

THE JOURNAL OF Allergy AND Clinical Immunology

VOLUME 103

NUMBER 6

Current reviews of allergy and clinical immunology

(Supported by a grant from Astra Pharmaceuticals, Westborough, Mass)

Series editor: Harold S. Nelson, MD

Food allergy. Part 2: Diagnosis and management

Hugh A. Sampson, MD *New York, NY*

Patients with food-induced allergic disorders may be first seen with a variety of symptoms affecting the skin, respiratory tract, gastrointestinal tract, and/or cardiovascular system. The skin and respiratory tract are most often affected by IgE-mediated food-induced allergic reactions, whereas isolated gastrointestinal disorders are most often caused by non-IgE-mediated reactions. When evaluating possible food-induced allergic disorders, it is often useful to categorize disorders into IgE- and non-IgE-mediated syndromes. The initial history and physical examination are essentially identical for IgE- and non-IgE-mediated disorders, but the subsequent evaluation differs substantially. Proper diagnoses often require screening tests for evidence of food-specific IgE and proof of reactivity through elimination diets and oral food challenges. Once properly diagnosed, strict avoidance of the implicated food or foods is the only proven form of treatment. Clinical tolerance to food allergens will develop in many patients over time, and therefore follow-up food challenges are often indicated. However, a number of novel immunomodulatory strategies are in the developmental stage and should provide more definitive treatment for some of these food-induced allergic disorders in the next several years. (*J Allergy Clin Immunol* 1999;103:981-9.)

Key words: Diet diary; double-blind, placebo-controlled, food challenge; skin prick test; RAST; CAP-RAST FEIA; basophil histamine release

In the first segment of this 2-part series on food allergy, a number of disorders affecting the skin, gut, respiratory tree, and cardiovascular system were described. The repertoire of symptoms manifested by these target organs is relatively limited and may be the result of both allergic

Abbreviations used

BHR: Basophil histamine release

DBPCFC: Double-blind, placebo-controlled, food challenge

PST: Prick/puncture skin test

and nonallergic insults. Given the public's increasing awareness of food allergy and their frequent misperception that various ailments are caused by food-induced allergic reactions, the physician must retain some skepticism throughout the evaluation and rely on objective measures to arrive at the final diagnosis. Overdiagnosis of food allergy has led to malnutrition, eating disorders, and psychosocial problems, as well as family disruption, whereas underdiagnosis leaves the patient suffering unnecessarily and may result in growth failure and permanent physical impairments. The following discussion provides an approach that the author has adopted over the years in an attempt to reach the correct diagnosis. Once a diagnosis is achieved, efforts must be directed at teaching the patient and his or her family how to avoid the responsible food or foods and to prepare them for the appropriate medical response in case of an accidental ingestion.

DIAGNOSING ADVERSE FOOD REACTIONS

The diagnostic approach to suspected adverse food reactions begins with the medical history and physical examination. The goal of this exercise is to determine whether the patient is likely to have experienced an adverse reaction to food and whether it is likely to involve an immunologic (allergic) mechanism. If an allergic mechanism is suspected, it is useful to categorize reactions mechanistically (ie, IgE-mediated or non-IgE-mediated) because subsequent laboratory evaluations and oral challenges will differ based on the suspected mechanism. A number of diagnostic schemes have been suggested for both clinical^{1,2} and research³ settings.

From the Jaffe Food Allergy Institute, The Mount Sinai School of Medicine, New York.

Received for publication Mar 11, 1999; accepted for publication Mar 15, 1999.

Reprint requests: Hugh A. Sampson, MD, Department of Pediatrics, Box 1198, The Mount Sinai Medical Center, One Gustave L. Levy Place, New York, New York 10029-6574.

Copyright © 1999 by Mosby, Inc.

