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Tips when considering the diagnosis of food allergy

Studies show that 4% to 8% of infants and young children and 1% to 2% of adults have documented food allergy. Infant's rashes due to cow's milk, eggs, wheat, or soy food allergy are usually self limited. The risk of anaphylaxis that older children and adults develop due to food allergy such as to peanuts, nuts, fish, or seafood, usually are lifelong. Several food intolerances may be mistaken for food allergy problems. The only sure way to demonstrate a cause and effect relationship between dietary items and symptoms is to challenge the individual, under controlled conditions. The demonstration of IgE food allergen-specific antibodies helps to "narrow the field" of which food may cause allergy, but does not designate clinical reactivity. Key words: *diagnosis of food allergy, food allergy, food allergy skin testing, food challenge procedures, food intolerance*

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DIAGNOSING AN adverse reaction to a food may not be difficult if the individual always has the same reaction each time upon repeated exposure. For example, the diagnosis of an allergic reaction to shrimp may be obvious in a person who develops urticaria and angioedema each time this food is eaten at the local restaurant. On the other hand, there may be many different causes of unwanted or annoying reactions associated with food ingestion—only some of which are allergic in nature. The "simple" diagnosis of food allergy may be difficult.

There is a strong public perception that allergic reactions to foods occur quite commonly. There are reliable reports that one in four allergic adults believe that they, personally, have had an allergic reaction to a food.¹ Similarly about one third of parents report that their infant had a rash or gastrointestinal problem as the result of something in the child's diet.²

Part of the problem has to do with the definition of terms used to describe an unwanted or bothersome problem related to diet or other exposure to a food or food additive. In 1986, Anderson³ published a glossary of standard terms concerning adverse reactions to food and food additives. According to these definitions, an adverse reaction to food falls into two broad categories: (1) *food allergy* (or hypersensitivity) or (2) *food intolerance*. Food allergic reactions are due to an immunologic event—usually, with an IgE mechanism. Food intolerance reactions include all other types of adverse food reactions in which the cause is either recognized or unknown. Some of these “non-immunologic” reactions may resemble a food allergy, clinically. An example would be lactose intolerance in which gastrointestinal signs and symptoms related to cow’s milk ingestion are due to a lack of bowel wall enzyme, lactase, that is important in the digestion of milk sugar. Gastrointestinal symptoms, as a result of this enzyme deficiency, may be confused by the individual with symptoms of milk allergy.

In a prospective study of 500 infants and children up to 6 years of age, 8% had proven adverse reactions to foods and 4% of these had reproducible symptoms on a combination of open and double-blind, placebo-controlled food challenges (DBPCFC).⁴ The prevalence of adverse reaction to cow’s milk protein in infants during the first year of life is best estimated at 2% based upon three well done, open challenge and DBPCFC prospective controlled studies in the United States, Sweden, and Denmark.⁴⁻⁶ Similar prevalence studies have not been completed in adults, but it is estimated that 1% to 2% of the general adult population is sensitive to a food or food additive.¹

EVIDENCE FOR IMMUNOLOGIC REACTIVITY VERSUS CLINICAL REACTIVITY TO A FOOD PROTEIN

Individuals who become allergic to a specific food protein are not born with that allergy. They are born with the potential to become allergic. It takes time and exposure to various foreign proteins to determine the specific allergy individuals subsequently develop.⁷ Most food allergic reactions involve an IgE mechanism. In infants and young children, IgE specific food antibodies can be readily identified in the foods to which allergic children clinically react.⁸ Although, potentially young children could become allergic to any food, most allergic children in the United States become sensitive to a relatively narrow spectrum of foods including egg, cow’s milk, peanut, wheat, and soy. The practice of introducing certain foods into the diet at a young age may determine the importance of specific food allergies among different cultures. This is probably the reason that peanut allergy is so common in the United States (through the early introduction of peanut butter) or soy allergy in Japan and fish allergy in the Scandinavian countries.

