2,3} The public's perception of the importance of allergic reactions to food ingredients, however, substantially exceeds the prevalence of such reactions identified in limited clinical studies. In some surveys, one in four atopic adults believed they had experienced an adverse reaction following ingestion of a specific food.⁴ The prevalence of adverse reactions to food confirmed by a double-blind, placebo-controlled food challenge (DBPCFC) during the first 3 years of life among 480 consecutively born infants in Denver, Colorado, was 8%.⁵ Of these children, 25 (5.2%) were suspected to be milk allergic, but only 11 (2.3%) could be confirmed to be so by

DBPCFC. In a prospective study among a cohort of 1749 newborns born in a single hospital from a municipality in Denmark during the calendar year 1985, 39 (2.2%) were found to have systemic adverse reactions after cow's milk protein challenge.⁶

The prevalence of food additive reactions in children is also unknown and a subject of debate. For example, a recent prevalence study among 4274 Danish school children age 5 to 16 years has been reported.⁷ Following selection through a screening questionnaire and open challenges with mixes of food preservatives, dyes (colors), and flavors, 12 of 17 positive responders were challenged using the DBPCFC method and 6 (50%) were positive. Five of the six reacted to the coloring agent and one reacted to citric acid. (One had urticaria and five had exacerbation of atopic dermatitis [AD].) Based on this study, it was estimated that the incidence of adverse reactions to food additives among Danish children is 1 to 2%, although 6/4274 is 0.14%.⁷

The most common respiratory allergic manifestation in adults is allergic rhinitis due to pollens from trees, grasses, weeds, and, in North America, from ragweed. Although such respiratory symptoms are not commonly involved in food allergies, some individuals with pollen allergies experience mild adverse reactions confined to the oropharyngeal area after ingestion of certain fresh fruits and vegetables. In this oral allergy syndrome, localized itching and swelling of the oropharyngeal area occurs when exposed to such fresh fruits or vegetables.⁸⁻¹⁰ In a series of 1447 ragweed hay fever patients, 6.2% were found to have local allergy symptoms to melons and bananas.^{11,12} Of 274 patients allergic to one or more

TABLE 1
Adverse Reactions to Food: Classification

I. Toxic reactions

These occur in any exposed individual if the dose is high enough. Toxic compounds may be naturally occurring or are induced during food processing or by contaminants. Symptoms of some toxic reactions may resemble those caused by allergy.

II. Nontoxic reactions

A. Immune-mediated

The term *food allergy* is recommended for immune-mediated reactions. Allergens are defined as the antigenic molecules giving rise to the immune response.

1. IgE-mediated

Symptoms include anaphylaxis and symptoms from the skin, respiratory, and GI tracts. None of these symptoms are specific.

2. Non-IgE-mediated

Diseases include protein-induced gastroenteropathy and celiac disease. The precise role of food in immune mechanisms involved in such disorders is not known.

B. Non-immune mediated

The term *food intolerance* is recommended for nonimmune-mediated reactions.

1. Enzymatic

Secondary lactase deficiency affects most of the world population, whereas most other enzyme deficiencies are rare inborn errors in metabolism.

2. Pharmacologic

This form of intolerance is present in individuals who are abnormally reactive to substances such as vasoactive amines normally present in some foods.

3. Undefined

This includes adverse reactions to food for which the offending mechanisms are unknown, including some additive intolerances.

Adapted from Bruijnzeel-Koomen et al.¹²⁵

of three pollens (birch, grass, and/or mugwort), 111 (47%) had clinical symptoms or IgE antibodies to apples, potatoes, carrots, celery, peaches, or melons.⁸

Finally, an estimate of the prevalence of anaphylaxis and other systemic reactions to food and food additives (especially sulfites) was obtained through a prospective survey of 73 Colorado emergency departments over a 2-year period.¹³ Twenty-five individuals ranging in age from 2 to 71 years (2/3 over 18 years) had a serious reaction. Two required cardiopulmonary resuscitation and one patient died. Based on the prevalence of food-associated reactions in comparison to overall emergency room admissions for life-threatening reactions, it is estimated that approximately 950 severe reactions to food and food additives requiring emergency intervention occur annually in the U.S., or 0.0004% for a population of 250

million. These observations in total present a variety of perspectives on the prevalence of adverse reactions to foods.

III. NATURAL HISTORY OF FOOD ALLERGY

Studies of the prevalence of food allergy have shown that the clinical manifestations of food reactions are most commonly observed in the first 3 years of life. In prospective studies, in 80 to 87% of situations, a child once proven reactive to a food can be shown to clinically tolerate that food by 3 years of age.⁵ Clinical tolerance develops with soy, wheat, cow's milk, and egg allergy. The more serious the initial clinical reaction to food, however, the longer it takes the child to develop tolerance.¹⁴ It has also been shown in

older children and adults that if the offending food can be identified and totally eliminated from the diet for a given period of time, clinical tolerance to that food develops in some patients.^{15,16}

In patients who develop anaphylaxis to foods such as peanuts, tree nuts, fish, and crustacea such as shrimp, prawns, crab, lobster, and crayfish, the exact duration of the risk of repeat anaphylaxis upon further exposure is unknown, but may be lifelong.⁴ In a group of peanut allergic individuals, the risk of repeat reactions to peanut lasts for at least 14 years.¹⁷

IV. EXPOSURE TO FOOD ALLERGENS

Most food exposure is initially through the gastrointestinal (GI) tract. The GI tract provides a barrier of immunologic and nonimmunologic defense mechanisms where unwanted, intact proteins are prevented from gaining ready access to the body.⁴ Some intact food proteins do gain access. However, oral tolerance develops to most food proteins. The increased susceptibility of infants to food allergy is believed to result to some extent from the relative immunologic immaturity of the GI barrier at a young age. As a result, in familiarly predisposed infants, ingested and absorbed food protein may stimulate specific IgE antibody formation as well as other abnormal immune responses. Reexposure to these food proteins may result in clinical reactions (for pathophysiology, see "Introduction to Allergic Diseases" by Yoseph A. Mekori). Subsequent contact of the mucous membrane in the mouth or inflamed skin with food antigen may also be enough to bring on a reaction.⁹ An example of the latter was an infant allergic to milk whose inflamed skin was exposed to a cow's milk protein that was an ingredient in a diaper rash ointment containing 5% calcium caseinate causing anaphylaxis.¹⁸

The major identified allergens responsible for IgE-mediated reactions to foods are detailed in "Allergenic Foods" by Susan L. Hefle et al. and "Principles and Characteristics of Food Allergens" by Steve L. Taylor and Samuel B. Lehrer in this issue. These food allergens are usually heat stable and resistant to proteolysis. Clinically, many patients react to only one or a few items from one food family. Peanut allergic individuals usually

can be found to possess IgE antibody reactivity to other legumes (peas, beans, soy), yet can regularly ingest these foods without clinical reactions.¹⁹ The major fish allergen is *Gad c 1*.⁴ Although this allergen is found in a diversity of freshwater and seawater fish, some individuals only react clinically when challenged with specific fish types.²⁰

In occupationally acquired food allergy in adults, the initial contact with food protein may be through inhalation or skin contact.²¹ Probably the best known example is baker's asthma. Some bakers developed asthma and rhinitis after inhaling or being in skin contact with flour.²² Most bakers, however, ingest bread without a reaction. Other workers, though, after being first sensitized through the respiratory or skin contact route, later become reactive when the same processed or cooked food is ingested. Such is the case with snow crab processors with crab;²³ bakery workers with egg;²⁴ and garlic spice processors with garlic.²⁵ IgE reactions may also occur through exposure to the aerosolized fish or seafood protein.²³ Aerosolization of food proteins during cooking may therefore pose a risk to certain highly food allergic individuals.

V. CLINICAL MANIFESTATION OF FOOD ALLERGY

There are a variety of clinical manifestations of food allergy (Table 2) and these are reviewed in this section.

TABLE 2
Clinical Manifestations of Food Allergy

- I. Anaphylaxis
- II. Oral allergy syndrome
- III. Food-dependent, exercise-induced anaphylaxis (F-EIA)
- IV. Atopic dermatitis (AD)
- V. GI reactions
 - A. IgE-mediated immediate reaction
 - B. Food protein-induced enterocolitic syndromes
 - C. Eosinophilic gastroenteritis
 - D. Celiac disease (gluten-sensitivity enteropathy)
- VI. Respiratory reactions
 - A. Rhinitis
 - B. Asthma
- VII. Occupationally acquired food allergy
 - A. Urticaria/angioedema/anaphylaxis
 - B. Asthma
 - C. Hypersensitivity pneumonitis

A. Anaphylaxis

Anaphylaxis is a systemic reaction characterized by urticaria, angioedema, laryngeal edema, bronchospasm, hypotension, diarrhea, cardiac arrhythmias, nausea, vomiting, abdominal cramping, and even death. The initial symptoms of anaphylaxis usually begin within a few minutes and almost always within 30 min after exposure.²⁶ Three clinical patterns of anaphylaxis have been described regardless of the initiating allergen: uniphasic, biphasic, and protracted.²⁷ In uniphasic reactions, symptoms appear shortly after food ingestion and last for several hours. In the biphasic reactions, an early and a late phase are separated by an interval of 1 to 8 h. In protracted anaphylactic reactions, symptoms persist for 5 to 32 h without remission.

Most individuals who experience life-threatening food-induced anaphylaxis have multiple clinical manifestations of allergy including asthma, and have demonstrable IgE antibodies to specific incriminated allergens.^{28,29} Foods incriminated in life-threatening reactions include, but are not limited to, peanuts, crustacea (crab, shrimp, lobster, and crayfish), tree nuts, milk, and egg. A more complete list of foods eliciting life-threatening reactions is found in "Allergenic Foods."^{28,29} Most deaths occur in proven allergic individuals who inadvertently eat these foods away from home (e.g., restaurant or party) and in a disguised form (e.g., pastry, candy, salad, sandwich, or hors d'oeuvre).