0091-6749/99 \$8.00 + 0 1/1/98507

TABLE I. Differential diagnosis of adverse food reactions

Gastrointestinal disorders (vomiting and/or diarrhea)	
Structural abnormalities	
Hiatal hernia	
Pyloric stenosis	
Tracheoesophageal fistula	
Hirschsprung's disease	
Enzyme deficiencies (primary vs secondary)	
Disaccharidase deficiency (lactase, sucrose-isomaltase, glucose-galactose)	
Galactosemia	
Phenylketonuria	
Malignancy	
Other	
Pancreatic insufficiency (cystic fibrosis, Schwachman-Diamond syndrome)	
Gallbladder disease	
Peptic ulcer disease	
Contaminants and additives	
Flavorings and preservatives	
Sodium metabisulfite	
Monosodium glutamate	
Nitrites/nitrates	
Dyes	
Tartrazine, ? other azo dyes	
Toxins	
Bacteria (<i>Clostridium botulinum</i> , <i>Staphylococcus aureus</i>)	
Fungal (aflatoxin, trichothecene, ergot)	
Seafood-associated disorders	
Scrombroid poisoning (tuna, mackerel)	
Ciguatera poisoning (grouper, snapper, barracuda)	
Saxitoxin (shellfish)	
Infectious organisms	
Bacteria (<i>Salmonella</i> , <i>Shigella</i> , <i>Escherichia coli</i> , <i>Yersinia</i> , <i>Campylobacter</i>)	
Parasites (<i>Giardia</i> , <i>Trichinella</i> , <i>Anisakis simplex</i>)	
Virus (hepatitis, rotavirus, enterovirus)	
Mold antigens (?)	
Accidental contaminants	
Heavy metals (mercury, copper)	
Pesticides	
Antibiotics (penicillin)	
Pharmacologic agents	
Caffeine (coffee, soft drinks)	
Theobromine (chocolate, tea)	
Histamine (fish, sauerkraut)	
Tryptamine (tomato, plum)	
Serotonin (banana, tomato)	
Tyramine (cheeses, pickled herring)	
Glycosidal alkaloid solanine (potatoes)	
Alcohol	
Psychologic reactions	

Adapted from Sampson H. *J Allergy Clin Immunol* 1986;78:212-9.

Medical history

The medical history relies on the patient's or his or her parents' recollection of events surrounding the development of symptoms and generally must be considered subjective at best. Loveless⁴ was among the first to point out the frequent inaccuracy of patient history, and May⁵ repeatedly warned of the power of the mind to misperceive the etiology of an ailment. A review of several pub-

TABLE II. Signs and symptoms of food-induced allergic reactions in various target organs

Skin	Urticaria/angioedema Flushing Erythematous pruritic rash Atopic dermatitis
Gastrointestinal tract	Pruritus and/or swelling of the lips, tongue, or oral mucosa Nausea Abdominal cramping or colic Vomiting or reflux Diarrhea
Respiratory tract	Nasal congestion Rhinorrhea Pruritus/sneezing Laryngeal edema, staccato cough, and/or dysphonia Wheezing/repetitive cough
Cardiovascular	Hypotension/shock Dizziness
Other	Cramping back pain (uterine contraction) Feeling of "impending doom"

TABLE III. General guidelines to consider when evaluating potential food-induced allergic reactions

1. Patient history is notoriously inaccurate.
2. Food allergy is most common in young children, especially with atopic dermatitis.
3. Relatively few foods are responsible for the vast majority of allergic reactions.
4. Except in allergic eosinophilic esophagitis or gastroenteritis, it is rare for patients to react to more than 3 foods.
5. When a child with food allergy has "new" or "multiple" food allergies, it is most likely that he or she is ingesting "hidden" sources of common food allergens.
6. Except in gastrointestinal allergies, most food-induced allergic symptoms develop within minutes to a few hours of ingesting the food allergen.
7. True food allergies generally involve "classical" signs and symptoms affecting the skin, gastrointestinal, and/or respiratory systems.
8. Subjective or behavioral symptoms as a sole manifestation of food allergy are very rare.
9. "Adverse reactions" to dyes and additives are rare.