There is a natural history of the clinical manifestations of food allergy. In the case of allergy to egg, cow’s milk, soy, and wheat proteins, infants and children who develop sensitization and clinical reactions early in life can tolerate at least some of these proteins without significant reactions by 2 to 4 years of age.⁹ In general, the more severe the initial clinical reaction to the food, the longer it takes for the child to become clinically tolerant. Foods that are cooked, processed, or combined with other foods are usually tolerated, clinically, earlier than whole or raw foods.¹⁰ It is important to recognize that clin-

ical tolerance to foods may occur in spite of long lasting evidence of immunologic reactions to those same food proteins (eg, positive IgE food allergen-specific immediate-reacting epicutaneous skin tests or the demonstration of IgE food allergen-specific IgE antibodies in in vitro radioallergosorbent test [RAST]).¹¹ Sensitization to some other foods and the subsequent risk of clinical reaction to that food, may be lifelong. A lifelong risk of clinical reaction is felt to exist in those individuals who become allergic to peanut, fish, crustacean seafood (shrimp, lobster, crayfish), and individual tree nuts (Brazil nut, hazelnut or filbert, cashew, walnut, and pecan). Peanut allergy has been shown to last at least 14 years.¹² In the case of peanut allergy, it has been shown that individuals who are allergic may have immunologic IgE antibody to other members of the legume family (eg, peas, beans, soy) but only clinically react to peanut.^{13,14}

THE TYPICAL INDIVIDUAL WHO PRESENTS WITH FOOD ALLERGY REACTIONS

Most individuals who can subsequently be proven to have an allergic reaction to a food protein have other manifestations of allergy. They and their family can be called "atopic." Thus, a good clue is the presence of either an individual history or a past history of atopic dermatitis, allergic rhinitis, asthma, or urticaria in an individual who presents with a suspected allergy to food. Potentially, the most serious reaction type of allergic food reaction is *anaphylaxis* (see Table 1). The range of manifestations of anaphylaxis is broad and may be as mild as localized contact urticaria on the face of a child touched by a drop of milk or a bit of egg. It can range

Table 1. Clinical reactions proven to be caused by food allergy

Anaphylaxis
<i>Cutaneous (single, mild)</i> localized contact urticaria, itching, flush or erythema, generalized urticaria or hives, angioedema
<i>Systemic (more severe—potentially life threatening)</i> hay fever-like symptoms of runny nose, stuffiness, sneezing, red, itchy, swollen eyes, tearing
<i>Oral allergy syndrome (OAS) (fruit and vegetable syndrome)</i> "localized" anaphylaxis to mouth parts; primarily swelling, itching of mouth parts but occasionally with more systemic manifestations when contacting certain foods in pollen-allergic individual's cross-reactions between food protein and pollen
<i>Food-dependent exercise-induced anaphylaxis (EIA)</i> anaphylaxis only within 2 hours of meal or ingestion of a specific food
Atopic dermatitis
Gastrointestinal manifestations
Nausea, vomiting, diarrhea, bleeding and blood loss (enterocolitis and colitis), cellular infiltrates particularly eosinophils (eosinophilic gastritis)
Pulmonary manifestations
Wheezing (asthma), pulmonary infiltrates associated with milk precipitins (Heiner's syndrome)

through generalized itching, erythematous skin or a flush, generalized urticaria, and angioedema (swelling of various parts of the body, particularly the mouth parts or around the eyes). Often experts distinguish *systemic anaphylaxis* from the milder cutaneous manifestations. These generalized symptoms include all or some of the following: hay fever-like symptoms (nasal stuffiness, runny nose, itching or sneezing, with or without redness, itching, swelling or tearing of the eyes); symptoms of asthma or bronchospasm;

hoarseness or swelling of the throat; gastrointestinal complaints of nausea, vomiting, cramping, diarrhea; vascular shock, or death. Almost any food can cause anaphylaxis but usually peanut, fish, crustacean seafood, tree nuts, egg, and cow's milk are likely causes.^{15,16}

In a recent report of 18 children and adolescents who had fatal or near fatal anaphylactic food reactions, all were asthmatics and highly allergic otherwise.¹⁶ In studies of patients who developed anaphylaxis due to other causes, such as reactions to allergen injections (in allergic individuals undergoing allergen immunotherapy in doctors' offices), the presence of asthma per se was not found to be a risk factor for a systemic allergic reaction, but it was found to be a risk factor for more serious, life-threatening reactions.^{17,18}