The principal difference between death and near death in a group of known allergic children and adolescents who were exposed to a food to which they were sensitive was how rapidly epinephrine was given. Most children survive when epinephrine is given within 1 h.²⁹

B. Oral Allergy Syndrome (OAS) (Fruit and Vegetable Syndrome)

In individuals allergic to trees (particularly birch), grasses and weeds (particularly mugwort), and ragweed pollens, symptoms may develop after contact exposure in the mouth with allergens in fresh fruits and vegetables.⁸⁻¹¹ The initial symptoms of OAS usually include a tingling oral sen-

sation while eating the fresh fruit or vegetable, followed by itching of the lips, tongue, or buccal mucosa.⁹ Swelling of the mouth parts occurs in about one half of the cases. Although most symptoms are localized to the mouth, in some cases the localized symptoms are also associated with systemic symptoms, particularly a stuffy or runny nose or conjunctivitis as well as, in a few cases, systemic anaphylaxis.¹⁰

In the majority of cases, the symptoms begin within 5 min of food contact.³⁰ Usually the localized symptoms abate within 30 min. Almost all symptoms disappear without therapy 90 min after discontinuation of eating the specific offending food, and after rinsing the mouth with water.

The foods associated with OAS include melons and bananas among ragweed allergic individuals; apples, pears, potatoes, hazelnuts, carrots, celery, and kiwi among birch pollen-sensitive patients; peach, tomatoes, and celery among grass allergic individuals; and celery in mugwort-sensitive individuals.^{9,10,30}

Some individuals with documented latex allergy are also allergic to bananas, chestnuts, avocado, and kiwi.³¹⁻³³ Information points to the existence of cross-reactivity between the natural rubber latex allergens and both ragweed and blue grass pollens.³⁴

C. Food-Dependent Exercise-Induced Anaphylaxis (F-EIA)

Exercise-induced anaphylaxis (EIA) is a form of physical allergy involving urticaria, angioedema, or shock after vigorous exercise. Almost any exercise may be involved, but jogging is the most frequent cause in the U.S.³⁵ This syndrome must be differentiated from exercise-induced asthma and from cholinergic urticaria induced by exercise. Although the exact pathophysiology of EIA is unknown, induced histamine release is one factor. An epidemiologic survey of 199 individuals with EIA showed that the process of eating and/or the ingestion of a specific food was an additional factor in the development of EIA in 54% of the cases.³⁵

Foods associated with F-EIA include celery, shrimp, oyster, chicken, peach, and wheat. Some evidence exists for a late-onset F-EIA reaction,

presumably due to reactions to digestive breakdown products of wheat allergens.³⁶ Finally, in some individuals with F-EIA, the ingestion of any type of a meal, may precipitate symptoms within several hours of vigorous exercise.

D. Atopic Dermatitis (AD)

AD is a primary skin condition of childhood whose pathogenesis involves both immune and nonimmune factors. In a large series involving DBPCFC, approximately one-third of children with AD had food-related hypersensitivity.³⁷ In these cases, the eczema associated with AD may be at least partially explained by an IgE-mediated late-phase allergic food reaction. Studies using DBPCFC in AD children have shown that children are usually allergic to only one or a few foods such as eggs, cow's milk, peanuts, wheat, or soy. Data from *in vitro* studies have shown that basophils from patients with active AD will spontaneously release histamine when such patients routinely ingest the specific food to which they are sensitized.³⁸ Mediator release under these circumstances may be modulated by local, IgE-dependent, histamine-releasing factors. After eliminating the incriminated food from the AD patient's diet, the tendency for spontaneous *in vitro* basophil histamine release disappears with concomitant improvement in the skin condition.³⁸

Children with AD and food allergy have been studied to assess the value of DBPCFC compared to skin testing (ST) and *in vitro* tests for food-specific IgE antibodies. For instance, the result of challenge testing correlated poorly with the mother's history of which food may be involved with the rash exacerbation.^{37,39} Allergy ST and, to a lesser degree, *in vitro* testing to specific food allergens suggested which foods might be involved when subsequent DBPCFC testing was used for a final diagnosis.³⁹

E. Gastrointestinal Reactions

GI signs and symptoms are the most common clinical manifestation of food allergy. These include itching and swelling of the mouth parts, nausea, vomiting, diarrhea, malabsorption, and

blood and protein loss in the stool (in children).⁴⁰ These reactions may be immediate, IgE-mediated reactions, or delayed reactions such as observed in food-induced enterocolitis. In allergic children, symptoms may begin in infancy and be associated with either intolerance or allergy to cow's milk protein found in conventional baby formula.⁶

1. Food-Induced Enterocolitis

Several terms have been used to distinguish the GI food reaction in children, such as food-induced enterocolitis, protein intolerance, or milk-sensitive enteropathy. Both the small and large intestine may be involved. The small intestine may be damaged to varying degrees to include thinning of the mucosa, villous atrophy, crypt hyperplasia, and inflammatory infiltrates of lymphocytes, plasma cells, and eosinophils.⁴⁰ Prolonged diarrhea in some cases can lead to dehydration, malabsorption, and failure to thrive.

Milk-induced colitis is related to enterocolitic syndromes and may closely resemble ulcerative colitis. Biopsy is used to make the diagnosis and demonstrate eosinophilic inflammatory infiltrates in the bowel wall.⁴ A friable mucous membrane may lead to either occult or gross blood loss.

In these syndromes, GI symptoms may occur late (after hours to days). They often can be proven to be related to cow's milk in the diet through challenge. However, these reactions cannot be categorically proven to be due to IgE-mediated reactions (allergy).⁴¹ Such reactions may also occur to fish, soy, rice, and chicken.

2. Eosinophilic Gastroenteritis

Eosinophilic gastroenteritis affects both children and adults. This disorder is characterized by eosinophilic infiltrates of the bowel wall, peripheral blood eosinophilia, and GI symptoms.^{4,40,42} The degree of clinical symptoms depends on the extent of disease involvement. Patients develop cramping abdominal pain, nausea and vomiting, diarrhea, and fecal blood loss. Disease may lead to either growth retardation (children) or weight loss (adults).

About one half of the 150 case reports of eosinophilic gastroenteritis have been in highly allergic individuals. In children, milk is a major allergen involved in this condition.³⁰ In adults with this condition, multiple food allergies are consistently demonstrated. Patients with the allergic form of eosinophilic gastroenteritis have high total IgE levels and have additional clinical manifestations of allergy including asthma and rhinitis. The disease is managed with diet and steroids.

F. Respiratory Reactions

Food allergy is not a major cause of either upper respiratory (rhinitis) or lower respiratory (asthma) symptoms.⁴³ However, during a systemic anaphylactic reaction to foods, it is common for individuals to have hay fever or asthma-like symptoms.²⁶ Most individuals who have had serious, life-threatening anaphylaxis to foods are highly allergic to many substances, and have both rhinitis and asthma.^{28,29} Some of the more convincing evidence that food can cause rhinitis and asthma include reports that approximately one-third of children who manifest their allergy primarily with AD develop upper or lower respiratory symptoms during DBPCFC to foods to which they are sensitive.³⁷

A syndrome has been described in infants characterized by cow's milk protein-induced recurrent pulmonary infiltrates associated with precipitins to cow's milk protein.⁴⁴ Some of these infants had pulmonary hemosiderosis with deposition of iron in the lung. This childhood syndrome is now rarely reported and there is no similar condition reported in adults. The pathogenesis is suspected to involve aspiration of milk-based formula in the first few days of birth, sequestration of these proteins in the lung, followed by a hyperimmune response with the production of large amounts of milk-specific IgG antibodies. Subsequent feeding of milk results in immune complex as well as cell-mediated tissue reactions.⁴⁵ Infiltrates resolve with milk elimination.

VI. GLUTEN-SENSITIVE ENTEROPATHY

Celiac disease or gluten-sensitive enteropathy is a permanent condition of wheat or gluten

intolerance in children and adults.⁴⁶ This disease is more prevalent in the U.K. and Europe than in the U.S. Diagnosis depends on the results of a jejunal biopsy that demonstrates abnormal, short (flattened), or absent villi, crypt hyperplasia, and cellular inflammatory infiltrates of lymphocytes and plasma cells in the lamina propria. These bowel wall changes disappear after the patient is placed on a gluten-free diet, only to reappear after reinstitution of gluten. Clinically, the classic textbook description of an irritable "pot-bellied" growth-retarded child with chronic diarrhea, anemia, rickets, and muscle wasting is now rarely seen. Typically, the disease is less severe and single manifestations, such as growth retardation or anemia in a child or chronic weight loss and persistent diarrhea in an adult, will require investigation and intervention.

Although the pathogenesis of this condition is still being debated, and a toxic reaction to gluten is still possible, evidence points to a cell-mediated immune sensitivity to gluten as a principal pathologic event.⁴⁶ Some patients with celiac disease have dermatitis herpetiformis (DH), an associated skin condition. Most patients with DH have small bowel intestinal biopsies that are indistinguishable from those of celiac disease. Most DH patients respond to a gluten-free diet. Patients with celiac disease have a 50 to 100 times increased risk of developing a malignant lymphoma compared to the general population.

VII. OCCUPATIONALLY ACQUIRED FOOD ALLERGY

Reactions to food allergens in adults also occur in occupational settings (Table 3). Occupational exposure results in susceptible individuals developing IgE sensitization to food proteins, often through the respiratory or dermal route.^{21,23,47} Continued exposure to these allergens results in rhinitis, bronchial asthma, conjunctivitis, contact and generalized urticaria, and in some instances, systemic anaphylaxis.²¹

The most important manifestation of occupationally acquired food allergy is occupational asthma. Approximately 2 to 15% of all adult-acquired asthma results from occupational exposure to chemicals, toxins, and natural proteins.