lished series in which double-blind, placebo-controlled, food challenges (DBPCFCs) were used to establish the diagnosis of food allergy reveals that only about 40% of patients' histories of food-induced allergic reactions can be verified.⁶⁻¹³ Consequently, the physician must differentiate between disorders provoked by food hypersensitivity and other etiologies. Table I lists a number of alternatives that should be considered in the differential diagnosis, Table II lists symptoms frequently provoked in various target organs during food-induced allergic reactions, and Table III provides a number of principles that should be kept in mind when assessing the patient history.

With the medical history, the physician is attempting to determine the likelihood that the patient has a food-induced allergic disorder on the basis of the symptoms, the timing of the reaction, and food suspected of causing the

reaction. The following facts should be established: (1) the food suspected of provoking the reaction and the quantity ingested, (2) the length of time between ingestion and the development of symptoms, (3) whether ingesting the suspected food produced similar symptoms on other occasions, (4) whether other factors (eg, exercise or alcohol ingestion) are necessary to induce symptoms, and (5) the length of time since the last reaction to the food occurred. As outlined in part 1 of this series,¹⁴ there are a variety of disorders with well-characterized symptom complexes that have been associated with food-induced allergic reactions. Other symptom complexes (eg, behavioral disorders, learning disabilities, and arthritis) are unlikely to be the result of food-induced allergic mechanisms. In addition, a few foods account for about 80% to 90% of verified reactions (excluding oral allergy syndrome): egg, milk, peanuts, soy, fish, nuts, and wheat in children and peanuts, nuts, fish, and shellfish in adults. In chronic disorders provoked by food allergies (eg, atopic dermatitis, asthma, and allergic eosinophilic gastroenteritis), the medical history has a poor predictive accuracy, but in cases of acute reactions (eg, anaphylaxis and urticaria) after the isolated ingestion of a single food (eg, a peanut butter sandwich), personal history carries a much higher predictive value. Once the symptom complex is established, the search for a food-related etiology should be tempered by a consideration of the prevalence that food allergy is implicated as a causative factor (ie, about 40% in children with moderate-to-severe atopic dermatitis¹⁵ and less than 10% in children with chronic urticaria).¹⁶

In obtaining the history, one must always be cognizant of other foods eaten at the same time, of potentially contaminated foods, and of "hidden ingredients."¹⁷ This often requires a certain degree of detective work. For example, sufficient milk contamination may occur to provoke an allergic reaction when a "boxed" fruit drink is packaged on a "nondedicated" line used to package milk drinks or when tofu desserts are packaged in an ice cream plant. A banana slice lying against a slice of kiwi may contain sufficient protein to initiate an allergic response to kiwi. Hidden sources of food are commonplace in our health-conscious, frenetic society, which is increasingly dependent on processed foods. Milk and soy proteins are often added to increase protein content or enhance flavor, spices (eg, garlic and coriander) and seed derivatives (eg, mustard and sesame seeds) are included for flavoring many prepared foods, peanut and nut products are added to flavor and thicken sauces (eg, spaghetti sauce, gravies, and barbecue sauces) and baked goods, and egg and milk are frequently added to improve the integrity of other food products (eg, egg for meatballs and pasta and milk for canned tuna fish and bologna). Young children are most likely to react to the common foods, and therefore persistent food-induced allergic reactions should prompt a search for contamination or hidden sources of common food allergens. On the other hand, persistent food-induced allergic reactions in adults should prompt a search for reactions to spices or hidden sources of less common food allergens.

Diet diaries

Diet diaries may be used as an adjunct to history, providing a less biased recall of foods eaten and the timing of symptoms provoked. Patients are instructed to keep a chronologic record of all foods ingested over a specified period of time, including items just placed in the mouth, such as teething biscuits or chewing gum, and any symptoms that develop. Most often a review of the diary reveals unknown sources of contamination or hidden food allergens. Occasionally such diaries may suggest relationships between foods ingested and symptoms experienced. Diet diaries have often proved effective in the evaluation of chronic disorders, such as atopic dermatitis and allergic eosinophilic esophagitis or gastroenteritis.