In the *oral allergy syndrome* (OAS), individuals who are allergic to airborne pollens and who usually have hay fever, develop localized swelling and itching of the lips, tongue, and buccal mucosa when they eat certain raw fruits or vegetables.¹⁹ Cross-reacting allergens exist between the ragweed pollen and the following foods: melons (watermelon and cantaloupe), bananas, and squash.²⁰ Recently, it has been recognized that there also has been a link between some patients allergic to natural rubber latex and bananas.²¹ There are also reports of the association of anaphylaxis to latex in patients allergic to kiwi, avocado, and chestnuts. When allergic individuals are sensitive to other airborne pollens (such as birch tree pollen or various grass pollens), cross-reactivity may occur in patients who have the OAS to foods such as raw carrots, potatoes, and hazelnuts or to fresh fruits such as apples, pears, or cherries.²²

Exercise-induced anaphylaxis (EIA) is a form of anaphylaxis that may be induced by any type of physical exercise. It usually occurs, however, after fairly vigorous exercise such as jogging. EIA is distinguished by the development of urticaria or shock after beginning this physical activity and should be differentiated from cholinergic urticaria or exercise-induced asthma. In about one half of the cases of EIA, the symptoms begin within 2 hours of eating a meal or eating a specific food and, thus are called *food dependent EIA*.²³ Specific foods such as celery, shrimp, oysters, peaches, wheat, and chicken have been reported to be associated with the development of this condition.

Atopic dermatitis is a primary skin condition of childhood whose pathogenesis involves both immunologic and nonimmunologic factors. The eczema rash may be the result of an IgE "late-phase" allergic reaction. The importance of food allergy in atopic dermatitis has been proven using the DB-PCFC technique.²⁴ The foods that are predominantly involved include egg, cow's milk, peanut, wheat, and soy.

In *in vitro* studies, it has been demonstrated that basophils from the patient with active atopic dermatitis will spontaneously release the chemical mediator histamine, providing that these patients are routinely ingesting the foods to which they are allergic.²⁵ This experimental evidence helps to explain how food allergy can play a broad role in the chronic inflammation demonstrated in this type of dermatitis. It has been further shown that when the specific food to which the atopic dermatitis patient is allergic is eliminated from the diet for an extended period of time, this tendency for the blood cells of the atopic dermatitis patient to spontaneously release

nonspecific histamine goes away. Such information supports the view that food allergic patients with atopic dermatitis should be evaluated for the presence of food allergy, so that these foods can be restricted from the diet.

Other than cutaneous reactions such as urticaria and eczema, the next most common manifestation of true food allergy are gastrointestinal symptoms. This includes nausea, vomiting, blood loss, and diarrhea. Probably the most serious reactions occur in young infants who react to infant formula, primarily those containing cow's milk protein. Blood loss due to a colitis is a more frequent problem than is diarrhea.²⁶ These infants improve dramatically when conventional cow's milk-based formula is removed from the diet and replaced by a casein hydrolysate formula. Food allergy related to eosinophilic gastroenteritis may occur in older children and adults.

Respiratory symptoms to food allergy are generally uncommon, except as a manifestation of systemic anaphylaxis. In spite of this fact, when children who have atopic dermatitis and food allergy are challenged with the food to which they are allergic, approximately one third will wheeze.²⁴ A rare pulmonary immunologic reaction to cow's milk occasionally can be found in young infants who aspirate cow's milk-based formula in the newborn period. As a result, a hyperimmune, IgG antibody response occurs directed towards the milk protein sequestered in the lung of the newborn infant.²⁷ When these children are reexposed to milk allergen by mouth, an antigen-antibody interaction occurs with immune complex formation and complement activation, which results in infiltrates in the lung. This condition appears to

be self limited and is reversed when milk protein is taken out of the diet.