TABLE 3
Materials Used in Food or Related Industries That Are Known to Induce Occupational Asthma or Rhinitis

Agents	Occupational exposure	Agents	Occupational exposure
Animal products		Plant/Fungi	
<i>Sea animals</i>		<i>Grains/Flours</i>	
Prawn	Seafood processing	Flour (wheat, rye)	Bakers, millers
Crab (including king and snow)	Seafood processing	Buckwheat	Food workers
Oyster	Culture oyster workers	Rice	Rice millers
Shrimpmeal	Aquaculture	Soybeans	Agricultural workers
Fishmeal	Factory workers	Grain dust	Grain handlers
Mother of Pearl	Button factory workers		
Seasquirt	Oyster shuckers	<i>Spices/Herbs</i>	
Seashells	Shell grinders	Garlic	Factory workers, farmers
<i>Farm Products</i>		Coriander, mace, ginger, paprika	Factory workers
Cows	Dairy farmers	Cinnamon	Spice workers
Hogs	Hog farmers	Paprika plants	Greenhouse workers
Poultry	Poultry workers		
Pheasants, quail, doves	Breeders	<i>Enzymes</i>	
Eggs	Egg processors, bakery workers	Bromelin	Factory workers
		Papain	Factory workers
<i>Insects</i>			
Poultry mites	Poultry workers	<i>Miscellaneous</i>	
(<i>Ornithonyssus sylvianum</i>)		Coffee	Coffee factory workers
Grain storage mites	Grain workers	Tea	Tea factory workers, tea garden workers
(<i>Glyciphagus destructor</i>)		Herbal tea	Herbal tea workers
Honey bees	Beekeepers, honey processors	Pollen	Sugarbeet, sunflower, grape workers
Bee-moth	Fish bait breeders	Alkaline hydrolysis derivative of gluten	Bakers
		<i>Alternaria/Aspergillus</i>	
<i>Enzymes</i>		Colophony	Poultry vendors
Pepsin	Pharmaceutical workers	Hops	Poultry vendors
Trypsin	Pharmaceutical workers	Devil's Tongue (<i>Amorphophallus konjac</i>)	Brewery chemists
Pancreatic enzymes	Pharmaceutical workers	Mushrooms	Food workers
		Fungal amylase	Soup manufacturers, growers
<i>Miscellaneous</i>		<i>Verticillium albo-atrum</i>	Bakers
Spiramycin	Chick breeders		Greenhouse workers
Pyrolysis products of polyvinyl chloride or label adhesives	Meat wrappers		

Modified from O'Neil and Lehrer.⁴⁷

For example, the prevalence of occupational asthma ranges from 10 to 30% in bakers,⁴⁸ 15% in snow crab workers,²³ and 3% among workers exposed to green coffee beans.⁴⁹

Occupational asthma may be the result of irritation, pharmacologic, or IgE (allergic) mechanisms. Some of the clearest examples of IgE-mediated occupational food allergy are baker's asthma due to flour exposure,⁴⁸ snow crab processors exposed to water vapor from cooking snow crab,²³ spice workers exposed to garlic dust,²⁵ and bakery workers exposed to aerosolized egg protein.²⁴

In baker's asthma, wheat and rye flour are the usual etiologic agents. Sensitization occurs through the respiratory route and correlates with a personal or family history of atopy, duration of exposure, and wheat and rye dust levels in the area of employment. Among apprentice bakers, the prevalence of positive immediate skin test reactions to wheat has increased from 8 to 30% over a 5-year period of exposure.⁴⁸ Bakers with asthma can usually eat the bread they bake. Snow crab processors and spice workers who become sensitized through the respiratory route, however, may eventually react when they ingest cooked crab or garlic in a meal.^{23,25}

Hypersensitivity pneumonitis is another manifestation of occupational reactions to foods. In this condition, an intense, prolonged respiratory exposure to a number of different proteins from molds or fungus, insects, or foods (animal, fish, or avian sources) leads to a hyperimmune response and large amounts of IgG antibody. Reexposure on a continued basis to these causative proteins leads to an immune complex reaction characterized by diffuse mononuclear infiltrates in the lung that involve the interstitium and the alveoli.⁴⁷

VIII. FOOD INTOLERANCE

Many adverse reactions to foods are mediated by mechanisms that do not involve the immune system. Some of these reactions may be confused with allergy. These reactions may be due to naturally occurring toxicants, microbial or chemical food contaminants, metabolic disorders, and idiosyncratic reactions.⁵⁰

Scromboid fish poisoning is an example of a reaction occurring to a microbial-derived food contaminant. In this case, Scromboid fish (such as tuna, mackerel, and bonito) or other fish (such as mahi mahi or blue fish) have become spoiled but are cooked and eaten. Bacteria in the fish tissue, such as *Morganella morganii* or *Klebsiella pneumoniae*, can have decarboxylated histadine to create histamine. The individual who ingests such fish experiences a sharp peppery taste, and a burning sensation in the mouth, followed often by nausea, vomiting, abdominal cramps and diarrhea, as well as facial flushing and headache due to ingested histamine. Individuals may also develop urticaria, wheezing, or shock. Symptoms generally begin within 30 to 60 min of ingestion of the spoiled fish and last for 2 to 8 h.⁵¹

Other foods that contain histamine include cheese and some red wines.⁵¹ Oriental food may contain histamine, particularly if its preparation involves fermentation.⁵²

Endogenous pharmacologic agents in food that may mimic some symptoms of food allergy include tyramine, phenylethylamine, serotonin, caffeine, and theobromine.⁵² These natural substances are aggravating factors in headaches, especially in patients with migraines, but frequently these reports are not well documented.

Commonly eaten foods may contain naturally occurring toxicants, but fortunately the dose consumed in most cases is so low that adverse reactions are few in number.⁵¹ One example of an unsafe food, mistaken for a safe food, is the *Amanita* mushroom. When "poisoning" or toxic reactions do occur, however, rarely are allergic-like symptoms involved, except for the GI symptoms of nausea, vomiting, and diarrhea. A similar situation exists for foods contaminated with microbial toxins or bacterial or other infectious agents. These types of adverse reactions should be kept in mind when considering the possibility of an adverse reaction following a meal.^{50,51,53}

A metabolic reaction after ingestion of a specific food is due to differences in individuals in the ability to digest a specific substance, or may be associated with concomitant medication, disease states, or malnutrition. For example, vasoactive amines are metabolized by a family of isoenzymes called monoamine oxidases (MAO). In patients treated with MAO inhibitors for depres-

tion. ingestion of foods rich in tyramine (e.g., cheese) can cause a rapid rise in blood pressure and severe headaches. This reaction is caused by either the uninhibited action of tyramine or the indirect action of the secretion of epinephrine or norepinephrine, following the lack of the metabolism of the pharmacologic agents by the adrenal MAO.⁵¹ A similar reaction has occurred in patients taking the antituberculosis drug, isoniazid, while ingesting tuna. Reactions have occurred because isoniazid inhibits histaminases that normally degrade histamine present in the fish meat.^{53,54}

Probably the most common problem induced by diet that is confused with an allergic reaction is lactose intolerance due to lactase deficiency in the GI tract.⁵⁶ Lactose is a water-soluble disaccharide found in dairy foods. Prior to absorption lactase enzymes in the intestinal brush border break down lactose to its monosaccharide components. When this enzyme is deficient or totally absent, the undigested lactose ferments in the bowel with resulting symptoms of gas and bloating, abdominal cramps, flatulence, and loose stools.

Congenital lack of lactase is rare. Primary lactase deficiency is usually manifested after the infant weaning period, but before puberty.⁵⁰ A GI infection in infancy or childhood may hasten the onset of this condition. Once lactase deficiency has been established, ingestion of a moderate amount of lactose sugar (5 to 12 g in the amount of 100 to 240 ml of whole cow's milk) may result in symptoms in susceptible individuals.⁵⁰ Secondary (acquired) lactose intolerance due to lactase deficiency may occur in a variety of clinical conditions including alcoholism, sprue, and cow's milk allergy. It may also occur transiently after a rotavirus or other GI infection.⁵⁶ Naturally fermented foods may sometimes be tolerated by lactase-deficient individuals.⁵⁷

IX. ADVERSE REACTIONS TO FOOD ADDITIVES

Additives are often added to processed foods.⁵⁸ These agents are added to help preserve the food, stabilize the ingredients, or increase the appeal of the food through flavor or color. Food additives

that have sometimes been associated with allergic-like reactions include the antioxidants, butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT), aspartame, dyes, monosodium glutamate (MSG), and sodium benzoate. Because of their association with such reactions, some food additives (e.g., sulfites, Yellow no.5) must be affirmatively declared on food labels. Adverse reactions that are allergic-like may generally be either grouped as (1) urticaria, angioedema and generalized anaphylaxis or (2) asthma.^{57,58}

A. Cutaneous/Anaphylactic Responses

Sporadic reports have linked urticaria with tartrazine (Yellow no. 5). The majority of these studies were not well controlled. Using the strict criteria of DBPCFC, only occasionally has an individual been proven to develop urticaria after the ingestion of tartrazine.⁵⁹ There is also a single report of two individuals who developed urticaria to sunset yellow (Yellow no. 6) when challenged using the DBPCFC technique.⁶⁰ Other food colors that have been implicated in anecdotal reports of urticaria are amaranth, erythrocine, and ponceau (Reds no. 2, 3, and 40, respectively) and brilliant blue and indigotin (Blue no. 1 and 2, respectively).⁵⁷

There are at least two documented reports of sulfite-induced allergic reactions.⁵⁸ Each patient developed positive immediate reacting IgE skin tests to sulfites, and passive transfer of IgE sulfite antibodies was possible.^{61,62}

Reports of urticaria to BHA or BHT preservatives are rare. However, two patients who had chronic urticaria and who improved after eliminating these preservatives from their diet were challenge positive to these chemical agents using the DBPCFC technique.⁶³ There appears to be no proven case of urticaria involving sodium benzoate reported in the U.S.⁵⁸

Reported cutaneous adverse reactions to MSG include sweating, facial flushing, tightness and burning of the face and chest, and a sensation of "crawling skin."⁵⁷ The relationship of these symptoms to MSG consumption has been the subject of much research and debate. Oriental food meals may sometimes contain several grams of MSG.

Some of the symptoms in this syndrome may be due to the high histamine content of some foods served in a Chinese restaurant.⁵² There have been no proven (DBPCFC) cases of reproducible urticaria with MSG challenge.