Physical examination

During the physical examination, attention is directed toward the cutaneous, gastrointestinal, and respiratory systems and toward detecting the presence of atopic features, which are more commonly found in patients experiencing IgE-mediated reactions. The general nutritional status of the patient and any physical signs of underlying nonallergic disorders should be noted. Patients appearing wasted or experiencing severe atopic dermatitis or asthma should prompt a more aggressive evaluation.

Laboratory studies

During the history and physical examination, the physician should establish whether the patient's findings implicate a food-induced allergic disorder and whether an IgE-mediated or non-IgE-mediated mechanism is most likely responsible. A number of laboratory studies may be useful in delineating specific foods responsible for IgE-mediated disorders, whereas laboratory studies are of limited value in non-IgE-mediated disorders.

IgE-mediated disorders. When IgE-mediated food-induced allergic reactions are suspected, the prick/puncture skin test (PST) and the RAST provide useful methods for establishing whether the patient possesses IgE antibodies to specific foods. These tests indicate the presence of allergen-specific IgE, but they do not establish the diagnosis of clinical food allergy.

PSTs are used to screen patients with suspected IgE-mediated food allergies.¹⁸ Glycerinated food extracts (1:10 or 1:20 dilution) and appropriate positive (histamine) and negative (saline) controls are applied by the prick or puncture technique. Food allergens eliciting wheals at least 3 mm larger than those induced by the negative control are considered positive; all others are considered negative. Positive PST responses indicate the possible association between the food tested and the patient's reactivity to that specific food. In general, however, the positive predictive accuracies of PSTs are less than 50% compared with DBPCFCs, whereas negative PST responses virtually exclude IgE-mediated reactions (negative predictive accuracy is greater than 95%).^{12,18-21} Therefore negative PST responses are an excellent means of excluding IgE-mediated food allergies, but positive PST responses only "suggest" the presence of sympto-

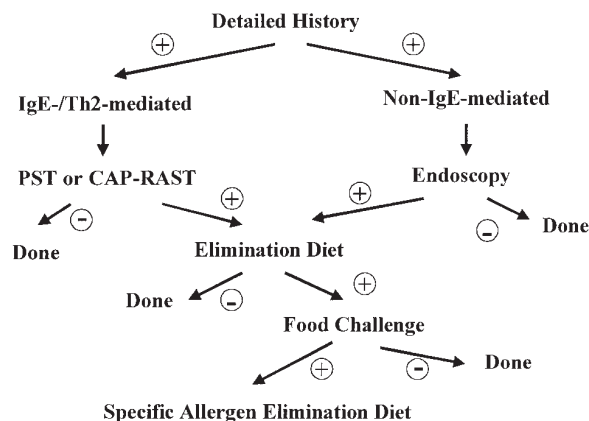


FIG 1. Diagnostic approach to the evaluation of food allergy.

matic allergy. However, a positive PST response may be considered diagnostic in patients who experience a serious systemic anaphylactic reaction after the ingestion of an isolated food.

A number of variables must be considered when interpreting PSTs. First, commercially prepared extracts frequently lack the labile proteins responsible for IgE-mediated sensitivity to many fruits and vegetables (eg, apples, oranges, bananas, pears, melons, potatoes, carrots, and celery).^{22,23} Second, children less than 1 year of age may have IgE-mediated food allergy in the absence of positive PST responses, and infants less than 2 years of age may have smaller wheals, presumably because of lack of antigen-specific IgE and skin reactivity.²⁴ Third, skin testing on surfaces that have been treated frequently with topical steroids (eg, for atopic dermatitis) may provoke smaller wheals than tests performed on untreated surfaces (eg, the back). Fourth, negative PST responses with commercially prepared extracts that contradict convincing histories of food-induced allergic reactions should be repeated with the fresh food before concluding that food allergen-specific IgE is absent.²⁵ Fifth, histamine control wheals less than 5 mm in diameter may indicate the presence of interfering antihistamines or decreased skin reactivity that reduces allergen-specific wheals, resulting in "false-negative" test responses. Finally, long-term, high-dose systemic corticosteroid therapy may reduce allergen-induced wheal size.