INDIVIDUALS WHO ARE SUSPECTED OF DEMONSTRATING FOOD ALLERGY, BUT WHO HAVE SOME OTHER REASON FOR THEIR COMPLAINTS

Problems in infants

Some food intolerances resemble food allergy reactions. Almost one third of complaints that mothers have about foods their infants eat have to do with the feeding of fruit and vegetables.^{4,11} Orange and tomato are frequently associated with irritation and redness around the mouth, which is probably due to the acids in these foods. Fruit juices, because of their high sugar content, are often responsible for loose stools. A full 20% of babies will develop colic, regardless of their diet.²⁸ Although no "allergic reaction" to milk protein has been found to cause infant colic, it has been shown in one controlled study that some babies with this condition have less symptoms after a formula change to either a casein hydrolysate or soy-based infant formula.²⁹

The effect of various components of the diet upon the behavior in children has been a matter of concern for many years. When the theory that food colors and preservatives could adversely affect the behavior of children with the attention deficit syndrome and hyperkinesis was tested experimentally under controlled conditions, only a few such children were found to be adversely affected by the ingestion of a food color mix.³⁰ Colors were found to act like a drug, not an allergen. When the theory of "sugar allergy" or abnor-

mal behavior because of the ingestion of large amounts of refined sugar was closely examined, the amount of sugar was either not found to be important or sugar was found to have a "calming effect" upon children's behavior.³¹

Problems in adults

A rash due to eating strawberries or nasal stuffiness, sneezing, and facial flush due to wine ingestion are most likely due to direct histamine release rather than food allergy.³² Ingestion of foods such as cheese or chocolate, which contain vasoactive amines, may result in a headache. Caffeine-containing beverages are well known to trigger nervousness, headache, or insomnia.

There is little evidence to support the view that food allergy plays a direct cause and effect role in migraine headaches. However, rare patients with migraines have been shown on challenge studies to react to a specific food because of direct histamine or other chemical mediator release.³³ Chewing foods preserved in sulfites will release SO₂ gas that, in turn, when inhaled by sensitive asthmatics, may exacerbate their asthma.³⁴ Although food colors and preservatives have been suggested as causative agents of chronic urticaria, these food additives have been found to be responsible in only a few individuals.³⁴ The ingestion of monosodium glutamate (MSG) may cause the "Chinese restaurant syndrome" (chest or neck muscle tightness, a crawling sensation of the skin, sweating, or headache). This syndrome has nothing to do with allergic reactions.³³ Although physicians have periodically speculated on the role of foods in initiating rheumatoid arthritis-like symptoms, there is little evidence to support these views.^{35,36}

In most cases, individuals who present with generalized somatic complaints supposedly related to food or food additives, rather than allergy-like symptoms, do not have food allergy. Some adults who believe they are allergic to food (but actually are not) may restrict their diet to such a degree as to adversely affect their nutrition. Many of these individuals may have severe psychological problems.³⁷ David Pearson³⁸ has coined a new term for this syndrome: pseudo-food allergy. The spectrum of generalized somatic complaints that individuals who have this syndrome present include fatigue, headaches, "mental fuzziness," malaise, myalgia, arthritis, listlessness, and depression. This constellation of symptoms resembles those reported in the older literature (among children) as the "allergic tension-fatigue syndrome" and in the newer literature (among adults) as the "chronic fatigue syndrome."^{39,40} There is no conclusive evidence that food allergy plays any role as causative factors for the symptoms discussed in any of these three syndromes.⁴¹

Narrowing the field

The practical aspects of diagnosing food allergy involve first taking a good history that includes

- a description of the problem;
- the timing of the onset and the duration of those symptoms in relationship to diet;
- the frequency of occurrence of symptoms, and
- circumstances involved with the food exposure in question.²

Most true food allergies occur in generally allergic individuals. IgE food allergen-specific antibody production will occur once

sensitization has been established. In studies involving children with atopic dermatitis who had food allergy confirmed by DBPCFC, history of the importance of the specific food has turned out to be poorly correlated with the challenge results.²⁴ On the other hand, food allergen epicutaneous, immediate-reacting skin tests or food allergen IgE in vitro tests were found, in these patients, to better predict the likelihood of given specific food involvement.⁸ The value of food allergen IgE skin testing or in vitro measurement of IgE allergen-specific antibodies in screening individuals, at all ages, suspected of food allergy has been verified by other studies.⁴²