Two cases of aspartame-induced urticaria/angioedema were reported to have been confirmed by DBPCFC.⁶⁴ Despite these two cases, when the allergic-like aspartame reactions were studied in the U.S. and Canada, the investigators were unable to substantiate any clear relationship between urticaria and angioedema and aspartame exposure using DBPCFC.⁶⁵ Furthermore, from the results of a combined single-blind, double-blind placebo-controlled study, other investigators reported that individuals who thought they were allergic to aspartame did not have reproducible reactions.⁶⁶

B. Asthma

The principal agents associated with non-IgE-mediated asthmatic reaction are the sulfite preservatives (e.g., sodium metabisulfite [$\text{Na}_2\text{S}_2\text{O}_5$] and related compounds, plus sulfur dioxide (SO_2). Common offending foods include sulfite-treated salads, avocado dishes, vinegars, sausages, dehydrated vegetables, fruit juices, cider, beer, and wine.⁵⁰

Asthmatics may wheeze when exposed to less than 1.0 ppm of SO_2 .⁵⁸ In line with this observation, there have been a series of reports of asthmatics, particularly in the early 1980s, who wheezed when eating restaurant foods, particularly from the salad bars, which had been treated with sulfiting agents.⁶⁷

The principle behind the acute asthma exacerbation with sulfites is often the inhalation of SO_2 gas, which is released when the foods containing sulfite preservatives are chewed and/or swallowed.⁶⁸ In addition, in select individuals a sulfite oxidase enzyme deficiency of uncertain significance has been reported. In others, a rare IgE-mediated response to sulfites may be important.⁵⁸ Approximately 3.9% of asthmatics are at risk for an acute attack with sulfites or SO_2 .⁶⁹ Of these, the risk is approximately 8.4% in serious or steroid-dependent asthmatics and 0.8% in mild to moderate asthmatics. Since U.S. federal guide-

lines were altered to require more labeling of sulfites on food packages and bar the use of sulfites on fresh fruits and vegetables other than potatoes, and since the food industry has adopted alternatives of sulfites for some applications, there have been fewer reports of sulfite-induced asthma.

A few patients have had an acute asthma attack after the ingestion of foods containing MSG in restaurants, similar to sulfite-induced asthma.⁷⁰ However, in DBPCFC studies, other investigators have been unable to substantiate claims that MSG in oral challenge up to 7.5 g causes significant asthma or alters bronchial reactivity to methacholine.^{71,72} Another food additive that has been implicated in the past as provoking asthma is tartrazine (Yellow no. 5).⁵⁸ Numerous reports have claimed to link tartrazine ingestion with asthma exacerbation. However, especially in the aspirin-sensitive asthmatic, more recent, well-done DBPCFC studies have failed to confirm this association.^{59,73}

X. OTHER CLINICAL REACTIONS INFLUENCED BY DIETARY FACTORS

A. Infantile Colic

There are a number of conditions in which claims have been made that food allergy plays a role when, in fact, there is little or no scientific confirmation. In each of these situations, diet may play an as yet undefined role. Such is the case in infant colic. Frequently, this syndrome is mentioned when discussing milk allergy or intolerance.⁴⁰ Approximately 20% of all infants develop colic. This condition is self-limited and occurs regardless of the type of diet fed to the infant or the breast-feeding mother.⁷⁴ In controlled studies, nondietary intervention such as increased motion or increased attention to the infant may be more helpful in controlling the colicky pain than any dietary manipulation.⁷⁵

In one controlled study of infants who developed colic while on conventional cow's milk-based formula, approximately 25% improved spontaneously during the study period while on the same diet, 25% improved on a soy-based infant formula, and 50% improved on a casein hydrolysate infant formula.⁷⁶ There has been no

explanation for these dietary differences affecting the course of infant colic, but food allergy as a cause has been implicated in some cases.

B. Behavioral Changes

Food allergy or another type of adverse reaction to dietary components has been commonly cited as being related to behavioral problems such as hyperactivity, aggressiveness, misbehavior, or poor learning attributes.⁷⁷ Probably the most widely known theory linking behavior to adverse food reactions was that of Feingold⁷⁸ in the mid-1960s who proposed that food additives, especially colors, flavors, and preservatives, as well as natural salicylates, could cause hyperkinesis in children with attention deficit disorder (ADD).⁷⁸

Although there was some initial enthusiasm about the use of the Feingold or the Kaiser Permanente (KP) diet, which is a diet devoid of colors, natural salicylates, and preservatives, subsequent analysis based on color challenge studies concluded that the KP diet is likely to help only in approximately 2% of children with hyperactive behavior.⁷⁹ One study found that children with ADD with hyperactivity, but not normal children who had active behavior, would perform progressively worse on a special laboratory learning test only when challenged with a color mixture, not with a placebo.⁸⁰ This study led to the conclusion that colors could act as pharmacologic agents, such as drugs, and affect behavior/learning. This problem was thought to be clinically important only in a small, select number of individuals with ADD with hyperkinesis. Although these studies seemed to stifle the enthusiasm surrounding the use of diets to help children with ADD, a Canadian report in 1989 fueled the flames of controversy again.⁷⁷ The behavior of 12 of 24 preschool hyperactive boys improved on a diet devoid of artificial colors, MSG, preservatives, caffeine, chocolate, and "any food" to which the family believed the child was allergic.⁸¹ Still, the consensus today is that if hyperkinesis is affected by a diet, there is no evidence that the effect is immunologic or allergic in nature.⁷⁷

Hyperactive and aggressive behavior has also been attributed to diets high in sugar content.⁷⁷ The term *sugar allergy* is a misnomer. This situ-

ation has no relationship to allergy nor is any immune function involved. Controlled studies have shown little or no evidence that sugar causes adverse behavioral effects in hyperactive children.⁸² Some studies actually demonstrate a calming effect from sugar in the diet in these individuals. In addition, a prospective double-blind aspartame-controlled dietary study involving juvenile delinquents and normal individuals demonstrated no evidence of adverse reactions to sugar (sucrose) in the diet.⁸³

C. Migraine Headache

Headache is a common complaint in the general population. The more serious migraine headache also is quite prevalent. Up to 25% of adult women, 15% of adult men, and 5% of children by the age of 15 may be afflicted by this condition.⁷⁷ Migraine headaches run in families; 63 to 88% of migraineurs have a close or distant relative who also suffers from migraines. Atopic diseases also run in families with approximately 20% of the population being involved. With these facts in mind, it is not unreasonable to hypothesize that some atopic individuals also have migraine headaches by chance. In fact, an association between migraine headache and food allergy has been suggested periodically since the nineteenth century, mostly in anecdotal reports.^{77,84}

There have been several studies utilizing DBPCFC techniques in recent years that support the association between diet and migraine.⁸⁵⁻⁸⁷ Among 104 adult migraine patients, 15% had reproducible double-blind, placebo-controlled, demonstrable food-associated migraine.⁸⁷ However, among children who have migraine, even those in whom diet improved migraine headache patterns, there was no correlation with immediate skin tests to foods.⁸⁵ In one study involving 36 children with migraine headaches, neither the food allergy skin test nor the history of an adverse reaction to a food could distinguish the patient who would react on DBPCFC with a headache.⁸⁸ In another study involving 43 adult migraineurs, the immediate skin test results seemed to be helpful in selecting the specific foods to which a patient would react with a headache on DBPCFC.⁸⁶ Most studies of migraine-prone individuals show

no immunologic differences between adults who have headaches and the normal population.⁸⁴

There is some evidence involving chemical mediator release with specific food challenge in dietary-induced migraines. Three patients were reported with elevated plasma histamine levels following specific food challenges that correlated with onset of a migraine headache.⁸⁶ A patient was also reported to have reproducible headaches with the ingestion of beef in which threefold increases in blood histamine and $\text{PGF}_2\alpha$ were demonstrated.⁸⁹ Finally, five other patients with food-induced migraines had 3- to 38-fold increases in plasma histamine and increases in PGD_2 with headache symptom onset, followed by a second rise in PGD_2 4 to 6 h after food ingestion.⁹⁰

To summarize, IgE-mediated food allergy probably plays little, if any, role in the pathogenesis of migraine headaches. Diet, apparently, does play a role in a subset of individuals. In select patients, migraine headache pathophysiology may include the release of chemical mediators.

XI. CONTROVERSIAL CONCEPTS

The allergic tension fatigue syndrome refers to children who demonstrate periods of hyperactivity, insomnia, and anxiety, alternating with periods of listlessness and fatigue.⁷⁷ This syndrome was once thought to be related to food allergy. However, there has never been a well-designed clinical study to prove such a relationship.

The diagnosis of chronic fatigue syndrome, particularly in adults, has become popular. A variety of explanations have surfaced to explain this symptom complex of long-standing or persistent fatigue associated with other constitutional symptoms, including myalgias, arthralgias, muscle weakness, sensations of being overheated or chilly, depression, apathy, headache, insomnia, soreness of the throat, and tenderness of the lymph nodes.⁷⁷ A variety of immune abnormalities have been reported in some of these patients. Although there is no proven relationship with food allergy or diet, one study showed that a high percentage of patients diagnosed with this disorder were also atopic as defined by skin tests.⁹¹

Since the early part of this century, foods and diet have been thought to play a role in the patho-

genesis of rheumatoid arthritis.⁷⁷ Although arthritis has never been consistently related to food allergy, single- and double-blind randomized controlled studies have shown that diet manipulation may influence or exacerbate rheumatoid arthritis in a subset (5%) of patients with this condition.⁷⁷

A. Pseudo-Food Allergy

A group of 23 adults who presented to the allergist with a series of complaints thought to be due to food allergy were examined in detail in a 1983 study.⁹² A few of these patients had allergy-like symptoms. The rest presented with symptoms of depression, fatigue, headache, mental fuzziness, malaise, myalgia, arthritis, and listlessness. Many of these patients restricted their diet to a degree that they also had signs of malnutrition. All patients were independently evaluated by a psychologist after seeing an allergist. Each patient was evaluated for food allergy and had DBPCFC to foods they thought were important. Four patients were found to be allergic and these patients had classic allergic-type presenting symptoms. When examined by a psychologist, all had a normal psychological profile. In the remaining 19 patients, no adverse reactions to foods were found with DBPCFC. These 19 patients had presented with constitutional symptoms, usually not attributed to allergic disease. When examined by a psychologist, all were found to have psychological problems, especially depression. When the patients were confronted with the results of the food challenge, most of these patients could subsequently eat the foods to which they had once believed themselves to be sensitive. The remainder, over time and with psychological counseling, could eat a normal diet. Pearson⁹³ coined the term *pseudo-food allergy* to denote the false belief that one suffers from food allergy so as to unnecessarily restrict their diet to the degree that it becomes nutritionally unsound.