Intradermal skin testing is not recommended for the evaluation of food allergy. Studies indicate that intradermal skin tests provide no significant increase in sensitivity or predictive value when compared with DBPCFCs,¹⁸ and fatalities have been reported after intradermal skin testing for foods.²⁶

RASTs and similar in vitro assays, including ELISAs, for identifying food-specific IgE antibodies also may be used to screen patients suspected of IgE-mediated food allergies. These tests are generally considered less sensitive than skin tests, but one study comparing Phadebas RAST with DBPCFCs found PSTs and RASTs to have similar sensitivity and specificity when a RAST score of 3 or greater was considered positive.¹⁹ The RAST may be preferred in the following clinical situations: (1) patients

TABLE IV. CAP System FEIA: 95% positive predictive values

Food	95% PPV (kU _A /L)	Sensitivity (%)	Specificity (%)
Egg	6	72	90
Milk	32	51	98
Peanut	15	73	92
Fish	20	40	99

Adapted from Sampson HA and Ho DG. *J Allergy Clin Immunol* 1997;100:444-451.

PPV, Positive predictive value.

with significant dermatographism, (2) patients with severe skin disease (eg, atopic dermatitis) and limited surface area for testing, (3) patients who have difficulty discontinuing antihistamines, and (4) patients with suspected exquisite sensitivity to certain foods. A recent study making use of the Pharmacia CAP-RAST FEIA in children with atopic dermatitis demonstrated that quantification of food-specific IgE provided increased positive predictive accuracies for egg, milk, peanut, and fish sensitivity compared with PSTs.²⁷ As depicted in Table IV, a patient with a serum food allergen-specific IgE level in excess of the 95% predictive value may be considered reactive, and an oral food challenge would not be warranted. A patient with a food allergen-specific IgE level less than the 95% predictive value may be reactive but would require a food challenge to confirm the diagnosis. In addition, recent data suggests that monitoring the allergen-specific IgE values may be useful in predicting when follow-up challenges are likely to be negative (ie, when patients "outgrow" their food allergy).²⁸ In the initial screening of IgE-mediated food allergy, the author frequently screens for suspected food sensitivities and then obtains food-specific IgE levels to determine the likelihood of clinical reactivity. The initial IgE antibody level can be used as a reference point for monitoring specific sensitivities.

Basophil histamine release (BHR) assays and intestinal mast cell histamine release assays are generally reserved for research settings. One study comparing BHR and intestinal mast cell histamine release assays to PSTs, RASTs, and food challenges in children with suspected food allergy reported that the BHR assay correlated most closely with RAST results.²⁹ However, a second study comparing food allergen-induced BHR assays, PSTs, and DBPCFCs found the BHR assay to be no more predictive of clinical sensitivity than PSTs.³⁰ Monitoring "spontaneous" BHR and generation of "histamine-releasing factor" has been shown to be highly predictive of IgE-mediated food allergy and ongoing ingestion of the responsible food allergen, but it has not proven to be practical in the clinical setting at this time.^{6,31}