In most situations, a negative IgE epicutaneous food skin test (using reliable allergenic material) as well as a comparable negative IgE in vitro food test practically rules out an IgE-mediated food reaction. When an adverse reaction to food, in food allergic individuals, has been verified by DBPCFC, all will have evidence of IgE food allergen-specific antibodies (positive test or in vitro assay). On the other hand, only some individuals who have positive IgE food allergy skin tests or in vitro assay will react clinically when challenged using DBPCFC.⁴² Thus, these IgE-mediated food allergy skin tests, or in vitro assays, can be used to screen out specific foods that are not a problem. These types of tests can also be used to narrow the field to those foods that would be most likely considered in making a food-allergy diagnosis.

The value of any allergy skin test or in vitro test depends upon the reliability of the food allergen used. It is important to recognize, for instance, that all commercially available food extracts are not reliable.⁴³ It is also important to recognize that freshly prepared food extracts may be necessary for reliable skin

testing under some circumstances such as in the case of the OAS.²²

FOOD AND FOOD ADDITIVE CHALLENGES

The only way to be certain about the possible association between a given set of symptoms and exposure to a food or food additive is to challenge the individual. Such a challenge, if positive, under controlled conditions such as the DBPCFC, will establish the true relationship of the patient's symptoms and a specific food or food additives. Such a procedure is an important basic criteria for doing subsequent research studies on patients allergic to food.⁴⁴

A positive food challenge, however, does not establish the mechanism of the adverse reaction. Such a positive challenge may be positive in both food allergy (usually an IgE mechanism) and food intolerances (nonimmunologic reactions).

Food challenges are not usually advocated in clinical situations where the risk of future exposure may be severe or life threatening in nature, such as in the case of systemic anaphylaxis.⁴⁵ Usually in the case where a patient presents with a clear-cut exposure to a food known to be commonly associated with anaphylaxis (eg, peanut), and *in vitro* IgE allergen-specific assay is positive, the *presumptive* diagnosis of food allergy is made and the patient is instructed to stay away from that food. In this situation, it is important to instruct the individual for a subsequent inadvertent exposure to the food that caused the anaphylaxis. Usually, the physician prescribes an epinephrine autoinjector* [*Epi-Pen (0.3 cc 1:1000 aqueous epinephrine) or Epi-Pen Jr (0.15 cc 1:1000 aqueous epinephrine) Center Laboratory, Port Washington, NJ.] to

Table 2. Clinical situations suspected of being caused by food allergy but are not usually related

Infants
Skin irritation due to fruits and vegetables Loose stooling due to fruit juices (sugar) Infant colic
Primary lactose intolerance
Bloating, gas, loose stooling
Asthma exacerbation due to SO₂ inhalation secondary to chewing sulfited foods
Behavior changes in children
Hyperactivity in ADS due to salicylates, color, or preservatives "Sugar" allergy resulting in hyperactivity due to excess refined sugar
Migraine headache
Urticaria due to colors or preservatives
Generalized somatic symptoms
Fatigue, headache, "mental fuzziness," malaise, myalgia, arthralgia, depression, listlessness, arthritis Allergic tension-fatigue syndrome Chronic fatigue syndrome Pseudo-food allergy

be on hand, so that this medication can be used in an emergency, at the first sign of anaphylaxis.

In the case of intermittent symptoms (eg, urticaria bouts with long intervals between), a diary of the events surrounding each episode may be helpful. In some nebulous situations, in which food allergy problems are unlikely (usually with negative food allergy skin tests) and in which the symptoms are mild and certainly not life threatening, a trial on a diet containing foods unlikely to be

associated with allergic reactions may be prescribed for home use followed by home addition of foods to the diet.⁴⁶ It is important to recognize, however, that unsupervised or uncontrolled dietary challenges, at home, could be dangerous.⁴²

If food allergy is suspected, and the group of likely foods can be narrowed through skin testing or *in vitro* tests, the ideal next step is a challenge procedure under controlled conditions. Usually, the first challenge is open or single-blinded in nature, but all positive challenges should be confirmed, if possible, by the DBPCFC procedure. Negative challenge should be substantiated by subsequent regular food intake.