XII. THE DIAGNOSIS OF FOOD ALLERGY

A. History

A history for a patient suspected of having food allergy should include: (1) the description of

the problems and typical symptoms, (2) the timing of the onset and duration of the symptoms in relation to diet and specific foods ingested or other routes of food exposure, (3) frequency of symptoms, and (4) other circumstances involved with food exposure. In the majority of situations, when the symptoms about which the patient complained were caused by food allergy, the individual had a history of allergies (e.g., AD, asthma, allergic rhinitis). The presence of asthma in a food allergic individual is considered a risk factor for a subset of individuals who have serious, life-threatening food reactions.

If a food causes immediate symptoms such as acute urticaria or systemic anaphylaxis, and a specific food is commonly involved in this event and is eaten occasionally, the food may be easily identified as a likely cause of the patient's symptoms. On the other hand, if the patient has a long-standing or chronic problem such as AD or asthma, it is often difficult by history to pinpoint a component of the diet specifically involved. In fact, in studies involving children with AD who had food allergy confirmed by DBPCFC, the mother's identification of the likely food culprit poorly correlated with challenge testing.³⁷

A food involved in provoking allergic symptoms may not be obvious and may require extensive detective work. Examples of unusual food allergies include a patient who had two systemic reactions while eating marinated chicken and was proven to be allergic by DBPCFC to coriander spice;⁹⁴ individuals known to be allergic to milk who reacted to cow's milk protein in "nondairy" products;^{95,96} a patient allergic to house dust mite who had an anaphylactic reaction while eating a beignet baked with a commercial mix contaminated with mite protein;⁹⁷ and a nurse sensitized to psyllium from exposure to a stool bulking agent who developed urticaria after eating a breakfast cereal containing psyllium placed as an ingredient to help lower cholesterol.⁹⁸

B. ST and *In Vitro* Assays

Allergy ST to detect IgE antibodies to food allergies is done almost exclusively by the epicutaneous route (prick or puncture technique), because the intradermal technique increases the

frequency of nonspecific positive reactions using food extracts.⁴ Food extracts are usually applied to the skin in a weight by volume concentration of 1:10 onto the back or forearm. The prick or puncture tests are read in 15 to 20 min. Resulting wheals are positive if they are larger than the negative diluent control by 3 mm or more. It has been verified that almost all subjects who have IgE-mediated allergic reactions to foods by DBPCFC will have a positive IgE skin test and *in vitro* test to that food.^{5,9,15}

It is important to recognize that commercially available food allergen extracts are not always reliable as testing agents.⁹⁹ When investigating fruits and vegetables suspected of causing the oral allergy syndrome, epicutaneous skin tests utilizing the fresh juice of these items may be necessary, because the allergens responsible for IgE-mediated reactions are sometimes quite labile.³⁰

ST with food extracts must be performed with caution in the evaluation of individuals who have histories of systemic anaphylaxis to a food. This is because minute quantities of food allergen introduced by ST may induce adverse symptoms.⁴ An option is to use a food allergen IgE-specific *in vitro* assay even though these tests are somewhat less sensitive.⁴¹ Food allergy ST is sometimes not possible in individuals with extensive skin disease (e.g., AD or urticaria) or in individuals on antihistamines that will block skin test reactivity (e.g., for rhinitis or urticaria). In these situations, *in vitro* antigen-specific IgE assays may be helpful. Basophil degranulation tests are occasionally used to evaluate IgE-mediated reactions to food allergens. The results of this type of test are comparable to those obtained by *in vitro* measures of allergen-specific IgE antibodies, but are not generally routinely available.⁴

The relationship between proven clinical reactions to food as measured by DBPCFC and positive allergy skin tests or *in vitro* tests has been well documented in AD.³⁹ If the allergy skin test to a major food (milk, eggs, peanut, wheat, soy) is positive, the chances are approximately 50% that the DBPCFC to that food will be positive. If an IgE skin or *in vitro* test to a specific food is negative, the probability is virtually 98% that a DBPCFC will be negative to that food.⁴ For foods

that were shown positive on DBPCFC, either the IgE skin test or RASTTM was positive.^{4,19,39}

XIII. DIARIES, DIETS, AND FOOD CHALLENGES

Diet diaries may be useful to record repeated episodes of isolated bouts of acute urticaria. The record of the foods consumed, as well as other events surrounding these specific episodes, may help narrow the variables and assist in identifying the probable offending food. Specific diets, made up of foods less likely to be involved in allergic reactions, may be helpful in nebulous situations in which food allergy is unlikely to be the cause of a problem (usually with negative food allergy skin tests) or in situations where there are positive allergy skin tests but no history of clinical activity.⁵³ In these situations, there are no suspected serious life-threatening reactions such as systemic food anaphylaxis. The specified diet is tried at home for 2 weeks. New foods are then added sequentially at 2- to 3-d intervals. The most common foods, such as milk, eggs, and wheat, are added first to quickly return the patient's usual diet to one that is nutritionally sound. The only way to be certain about a possible association between a given set of symptoms and exposure to a food, however, is to challenge the individual.⁴ A positive DBPCFC under controlled conditions establishes the relationship.¹⁰⁰ Negative DBPCFCs need to be confirmed by follow-up ingestion of the food used in the challenge procedure.

DBPCFCs are important to research studies examining the pathogenesis of adverse food reactions. It is important to prove that a given group of individuals actually are reactive to the dietary item before proceeding with further research.¹⁰¹⁻¹⁰⁴ A positive food challenge does not establish the mechanism of the adverse event. Positive food challenges occur both in food allergy and in food intolerance.

Food challenges are not usually advocated in the clinical office in cases where the risk of further exposure to the food may be severe or life-threatening.²⁶ Usually, when a patient presents with clear-cut repeated reactions to a food known to be commonly associated with anaphylaxis (e.g.,

generalized urticaria, angioedema, and wheezing within minutes of eating a shrimp at a restaurant), only an *in vitro* assay to the probable offending food is performed. If this test is positive, a presumptive diagnosis of food allergy may be made and the patient is instructed to not eat the specific food.

In the case of inadvertent exposure to a food to which the patient has developed anaphylactic symptoms, the patient is instructed to use an epinephrine autoinjector syringe or a traditional epinephrine syringe. Three of these units are prescribed and positioned by the patient so that one unit is likely to be handy when needed. The patients are instructed to use epinephrine where there is proven or presumed systemic food anaphylaxis at the first sign of symptoms and then proceed to an emergency department.^{26,29} They are cautioned against using an antihistamine first or "waiting and watching."

Sampson and Metcalfe⁴ advocate the following steps in a DBPCFC technique.

1. The procedure should be done under controlled conditions, by personnel capable of recognizing and managing anaphylaxis, should this situation occur. DBPCFC can be done in the hospital, clinic, or office.¹⁰⁰
2. The suspected food should be eliminated from the diet 10 to 14 d prior to challenge.
3. Antihistamine medication should be discontinued 12 h prior to challenge.
4. The individual to be challenged should be in a stable cardiovascular, pulmonary, and metabolic condition prior to challenge.
5. The food challenge should be done in a fasting state.
6. The challenge itself should involve gradually increasing doses of food, beginning either with the placebo or a dose low enough to be unlikely to provoke symptoms (such as 10 to 50 mg or less of lyophilized food).
7. The food challenge dose or the placebo dose is usually doubled every 15 to 20 min as tolerated.
8. The maximum food challenge dose approximates 10 g of lyophilized food.
9. Following completion of the DBPCFC procedure, a minimal recommended observa-

tion for the individual given the food challenge is 2 h for food allergic reactions and 4 to 8 h for food intolerances. All challenged individuals with GI symptoms as an end point should be observed for 4 to 8 h following completion of the challenge.

10. In the case of a negative food challenge, follow-up open feeding of the suspected food is recommended for the subsequent 24 to 48 h.

XIV. MANAGEMENT OF FOOD ALLERGY

A. Proven Food Allergy

Strict elimination of the offending food from the diet of the allergic individual is the only proven therapy once the diagnosis of food allergy has been established.⁴ Long-term avoidance of certain foods may prove difficult, especially when dealing with processed foods and when eating away from home in restaurants, cafeterias, and at parties. Carrying a "lunch" prepared at home with known safe foods becomes important for some allergic individuals. Nutritional support may be necessary so as to maintain a sound diet.⁴ Health professionals can obtain information concerning diets, recipes, and lists of processed foods containing the usual food allergens or food additives.¹⁰⁵ Patient support groups are helpful to patients or parents of patients afflicted with food allergy. Proper food labeling of ingredients in processed foods is extremely important for the patient when managing food allergy.

Patients who have had presumed or proven anaphylactic reactions to foods should be prepared at all times for inadvertent exposure to that food, especially when away from home.^{28,29} The difference between life and death depends on how quickly epinephrine is administered after the anaphylactic symptoms begin.²⁸

B. Hypoallergenic Cow's Milk Infant Formulas

Management of the infant who has a food allergy to cow's milk may be a particular prob-

lem. Often babies are switched from conventional milk-based infant formula to a soy-based formula because of problems of "fussiness" or true infant colic. Such switches have merit in some cases, but not because of food allergy.⁷⁶ Soy protein-based infant formula has caused the same spectrum of clinical reactions as those caused by cow's milk protein, especially GI reactions.^{40,106-108} Often soy sensitivity quickly follows cow's milk sensitivity. Approximately 33 to 50% of all children with GI allergy or intolerance to conventional cow's milk infant formula cannot tolerate soy-based formula.¹⁰⁹⁻¹¹¹ Therefore, the Nutrition Committee of the American Academy of Pediatrics recommends that conventional soy-based infant formula should not be used in the case of either milk or soy intolerance or in proven allergy.¹⁰⁹

For the infant who has a documented allergic reaction or intolerance to cow's milk, an ideal substitute would be one that (1) has been proven safe by DBPCFC in infants who have documented cow's milk allergy or intolerance;⁴ (2) is nutritious and allows for normal growth and development; and (3) is palatable for a long period of time.