Non-IgE-mediated disorders. Although the results of a number of nonspecific laboratory studies may be abnormal in non-IgE-mediated food-induced allergic disorders, no laboratory test has been shown to identify foods responsible for non-IgE-mediated reactions. For example, a white blood cell count may reveal peripheral blood eosinophilia in about 50% of patients with allergic

eosinophilic gastroenteritis,³² or an increase in the neutrophil count with a “left-shift” is frequently found in patients with dietary protein-induced enterocolitis who recently experienced an allergic reaction.³³ Eosinophils may be found in the stools of patients with dietary protein-induced enterocolitis and proctocolitis and allergic eosinophilic gastroenteritis. Food antigen-specific IgG (or IgG₄) antibodies are generally elevated in patients with food allergy affecting the gastrointestinal tract, but their specificities typically reflect the type of foods ingested and are not indicative of specific food-related pathogenesis.³⁴ For most gastrointestinal allergies, histology of biopsy samples often confirms the diagnosis but does not indicate which foods are responsible for the reaction. A diagnostic approach is indicated in Fig. 1

Diagnostic allergen elimination diet

Once certain foods are suspected of being responsible for a food-induced allergic disorder, an elimination diet is initiated in an attempt to support the diagnosis. The success of this procedure requires the exclusion of the correct allergen or allergens in the elimination diet, the ability of the patient to maintain a diet completely free of all forms of the offending allergen, and the absence of other factors that may aggravate symptoms during the period of study (eg, *Staphylococcus aureus* infection of the skin in a patient with atopic dermatitis, a respiratory viral infection in a patient with asthma, and secondary lactase deficiency in an infant with dietary protein-induced enterocolitis syndrome). If these confounding factors are excluded, a lack of response to the elimination diet essentially excludes the foods eliminated as the cause of the allergic disorder.³⁵ However, in some gastrointestinal food allergies (eg, allergic eosinophilic esophagitis and gastroenteritis) multiple food allergies may be responsible for the disorder, and an elemental diet (eg, EleCare, Neocate, or Vivonex plus one food [corn]) may be necessary to establish the diagnosis. In some cases the resolution of symptoms during a diagnostic elimination diet does not definitively identify the responsible food allergen. For example, in a young infant allergic to cow's milk, resolution of symptoms after a trial of soy formula, casein hydrolysate (Alimentum or Nutramigen), or amino acid-derived formula (Neocate or EleCare) is highly suggestive of cow's milk allergy but also could be due to lactose intolerance. If symptoms resolve while a patient is maintaining an elimination diet, some form of food challenge is generally required to confirm the diagnosis of food allergy, especially in chronic disorders such as atopic dermatitis or asthma. With gastrointestinal allergies, endoscopy and biopsy, showing significant resolution of gut pathology after 6 to 8 weeks on an elimination diet will confirm that the implicated food or foods were likely responsible for the disorder.

Oral food challenges

Oral food challenges may be performed openly (ie, patient and physician are aware of the challenge content), single-blind (patient unaware, but physician knows the

content of the challenge), or double-blind and placebo-controlled (neither the patient nor the physician knows the contents of the challenge). The DBPCFC has been considered the “gold standard” for the diagnosis of food allergies⁹ and has been used successfully by many investigators in both children and adults to examine a variety of food-related complaints.^{7,8,10-12,36-39} For research studies, chronic disorders such as atopic dermatitis or asthma, patients who appear to have multiple food allergies, or situations in which patients' perceptions may bias accurate symptom assessment (ie, subjective complaints, such as abdominal pain and myalgias), DBPCFCs are required. The selection of foods to be tested by oral challenge is determined by history, laboratory results, or both. Foods implicated by laboratory tests, but unlikely to provoke food-induced allergic reactions, may be screened with open challenges. Suspected food allergens should be eliminated for 7 to 14 days before challenge in IgE-mediated disorders and up to 12 weeks in some gastrointestinal disorders. Antihistamines should be discontinued long enough to establish a normal positive histamine skin test response, and other medications should be minimized to levels sufficient to prevent breakthrough of acute symptoms. In some asthmatic patients short bursts of corticosteroids may be necessary to ensure adequate pulmonary reserve for testing (FEV₁ >70% of predicted value).