The procedures for food challenges may be found in several recent publications.^{1,47-49} Challenge procedures can also be adopted to the study of food additives.^{50,51} DBPCFC can also be used to convince patients who are not allergic to foods but think they are, that it is safe to eat those foods.³⁷

In a simplified manner, Sampson and Metcalfe¹ advocate the following procedures for the DBPCFC procedure:

- The procedure should be done under controlled conditions, by trained personnel capable of managing anaphylaxis—if the situation occurs. This could be done either in a clinic or a hospital setting depending upon individual circumstances.
- Prior to the challenge procedure, the suspect food should be eliminated from the diet for 10 to 14 days.
- Antihistamines should be terminated for 12 hours prior to the challenge.
- The patient should be in a stable cardiovascular, pulmonary, and metabolic condition on the day of challenge.

- The challenge should be done in a fasting state.
- A graded challenge should be performed, beginning with either the placebo or food dose "unlikely to provoke symptoms" (such as 125 to 500 mg of lyophilized food).
- The food challenge (or placebo) dose should be doubled every 15 to 60 minutes.
- The maximum food challenge dose should be 10 g of lyophilized food.
- Following challenge, the minimum observation period should be 2 hours for IgE mediated reactions and from 4 to 8 hours for food intolerances including GI reactions.
- Subsequent open feeding of foods found negative on challenge should be performed over the following 24 to 48 hours.

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When considering the diagnosis of food allergy, it is important to remember it is more

likely to occur in a child than in an adult. The symptoms usually are typical of other allergic reactions, including urticaria, atopic dermatitis, systemic anaphylaxis, and gastrointestinal symptoms of nausea, vomiting, blood loss, and diarrhea. Many food intolerance reactions can be confused with food allergies. The best way to confirm an adverse reaction to a food is to challenge the individual with that food, under controlled conditions, especially DBPCFC. IgE food antibodies can be detected by immediate-reacting food-skin testing or *in vitro* assay. The absence of these antibodies practically eliminates the possibility of a food-allergy reaction. The presence of these antibodies helps to restrict the foods to which an individual may be allergic. Avoidance is the only treatment for food allergy. However, in cases of food anaphylaxis, subsequent inadvertent food exposure may be impossible to prevent. In these cases, which may be life threatening in nature, physicians are advised to supply the anaphylactic-sensitive food-allergy patient with an epinephrine autoinjector so that epinephrine may be used at the first sign of a subsequent anaphylactic reaction.

REFERENCES

1. Sampson HA, Metcalfe DD. Food allergies. *JAMA*. 1992;268:2840-2844.
2. Anderson JA. *Diagnosis of food allergy, Part I: The physician's perspective in food allergies and adverse reaction*. JE Perkin, ed. Gaithersburg, Md: Aspen Publishers; 1990: 15-30.
3. Anderson JA. The establishment of a common language concerning adverse reactions to foods and food additives. *J Allergy Clin Immunol*. 1986;78:140-144.
4. Bock SA. Prospective appraisal of complaints of adverse reactions to foods in children during the first three years of life. *Pediatrics*. 1987;79:683-688.
5. Jacobsson I, Lindberg TA. A prospective study of cow's milk protein intolerance in Swedish infants. *Acta Paediatr Scand*. 1979;68:853-859.
6. Horst A, Halken S. A prospective study of cow's milk allergy in Danish infants during the first three years of life. *Allergy*. 1990;45:587-596.
7. Anderson JA. Food allergy or sensitivity terminology, physiologic bases and scope of the clinical problem. In: Perkin JE, ed. *Food Allergies and Adverse Reactions*. Gaithersburg, Md: Aspen Publishers; 1990: 1-13.
8. Sampson HA, Albergo R. Comparison of results of skin test, RAST, and double-blind placebo-controlled food challenge in children with atopic dermatitis. *J Allergy Clin Immunol*. 1984;74:26-33.
9. Sampson HA, Scanlon SM. Natural history of food hypersensitivity in children with atopic dermatitis. *J*