Unfortunately, at present there is no perfect hypoallergenic formula for infants allergic or intolerant to milk.¹⁰⁶ Alternative formulas include those derived primarily from casein hydrolysate, whey hydrolysate, or crystalline amino acids. All marketed formulas have some reported, albeit apparently minor, instances of either intolerance or problems with taste.¹¹⁰⁻¹¹⁶

C. Prevention of Food Allergy

Manipulation of the mother's diet before delivery and the infant's diet following delivery for the child born to allergic parents has been a popular concept for many years because of the presumption that food allergy and perhaps other forms of allergy may be prevented. In infants at risk for allergic disease (born to parents with allergic disease) who were fed breast milk exclusively for as few as 4 months, it was found that the cumulative incidence and the severity of AD that developed by 18 months decreased.¹⁵ In this particular study,

some mothers avoided cow's milk, eggs, fish, peanut, and soy during the lactation period. Others ate a normal diet. The incidence of AD was lower (22%) in the group of breast-fed infants whose mothers ate a special diet compared with breast-fed infants whose mothers ate an unrestricted diet (44%). In another study, breast feeding was also found to be superior.¹¹⁷

Several controlled, long-term studies have shown that soy-based formula does not influence the development of early food allergy symptoms or long-term development of inhalant allergy.¹¹⁸⁻¹²⁰ One well-controlled study assessing the role of diet in the prevention of allergic disease is worth reviewing.¹²⁰ In the prevention-treated group of 101 infants and mothers, the mothers avoided cow's milk, eggs, and peanuts during the last trimester and during lactation. The infants, who were not breast fed, were fed Nutramigen, a casein hydrolysate. All infants were kept away from cow's milk, corn, soy, citrus, and wheat for 12 months; and eggs, peanuts, and fish for 24 months. In the control group of 185 infants and mothers, the regular accepted American Academy of Pediatrics feeding practices were followed. The cumulative prevalence of allergy at 1 year was less in the prophylactically treated group (16 vs. 27%) as were food-related symptoms (5 vs. 16% control).¹²¹ However, at 24 months, there were no differences in the incidences of rhinitis, asthma, skin, or GI allergy symptoms and the IgE skin test positivity to inhalants between the two groups. Thus, for the short term, diet may influence the incidence of food allergy symptoms in high-risk infants, but a special diet in the mother or infant has no long-term influence on the subsequent development of atopic disease.

XV. ROLE OF DRUGS AND ALLERGEN IMMUNOTHERAPY

Other preventive therapies have been tried in food allergies, such as the long-term use of antihistamines, corticosteroids, and oral cromolyn sodium. None has been proven to have more than minimal efficacy.⁴ The unproven therapies of oral desensitization, including sublingual food drops or subcutaneous neutralization, have not been

efficacious. If used at all, they should probably be restricted to research studies with appropriate informed consent.^{77,101}

Conventional allergen immunotherapy is not an approved therapeutic option for food allergy.⁴ This therapy has been tried experimentally, indirectly to help prevent the oral allergy syndrome (oral and injection birch tree pollen therapy) and directly with the use of a peanut extract to prevent peanut allergy.^{122,123} Tree allergen immunotherapy was not helpful in the management of food symptoms in the oral allergy syndrome.¹²² In the few patients treated with peanut extract, there was both clinical and immunologic evidence for some protection against peanut anaphylaxis. It was concluded from the latter study that more research involving immunotherapy for food allergy should be pursued because some patients with severe life-threatening symptoms to food are not always able to avoid these foods.¹²⁴ The potential risk of food allergen immunotherapy may be less than the real risk of inadvertent allergen exposure.^{28,29}

REFERENCES

1. **Anderson, J. A.**, The establishment of a common language concerning adverse reactions to foods and food additives, *J. Allergy Clin. Immunol.*, 78, 140, 1986.
2. **Niestijl Jansen, J. J., Kardinaal, A. F. M., Huijbers, G. H., Vlieg-Boerstra, B. J., Martens, B. P. M., and Ockhuizen, T.**, Prevalence of food allergy and intolerance in the adult Dutch population, *J. Allergy Clin. Immunol.*, 93, 446, 1994.
3. **Young, E., Stoneham, M. D., Petrukevitch, A., Barton, J., and Rona, R.**, A population study of food intolerance, *Lancet*, 343, 1127, 1994.
4. **Sampson, H. A. and Metcalfe, D. D.**, Food allergies, *JAMA*, 268, 2840, 1992.
5. **Bock, S. A.**, Prospective appraisal of complaints of adverse reactions to foods in children during the first three years of life, *Pediatrics*, 79, 683, 1987.
6. **Host, A. and Halken, S.**, A prospective study of cow's milk allergy in Danish infants during the first three years of life, *Allergy*, 45, 587, 1990.
7. **Fuglsang, G., Madsen, C., Saval, P., and Osterballe, O.**, Prevalence of intolerance to food additives among Danish school children, *Pediatr. Allergy Immunol.*, 14, 123, 1993.
8. **Bircher, A. J., VanMelle, G., Haller, E., Curty, B., and Frei, P. C.**, IgE to food allergens are highly prevalent in patients allergic to pollens with and with-

- out symptoms of food allergy, *Clin. Exp. Allergy*, 24, 367, 1994.
9. **Enberg, R. N.**, Food-induced oropharyngeal symptoms, *Immunol. Allergy Clin. N. Am.*, 11, 767, 1991.
 10. **Gall, H., Kalveram, K.-J., Forck, G., and Sterry, W.**, Kiwi fruit allergy: a new birch pollen-associated food allergy, *J. Allergy Clin. Immunol.*, 94, 70, 1994.
 11. **Enberg, R. N., Leickly, F. E., McCullough, J., Bailey, J., and Ownby, D. R.**, Watermelon and ragweed share allergens, *J. Allergy Clin. Immunol.*, 79, 867, 1987.
 12. **Anderson, L. B., Dreyfuss, E. M., Logan, J., Johnstone, D. E., and Glaser, J.**, Melon and banana sensitivity coincident with ragweed pollinosis, *J. Allergy Clin. Immunol.*, 45, 310, 1970.
 13. **Bock, S. A.**, The incidence of severe adverse reactions to foods in Colorado, *J. Allergy Clin. Immunol.*, 90, 683, 1992.
 14. **Bock, S. A.**, The natural history of adverse reaction to foods, *N.E.R. Allergy Proc.*, 7, 504, 1986.
 15. **Sampson, H. A. and Scanlan, S. M.**, Natural history of food hypersensitivity in children with atopic dermatitis, *J. Pediatrics*, 115, 23, 1989.
 16. **Pastorello, E. A., Stocchi, L., Pravettoni, V., Bigi, A., Schilke, M. L., Incorvaia, C., and Zanussi, C.**, Role of the elimination diet in adults with food allergy, *J. Allergy Clin. Immunol.*, 84, 475, 1989.
 17. **Bock, S. A. and Atkins, F. M.**, The natural history of peanut allergy, *J. Allergy Clin. Immunol.*, 83, 900, 1989.
 18. **Jarmoc, L. and Primack, W.**, Anaphylaxis to cutaneous exposure to milk protein in a diaper rash ointment, *Clin. Pediatr.*, 26, 154, 1987.
 19. **Bernhisel-Broadbent, J. and Sampson, H. A.**, Cross-allergenicity in the legume botanical family in children with food hypersensitivity, *J. Allergy Clin. Immunol.*, 83, 435, 1989.
 20. **Bernhisel-Broadbent, J., Scanlon, S. M., and Sampson, H. A.**, Fish hypersensitivity. I. *In vitro* and oral challenge results in fish allergic patients, *J. Allergy Clin. Immunol.*, 89, 730, 1992.
 21. **Anderson, J. A.**, The clinical spectrum of food allergy in adults, *Clin. Exp. Allergy*, 21(Suppl.), 304, 1991.
 22. **Metcalfe, D. D.**, Warning: eat, do not inhale, *Allergy Proc.*, 11, 35, 1990.
 23. **Cartier, A., Mabod, J., Ghezze, H., McCants, M., and Lehrer, S. A.**, IgE sensitization in snow crab processing workers, *J. Allergy Clin. Immunol.*, 78, 344, 1986.
 24. **O'Neil, C.**, Occupational respiratory diseases resulting from exposure to eggs, honey, spices and mushroom, *Allergy Proc.*, 11, 169, 1990.
 25. **Lybarger, J. A., Gallagher, J. S., Pulver, D. W., Litwin, A., Brooks, S., and Bernstein, I. L.**, Occupational asthma induced by inhalation and ingestion of garlic, *J. Allergy Clin. Immunol.*, 69, 448, 1982.
 26. **Yunginger, J. W.**, Anaphylaxis to foods, *Immunol. Allergy Clin. N. Am.*, 12, 543, 1992.
 27. **Stark, B. J. and Sullivan, T. J.**, Biphasic and protracted anaphylaxis, *J. Allergy Clin. Immunol.*, 78, 76, 1986.
 28. **Yunginger, J. W., Sweeney, K. G., Sturner, W. Q., Giannandrea, L. A., Tieglund, J. D., Brat, M., Benson, P. A., York, J. A., Biedrzycki, L., Squillace, D. L., and Helm, R. M.**, Fatal food induced anaphylaxis, *JAMA*, 260, 1450, 1988.
 29. **Sampson, H. A., Mendelson, L., and Rosen, J.**, Fatal and near-fatal anaphylactic reactions to foods in children and adolescents, *N. Engl. J. Med.*, 327, 380, 1992.
 30. **Ortolani, C., Ispano, M., Pastorello, E. A., Ansaloni, R., and Magri G. C.**, Comparison of skin prick tests (with fresh foods and commercial food extracts) and RAST in 100 patients with oral allergy syndrome, *J. Allergy Clin. Immunol.*, 83, 683, 1989.
 31. **Ross, B. D., McCullough, J., and Ownby, D. R.**, Partial cross-reactivity between latex and banana allergens, *J. Allergy Clin. Immunol.*, 90, 409, 1992.
 32. **deCorres, L. F., Moneo, I., Munoz, D., Bernaola, G., Fernandez, E., Audicana, M., and Urrutia, I.**, Sensitization from chestnuts and bananas in patients with urticaria and anaphylaxis from contact with latex, *Ann. Allergy*, 70, 35, 1993.
 33. **Moneret-Vartris, D. A., Beaudouin, E., Widmer, S., Mouton, C., Kanny, G., Prestat, F., Kohler, C., and Feldmann, L.**, Prospective study of risk factors in natural rubber latex hypersensitivity, *J. Allergy Clin. Immunol.*, 92, 668, 1993.
 34. **Appleyard, J. K., McCullough, J. A., and Ownby, D. R.**, Cross-reactivity between latex, ragweed and blue grass allergy, *J. Allergy Clin. Immunol.*, 93(Abstr.), 182, 1994.
 35. **Horan, R. F. and Sheffer, A. L.**, Food-dependent, exercise-induced anaphylaxis, *Immunol. Allergy Clin. N. Am.*, 11, 757, 1991.
 36. **Kushimoto, H. and Aoki, T.**, Masked type I wheat allergy. Relationship to exercise-induced anaphylaxis, *Arch. Dermatol.*, 121, 355, 1985.
 37. **Sampson, H. A.**, Role of food allergy and mediator release in atopic dermatitis, *J. Allergy Clin. Immunol.*, 81, 635, 1989.
 38. **Sampson, H. A., Broadbent, K. R., and Bernhisel-Broadbent, J.**, Spontaneous release of histamine from basophils and histamine-releasing factor in patients with atopic dermatitis and food hypersensitivity, *N. Engl. J. Med.*, 321, 228, 1989.
 39. **Sampson, H. A. and Albergo, R.**, Comparison of results of skin tests, RAST and double-blind, placebo-controlled food challenge in children with atopic dermatitis, *J. Allergy Clin. Immunol.*, 74, 26, 1984.
 40. **Gryboski, J. D.**, Gastrointestinal aspect of cow's milk protein intolerance and allergy, *Immunol. Allergy Clin. N. Am.*, 11, 773, 1991.
 41. **Schwartz, R. H.**, IgE mediated allergic reactions to cow's milk, *Immunol. Allergy Clin. N. Am.*, 11, 717, 1991.