The food challenge is administered in the fasting state, starting with a dose unlikely to provoke symptoms (25 to 500 mg of lyophilized food). Foods may be masked in various infant formulas for young children or in elemental formulas, fruit juices (eg, cranberry, apple, or grape), pureed foods, or meat patties for older children and adults. In suspected IgE-mediated reactions the dose generally may be doubled every 15 to 60 minutes. However, if the patient history describes a more delayed reaction, a longer time interval between doses may be required. Once the patient has tolerated 10 g of lyophilized food blinded in capsules or liquid (equivalent to about one egg white or one 4-oz glass of milk), clinical reactivity is generally ruled out. However, all negative challenges must be confirmed by an open feeding under observation to rule out the rare false-negative challenge response.

In non-IgE-mediated food allergies (eg, dietary protein-induced enterocolitis) allergen challenges may require up to 0.3 to 0.6 g of food/kg of body weight given in 1 or 2 doses.³³ In other non-IgE-mediated disorders (eg, allergic eosinophilic esophagitis or gastroenteritis) the patient may require several feedings over a 1- to 3-day period to elicit symptoms. The length of observation period is dependent on the type of reaction suspected (eg, generally up to 2 hours for IgE-mediated reactions, up to 4 to 8 hours for milk-induced enterocolitis, 24 to 48 hours for food-induced dietary protein-induced proctocolitis, and 3 to 4 days with multiple allergen feeds for allergic eosinophilic gastroenteritis). In most IgE-mediated disorders challenges to new foods may be conducted every 1 to 2 days, whereas with non-IgE-mediated disorders, challenges to new foods often need to be at least 3 to 5 days apart. Results of blinded challenges for objec-

TABLE V. Clinical cross-reactivity among members of plant and animal species

	Food	Cross-reaction	Percentage
Animal	Egg	Chicken meat	<5%*
	Cow milk	Beef/veal	~10%
	Cow milk	Goat milk	~90%
	Beef/veal	Lamb	~50%
	Fish	Other fish species	>50%
Plant	Peanut	Legumes (except lentil)	<10%
	Soybean	Legumes	<5%
	Wheat	Other cereal grains	~25%
	Peanuts	Tree nuts	~35%
	Tree nuts	Other nuts	>50%

*It should be noted that patients frequently have positive PST or RAST results to other members of a plant family or animal species (>80%), but this does not correlate with clinical reactivity. Clinical reactivity is typically very food-allergen specific.

tive signs and symptoms are rarely equivocal but can be made more objective by monitoring a variety of laboratory parameters, such as plasma histamine, pulmonary function tests, and nasal airway resistance. It should be noted, however, that serum tryptase is rarely shown to rise after food-induced allergic reactions.^{40,41}

DBPCFCs are the most efficient means of controlling for the variability of chronic disorders (eg, chronic urticaria and atopic dermatitis), any potential temporal effects, and acute exacerbations caused by the reduction or discontinuation of medications. Other confounding factors are also controlled or at least minimized, and psychogenic factors and patient or observer bias are eliminated. Oral food challenges should be conducted in a clinic or hospital setting, especially if an IgE-mediated reaction or dietary protein-induced enterocolitis are suspected, and only when trained personnel and equipment for treating systemic anaphylaxis are immediately available.^{1,42} Patients with histories of life-threatening anaphylaxis should be challenged only when the causative antigen cannot be conclusively determined by history and laboratory testing or the patient is believed to have "outgrown" his or her sensitivity. The evaluation of many "delayed" reactions (eg, most IgE-negative gastrointestinal allergies) can be conducted safely on an outpatient basis. In cases where patients' symptoms are largely subjective, a cause-and-effect relationship is established only after 3 cross-over trials demonstrate exacerbation of symptoms only during allergen ingestion. The reader is referred elsewhere for further information on food challenges.^{3,9,43}