- Pediatr.* 1989;115:23-27.
10. Bock SA. The natural history of adverse reactions to foods. *NER Allergy Proc.* 1986;7:504-510.
 11. Foucard T. Developmental aspects of food sensitivity in childhood. *Nutr Rev.* 1984;42:98-104.
 12. Bock SA, Atkins FM. The natural history of peanut allergy. *J Allergy Clin Immunol.* 1989;83:900-904.
 13. Bernhisel-Broadbent J, Sampson HA. Cross-allergenicity in the legume botanical family in children with food hypersensitivity. *J Allergy Clin Immunol.* 1989;83:435-440.
 14. Bernhisel-Broadbent J, Taylor S, Sampson HA. Cross-allergenicity in the legume botanical family in children with food hypersensitivity. II. Laboratory correlates. *J Allergy Clin Immunol.* 1989;84:701-709.
 15. Yunginger JW, Sweeney KG, Sturmer WQ, et al. Fatal food-induced anaphylaxis. *JAMA.* 1988;260:1450-1452.
 16. Sampson HA, Mendelson L, Rosen JP. Fatal and near fatal anaphylactic reactions to foods in children and adolescents. *N Engl J Med.* 1992;327:380-384.
 17. Hepner M, Ownby D, Anderson J, Rowe M, Sears-Ewald D, Brown E. Risk of systemic reactions in patients on beta blocker drugs receiving immunotherapy injections. *J Allergy Clin Immunol.* 1990;86:407-411.
 18. Lockey RF, Benedict LM, Turkeltaub PC, Bukantz SC. Fatalities from immunotherapy (IT) and skin testing (ST). *J Allergy Clin Immunol.* 1987;79:660-677.
 19. Amlot PL, Kemeny DM, Zachary C, et al. Oral allergy syndrome (OAS) symptoms of IgE-mediated hypersensitivity to foods. *Clin Allergy.* 1987;17:33.
 20. Enberg RN, McCullough J, Ownby DR. Antibody responses in watermelon sensitivity. *J Allergy Clin Immunol.* 1988;82:795-800.
 21. Ross B, McCullough J, Ownby DR. Partial cross-reactivity between latex and banana allergens. *J Allergy Clin Immunol.* 1992;90:409-410.
 22. Ortolani C, Ispano M, Pastorello ED, Ansaloni R, Margi GC. Comparison of results of skin prick tests (with fresh foods and commercial food extracts) and RAST in 100 patients with oral allergy syndrome. *J Allergy Clin Immunol.* 1989;83:683-690.
 23. Horan RF, Sheffer AL. Food-dependent exercise-induced anaphylaxis. *Immunol and Allergy Clin No Amer.* 1991;11:757-766.
 24. Sampson HA. Role in the pathogenesis of atopic dermatitis. *J Allergy Clin Immunol.* 1983;71:473-480.
 25. Sampson HA, Broadbent KR, 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.* 1989;321:228-232.
 26. Berezin S, Schwarz SM, Glassman M, Davidian M, Newman LJ. Gastrointestinal milk intolerance of infancy. *Am J Dis Child.* 1989;143:361-362.
 27. Anderson JA, Weiss L, Rebuck JW, Cabal LA, Sweet LC. Hyperreactivity to cow's milk in an infant with LE and tart cell phenomenon. *J Pediatr.* 1974;84:59-67.
 28. Thomas DW, McGilligan K, Eisenberg LD, Lieberman HM, Rissman EM. Infantile colic and type of milk feeding. *Am J Dis Child.* 1987;141:451-453.
 29. Lothe L, Lindberg T, Jakobsson I. Cow's milk formula as a cause of infantile colic: a double-blind study. *Pediatrics.* 1982;70:7-10.
 30. Lipton MA, Mayo JP. Diet and hyperkinesis—An update. *J Am Diet Assoc.* 1983;83:132.
 31. Mahan LK, Chase M, Furukawa CT, et al. Sugar "allergy" and children's behavior. *Ann Allergy.* 1988;61:453-458.