42. **Mim, K. U. and Metcalfe, D. D.**, Eosinophilic gastroenteritis, *Immunol. Allergy Clin. N. Am.*, 11, 799, 1991.
43. **Bousquet, J. and Michel, F. B.**, Food allergy and asthma, *Ann. Allergy*, 61, 70, 1988.
44. **Heiner, D. E. and Sears, J. W.**, Chronic respiratory disease associated with multiple circulating precipitins to cow's milk, *Ann. J. Dis. Child.*, 100, 500, 1960.
45. **Anderson, J. A., Weiss, L., Rebuck, J. W., Cabal, L. A., and Sweet, L. C.**, Hyperreactivity to cow's milk in an infant with LE and tart cell phenomenon, *J. Pediatr.*, 84, 59, 1974.
46. **O'Malory, S. and Ferguson, A.**, Gluten-sensitive enteropathy (Celiac disease), in *Food Allergies — Adverse Reactions to Foods and Food Additives*, Metcalfe, D. D., Sampson, H. A., and Simon, R. A., Eds., Blackwell Scientific, Boston, MA, 1991, 186.
47. **O'Neil, C. E. and Lehrer, S. B.**, Occupational reactions to food allergens, in *Food Allergies - Adverse Reactions to Foods and Food Additives*, Metcalfe, D. D., Sampson, H. A., and Simon, R. A., Eds., Blackwell Scientific, Boston, MA, 1991, 207.
48. **Herxheimer, H.**, The skin sensitivity to flour of baker's apprentices, a final report of long term investigation, *Acta Allergol.*, 28, 42, 1967.
49. **Jones, R. N., Hughes, J. M., Lehrer, S. B., Butcher, B. T., Glindmeyer, H. W., Diem, J. E., Hammad, Y. Y., Salvaggio, J., and Weill, H.**, Lung function consequences of exposure and hypersensitivity in workers who process green coffee beans, *Am. Rev. Respir. Dis.*, 125, 199, 1982.
50. **Furukawa, C. T.**, Non-immunologic food reactions that can be confused with allergy, *Immunol. Allergy Clin. N. Am.*, 11, 815, 1991.
51. **Zeitz, H. J.**, Pharmacologic properties of foods, in *Food Allergies — Adverse Reactions to Foods and Food Additives*, Metcalfe, D. D., Sampson, H. A., and Simon, R. A., Eds., Blackwell Scientific, Boston, 311, 1991.
52. **Chin, K. W., Garriga, M. M., and Metcalfe, D. D.**, The histamine content of oriental foods, *Food Chem. Toxicol.*, 27, 283, 1989.
53. American Academy of Allergy and Immunology Committee on Adverse Reactions to Foods and NIAID, *Adverse Reactions to Foods*, Anderson, J. A. and Sogn, D. D., Eds., U.S. Department of Health and Human Services, Public Health Service NIH Publ. No. 84-244 2, July 1984.
54. **Smith, C. K. and Durack, D. T.**, Isoniazid and reactions to cheese, *Ann. Intern. Med.*, 88, 520, 1978.
55. **Uragoda, C. G.**, Histaminic poisoning in tuberculosis patients after ingestion of tuna fish, *Am. Rev. Respir. Dis.*, 121, 157, 1980.
56. **Liebermann, L. S. and Barnes, K. C.**, Food allergies and adverse food reactions: an anthropological perspective, in *Food Allergies and Adverse Reactions*, Perkin, J. E., Ed., Gaithersburg, MD, Aspen Publishing, 1990, 207.
57. **Perkin, J. E.**, Adverse reactions to food additives and other food constituents, in *Food Allergies and Adverse Reactions*, Perkin, J. E., Ed., Gaithersburg, MD, Aspen Publishing, 1990, 129.
58. **Simon, R. A. and Stevenson, D. D.**, Adverse reactions to foods and drug additives, in *Allergy, Principles and Practice* 4th ed., Middleton, E. J., Yunginger, J. W., and Busse, W. E., Eds., Mosby, St. Louis, MO, 1993, 1687.
59. **Stevenson, D. D., Simon, R. A., Lumry, W. R., and Mathison, D. A.**, Adverse reactions to tartrazine, *J. Allergy Clin. Immunol.*, 78, 182, 1986.
60. **Murdoch, R. D., Pollock, I., Young, E., and Lessof, M. H.**, Food additive induced urticaria: studies of mediator release during provocation tests, *J. R. College Phys. London*, 21(4), 262, 1987.
61. **Prenner, B. M. and Stevenson, J. J.**, Anaphylaxis after ingestion of sodium bisulfite, *Ann. Allergy*, 37, 180, 1976.
62. **Young, W. H., Purchase, W. C. R., and Rivington, R. N.**, Positive skin tests and Prausnitz-Küstner reactions in metabisulfite-sensitive subjects, *J. Allergy Clin. Immunol.*, 78, 443, 1986.
63. **Goodman, D. L., McDonnell, J. T., Nelson, H. S., Vaughan, T. R., and Weber, R. W.**, Chronic urticaria exacerbated by the antioxidant food preservatives, butylated hydroxytoluene (BHT) and butylated hydroxytoluene (BHT), *J. Allergy Clin. Immunol.*, 86, 570, 1990.
64. **Kulczychi, A.**, Aspartame-induced urticaria, *Ann. Intern. Med.*, 104, 207, 1986.
65. **Geha, R., Buckley, C. E., Greenberger, P., Patterson, R., Polmar, S., Saxon, A., Rohr, A., Yang, W., and Drouin, M.**, Aspartame is no more likely than placebo to cause urticaria/angioedema: results of a multicenter, randomized, double-blind, placebo-controlled, cross-over study, *J. Allergy Clin. Immunol.*, 92, 513, 1993.
66. **Garriga, M. M., Berkebile, C., and Metcalfe, D. D.**, A combined single-blind, double-blind placebo-controlled study to determine the reproducibility of hypersensitivity reactions to aspartame, *J. Allergy Clin. Immunol.*, 87, 821, 1991.
67. **Simon, R. A.**, Sulfite sensitivity, *Ann. Allergy*, 56, 281, 1986.
68. **Delohery, J., Simmul, R., Castle, W. D., and Allen, D. H.**, The relationship of inhaled sulfur dioxide reactivity to ingested metabisulfite sensitivity in patients with asthma, *Am. Rev. Respir. Dis.*, 130, 1027, 1984.
69. **Bush, R. K., Taylor, S. L., Holden, K., Nordlee, J. A., and Busse, W. W.**, Prevalence of sensitivity to sulfiting agents in asthmatic patients, *Am. J. Med.*, 81, 816, 1986.
70. **Allen, D. H., Delohery, J., and Baker, G.**, Monosodium 1-glutamate-induced asthma, *J. Allergy Clin. Immunol.*, 8, 530, 1987.
71. **Germano, P., Cohen, S. G., Hahn, R., and Metcalfe, D. D.**, An evaluation of clinical reactions to monosodium glutamate (MSG) in asthmatics using a blinded,

- placebo-controlled challenge, *J. Allergy Clin. Immunol.*, 87(Abstr.), 177, 1991.
72. **Germano, P., Cohen, S., Hibbard, V., and Metcalfe, D. D.**, Assessment of bronchial hyperreactivity by methacholine challenge (MTC) in asthmatics before and after monosodium glutamate (MSG) administration, *J. Allergy Clin. Immunol.*, 91(Abstr.), 340, 1993.
73. **Weber, R. W., Hoffman, M., Raine, D. A., and Nelson, H. S.**, Incidence of bronchoconstriction due to aspirin, azo dyes, non-azo dyes and preservatives in a population of perennial asthmatics, *J. Allergy Clin. Immunol.*, 64, 32, 1979.
74. **Thomas, D. W., McGilligan, K., Eisenberg, L. D., Lieberman, H. M., and Rissman, E. M.**, Infant colic and type of milk feeding, *Am. J. Dis. Child.*, 141, 451, 1987.
75. **Hewson, P., Oberklaid, F., and Menahem, S.**, Infant colic, distress, and crying, *Clin. Pediatr.*, 26, 69, 1987.
76. **Lothe, L., Lindberg, T., and Jakobsson, I.**, Cow's milk formula as a cause of infantile colic, a double-blind study, *Pediatrics*, 70, 7, 1982.
77. **Goldberg, B. J. and Kaplan, M. S.**, Controversial concepts and techniques in the diagnosis and management of food allergies, *Immunol. Allergy Clin. N. Am.*, 11, 863, 1991.
78. **Feingold, B. F.**, Hyperkinesis and learning disabilities linked to artificial food flavors and colors, *Am. J. Nurs.*, 75, 797, 1975.
79. **Lipton, M. A. and Mayo, J. P.**, Diet and hyperkinesis — an update, *J. Am. Diet. Assoc.*, 83, 132, 1983.
80. **Swanson, J. M. and Kinbourne, M.**, Food dye impairs performance of hyperactive children on a laboratory learning test, *Science*, 207, 1485, 1980.
81. **Kaplan, B. J., McNichol, J., Conte, R. A., and Moghadam, H. K.**, Dietary replacement in preschool-aged hyperactive boys, *Pediatrics*, 83, 7, 1989.
82. **Wolraich, M. L.**, Sugar intolerance: is there evidence for its effect on behavior in children?, *Ann. Allergy*, 61(II), 58, 1988.
83. **Bachorowsky, J.-A., Newman, J. P., Nicols, J. L., et al.**, Sucrose and delinquency behavior assessment, *Pediatrics*, 86, 244, 1990.
84. **Weber, R. W. and Vaughan, T. R.**, Food and migraine headache, *Immunol. Allergy Clin. N. Am.*, 11, 831, 1991.
85. **Egger, J., Wilson, J., Carter, C. M., Turner, C. M., and Soothill, J. F.**, Is migraine a food allergy? A double-blind controlled trial of oligoantigen diet treatment, *Lancet*, 2, 865, 1983.
86. **Mansfield, L. E., Vaughn, T. R., Walker, S. F., Haverly, R. W., and Ting, S.**, Food allergy and adult migraine: double-blind and mediator confirmation of an allergic etiology, *Ann. Allergy*, 55, 126, 1985.
87. **Vaughn, T. R., Stafford, W. M., Miller, B. T., Weber, R. W., Tipton, R., and Nelson, H. S.**, Food and migraine headache (MIG): a controlled study, *Ann. Allergy*, 56(Abstr.), 522, 1988.
88. **Atkins, F. M., Ball, B. D., and Bock, A.**, The relationship between the ingestion of specific foods and the development of migraine headaches in children, *J. Allergy Clin. Immunol.*, 81(Abstr.), 185, 1988.
89. **Steinberg, M., Page, R., Wolfson, S., Friday, G., and Fireman, P.**, Food-induced late phase headache, *J. Allergy Clin. Immunol.*, 81(Abstr.), 185, 1988.
90. **Olson, G. C., Vaughan, T. R., Ledoux, R., Kossoy, A. E., Williams, B., Selner, J. C., and Weber, R. W.**, Food-induced migraine: search for immunologic mechanism, *J. Allergy Clin. Immunol.*, 83(Abstr.), 238, 1989.
91. **Strause, S. E., Dale, J. K., Wright, R., and Metcalfe, D. D.**, Allergy and the chronic fatigue syndrome, *J. Allergy Clin. Immunol.*, 81, 791, 1988.
92. **Pearson, D. J., Rix, K. J. B., and Bentley, S. V.**, Food allergy: how much is in the mind?, *Lancet*, 1, 1259, 1983.
93. **Pearson, D.**, Food allergy hypersensitivity and intolerance, *J. R. College Phys. London*, 19, 154, 1985.
94. **Bock, S. A.**, Anaphylaxis to coriander, a sleuthing story, *J. Allergy Clin. Immunol.*, 91, 1232, 1993.
95. **Jones, R. T., Squillace, D. L., and Yunginger, J. W.**, Anaphylaxis in a milk allergic child after ingestion of milk-contaminated Kosher "parve-labeled" dairy-free dessert, *Ann. Allergy*, 68, 223, 1992.
96. **Gern, J. E., Yang, E., Evrard, H. M., and Sampson, H. A.**, Allergic reactions to milk contaminated non-dairy products, *N. Engl. J. Med.*, 324, 976, 1992.
97. **Erben, A., Rodriguez, J. L., McCullough, J., and Ownby, D. R.**, Anaphylaxis after ingestion of beignets contaminated with *Dermatophygidies farinae*, *J. Allergy Clin. Immunol.*, 92, 846, 1993.
98. **James, J. M., Cooke, S. K., and Barnett, A.**, Anaphylactic reactions to a psyllium containing cereal, *J. Allergy Clin. Immunol.*, 88, 402, 1991.
99. **Sampson, H. A.**, Comparative study of commercial food antigen extracts for the diagnosis of food hypersensitivity, *J. Allergy Clin. Immunol.*, 82, 718, 1988.
100. **Bock, S. A., Sampson, H. A., Atkins, F. M., Zeiger, R. S., Lehrer, S., Sachs, M., Bush, R. K., and Metcalfe, D. D.**, Double-blind, placebo-controlled food challenge (DBPCFC) as an office procedure. A manual, *J. Allergy Clin. Immunol.*, 82, 986, 1988.
101. **VanMetre, T.**, Critique of controversial and unproven procedures for the diagnosis and therapy of allergic disorders, *Pediatr. Clin. North. Am.*, 30, 807, 1988.
102. **Sampson, H. A.**, Immunologically mediated food allergy: the importance of food challenge procedures, *Ann. Allergy*, 60, 262, 1988.
103. **Bock, S. A.**, Oral challenge procedures, in *Food Allergy, Adverse Reactions to Foods and Food Additives*, Metcalfe, D. D., Sampson, H. A., and Simon, R. A., Eds., Blackwell Scientific, Boston, MA, 1991, 81.
104. **Bahna, S. L.**, Practical considerations in food challenge tests, *Immunol. Allergy Clin. N. Am.*, 11, 843, 1991.

105. Appendix A-K., in *Food Allergy and Adverse Reactions*, Perkin, J. E., Ed., Gaithersburg, MD, Aspen Publishing, 1990, 243.
106. **Olejer, V.**, Diagnosis of food allergy. II. The dietitians perspective, in *Food Allergy and Adverse Reactions*, Perkin, J. E., Ed., Gaithersburg, MD, Aspen Publishers, 1990, 30 (Tables 2-4).
107. **Withington, P. F. and Gibson, R.**, Soy protein intolerance: four patients with concomitant cow's milk intolerance, *Pediatrics*, 59, 730, 1977.
108. **Berezin, S., Schwartz, S. M., Glassman, M., et al.**, Gastrointestinal milk intolerance of infancy, *Am. J. Dis. Child.*, 143, 361, 1989.
109. American Academy of Pediatrics Committee on Nutrition, Soy-based formula: recommendations for use in infant feeding, *Pediatrics*, 72, 359, 1983.
110. **Businco, L., Cantani, A., Longhi, M. A., and Giampietro, P. G.**, Anaphylactic reactions to a cow's milk whey protein hydrolysate (Alfa-Ré, Nestlé) in infants with cow's milk allergy, *Ann. Allergy*, 62, 333, 1989.
111. **Swartz, R. H. and Amonette, M. S.**, Cow milk protein hydrolysate infant formula are not all hypoallergenic, *J. Pediatr.*, 119, 839, 1991.
112. **Ellis, M. H., Short, J. A., and Heiner, D. C.**, Anaphylaxis after ingestion of a recently introduced whey protein formula, *J. Pediatr.*, 118, 74, 1991.
113. **Bock, S. A.**, Probable allergic reaction to casein hydrolysate formula, *J. Allergy Clin. Immunol.*, 84, 272, 1989.
114. **Saylor, J. D. and Bahna, S. L.**, Anaphylaxis to casein hydrolysate formula, *J. Pediatr.*, 118, 71, 1991.
115. **Sampson, H. A., Bernhisel-Broadbent, J., Young, E., and Scanlon, S. M.**, Safety of casein hydrolysate formula in children with cow's milk allergy, *J. Pediatr.*, 118, 520, 1991.
116. **Sampson, H. A., Jones, J. M., and Bernhisel-Broadbent, J.**, Safety of an amino acid-derived infant formula in children allergic to cow milk, *Pediatrics*, 90, 463, 1992.
117. **Chandra, R. K., Puri, S., and Hamed, A.**, Influence of maternal diet during lactation and use of formula feeds on development of atopic eczema in high-risk infants, *Br. J. Med.*, 299, 228, 1989.
118. **Chandra, R. K., Single, G., and Shrinidhara, B.**, Effect of feeding whey hydrolysate soy and conventional cow's milk formula on incidence of atopic disease in high-risk infants, *Ann. Allergy*, 63, 102, 1989.
119. **Kjellman, N. I. M. and Johansson, S. G. O.**, Soy versus cow's milk in infants with a biparental history of atopic disease. Development of atopic disease and immunoglobulins from 4 years of age, *Clin. Allergy*, 9, 347, 1979.
120. **Grunskay, F. L.**, Comparison of breast, cow, and soy feeding in the prevention of onset of allergic disease — a 15 year prospective study, *Clin. Pediatr.*, 21, 486, 1982.
121. **Zeiger, R. S., Heller, S., Mellon, M., Forsythe, A. B., O'Connor, R. D., Hamburger, R. N., and Schatz, M.**, Effect of combined maternal and infant food-allergen avoidance on development of atopy in early infancy: a randomized study, *J. Allergy Clin. Immunol.*, 84, 72, 1989.
122. **Moller, C.**, The effect of pollen immunotherapy on food hypersensitivity in children with birch pollinosis, *Ann. Allergy*, 62, 343, 1989.
123. **Oppenheimer, J. J., Nelson, H. S., Bock, S. A., Christensen, F., and Leung, D. Y. M.**, Treatment of peanut allergy with rush immunotherapy, *J. Allergy Clin. Immunol.*, 90, 256, 1992.
124. **Sampson, H.**, Food allergy and the role of immunotherapy, *J. Allergy Clin. Immunol.*, 90, 151, 1992.
125. **Bruijnzeel-Koomen, C., Ortolani, C., Aas, K., Bindselev-Jensen, C., Björkstén, B., Moneret-Vautrin, D., and Wüthrich, B.**, Position paper: Adverse reactions to food, *Allergy*, 50, 623, 1995.