 32. Perkin JE. Adverse reactions to food additives and other food constituents. In: Perkins JE, ed. *Food Allergy and Adverse Reactions.* Gaithersburg, Md: Aspen Publishers; 1990: 129-170.
 33. Weber R, Vaughan TR. Food and migraine headache. *Immunol and Allergy Clin North Am.* 1991;11:831-841.
 34. Simon RA, Stevenson DD. Adverse reactions to food and drug additives. In: Middle E Jr., Reed CE, Ellis EF, Adkinson NF Jr, Yunginger JW, Busse WW, eds. *Allergy, Principles and Practice.* 4th ed. St. Louis, Mo: Mosby; 1993: 1687-1704.
 35. Mandel M, Conte A. The role of allergy in arthritis, rheumatitis, and associated poly-symptomatic cerebroviscero-somatic disorders: a double-blind provocative test study. *Ann Allergy.* 1980;44:51(A).
 36. Felder M, DeBlecount ACE, Wuthrich B. Food allergy in patients with rheumatoid arthritis. *Clin Rheumatol.* 1987; 6:181-184.
 37. Pearson DJ, Rix KJB, Bentley SV. Food allergy: how much is in the mind? *Lancet.* 1983;1:1259-1261.
 38. Pearson D. Food allergy hypersensitivity and intolerance. *J R Coll Physicians London.* 1985;19:154-162.
 39. Crook WG. Nervous-system symptoms, emotional behavior, and learning problems: the allergic tension fatigue syndrome. In: *Your Allergic Child.* New York, NY: Med Coms Press; 1973: 62-63.
 40. Strauss SE, Dale JK, Wright R, et al. Allergy and the chronic fatigue syndrome. *J Allergy Clin Immunol.* 1980: 791-794.
 41. Goldberg BJ, Kaplan MS. Controversial concepts and techniques in the diagnosis and management of food allergy. *Immunol and Allergy Clin North Am.* 1991;11: 863-884.
 42. Bock SA, Sampson HA, Atkins FM, Zeiger RS, Lehrer S, et al. Double-blind placebo-controlled food challenge (DBPCFC) as an office procedure. A manual. *J Allergy Clin Immunol.* 1988;82:986-997.
 43. Sampson HA. Comparative study of commercial food antigen extracts for the diagnosis of food hypersensitivity. *J Allergy Clin Immunol.* 1988;82:718-726.
 44. VanMetre T. Critique of controversial and unproven procedures for the diagnosis and therapy of allergic disorders. *Pediatr Clin North Am.* 1983;30:807-813.
 45. Yunginger JW. Anaphylaxis to foods. *Immunol and Allergy Clin North Am.* 1992;12:543-557.
 46. Anderson JA, Sogen DD, eds. *American Academy of Allergy and Immunology—Committee on Adverse Reactions to Foods and NIAID.* Washington, DC: DHHS; 1984. NIH Publication 84-2442.
 47. Sampson HA. Immunologically mediated food allergy: the importance of food challenge procedures. *Ann Allergy.* 1988;60:262-269.

48. Bock SA. Oral challenge procedures. In: Metcalfe DD, Sampson HA, Simon RA, eds. *Food Allergy Adverse Reactions to Foods and Food Additives*. Boston, Mass: Blackwell Scientific; 1991: 81–95.
49. Bahna SL. Practical considerations in food challenge testing. *Immunol and Allergy Clin North Am*. 1991;11: 843–850.
50. Weber RW, Hoffman M, Raine DA, Nelson HS. Incidence of bronchoconstriction due to aspirin, azo dyes, non-azo dyes and preservatives in a population of perennial asthmatics. *J Allergy Clin Immunol*. 1979;64:32–37.
51. Taylor S, Bush R, Selner J, Nordlee JA, et al. Sensitivity to sulfited foods among sulfite-sensitive subjects with asthma. *J Allergy Clin Immunol*. 1988;83:1159–1167.