THERAPY FOR FOOD-INDUCED ALLERGIC DISORDERS

Once the diagnosis of food hypersensitivity is established, the only proven therapy is strict elimination of the offending allergen. Prescribing therapeutic elimination diets should be undertaken with the same consideration given to prescribing medications; both may result in unwanted side effects. Elimination diets may lead to malnutrition and/or eating disorders, especially if they

include a large number of foods and/or are used for extended periods of time.^{44,45} Patients and their families must be taught to scrutinize food labels to detect potential sources of hidden food allergens.⁴⁶ The elimination of a single food can be very difficult. For example, milk may be designated on the food label in several ways, such as casein, caseinate, whey, lactalbumin, nougat, natural flavoring, caramel flavoring, and hydrolyzed protein. In addition, milk protein is typically found in "nondairy" creamers and soy cheeses, in lunch meats and hot dogs, and not uncommonly in soy or rice frozen desserts. Various "high-risk" situations must be avoided, such as eating at buffets, receptions, some restaurants, friends' homes, school cafeterias, and ice cream shops. In certain situations airborne food particles may induce allergic reactions (occasionally fatal) in highly sensitive patients (eg, patients allergic to fish or shellfish in seafood restaurants, patients allergic to eggs next to cooking scrambled eggs, and patients allergic to peanuts in airplanes when passengers are opening peanut snack packs). The complexity of the therapeutic elimination diet for the patient increases with each additional food allergy, leading to increased frustration, lack of compliance, or both.

Clinical reactivity to food allergens is generally very specific, and patients rarely react to more than 1 member of a botanical family^{47,48} or animal species.^{49,50} Table IV depicts general approximations of botanical or species cross-reactivities. Consequently, therapeutic elimination diets should not be based on exclusion of food families but be based on individual foods proven to induce allergic symptoms. In patients in whom multiple food allergies have been identified, it is imperative to enlist the services of a dietitian who is knowledgeable in dealing with food exclusion diets and has experience with patients allergic to foods. In addition, patients should be placed in contact with the Food Allergy Network, an invaluable source of information dealing with food allergies and anaphylaxis (phone, 800-929-4040; on the Web, <http://www.foodallergy.org>).

Symptomatic food allergy is often "lost" over time, as discussed below, except in most cases of peanut, nut, and seafood allergy.^{10,47,51-53} Consequently, food challenges should be repeated at set intervals, or food-specific IgE antibody levels should be monitored to determine when food challenges should be repeated.

Medications such as H₁ and H₂ antihistamines, ketotifen, corticosteroids, and leukotriene inhibitors have been used in an attempt to modify symptoms of food-induced allergic disorders. Antihistamines may partially mask symptoms of oral allergy syndrome⁵⁴ and IgE-mediated skin symptoms, but overall they have minimal efficacy. Oral corticosteroids are generally effective in treating chronic IgE-mediated disorders (eg, atopic dermatitis or asthma) or non-IgE-mediated gastrointestinal disorders (eg, allergic eosinophilic esophagitis or gastroenteritis and dietary-induced enteropathy), but the steroid side-effects are generally unacceptable. Some anecdotal studies have suggested that oral cromolyn sodium is effective

in treating IgE-mediated food allergies and allergic eosinophilic gastroenteritis, but appropriately controlled studies are lacking or fail to show efficacy.⁵⁵

Given the difficulty of avoiding food allergens, it must be assumed that patients will experience accidental ingestion. Approximately 35% to 50% of patients allergic to peanuts will experience an accidental peanut ingestion within a 3- to 4-year period.^{47,56} If they are at risk for severe anaphylaxis (ie, they experienced a previous severe reaction or have asthma), they should be given auto-injectable epinephrine and liquid (or chewable) diphenhydramine and a written emergency plan describing their allergy, potential symptoms, medications to be given, and emergency phone numbers to call. It must be stressed to all caregivers that treatment must be initiated without delay in high-risk patients, and they must be transported to an emergency facility for further evaluation and treatment. About one third of patients with systemic anaphylaxis will experience a biphasic response.⁴⁰

Immunotherapy has been tried for treatment of food-induced allergic disorders. Using "standard" immunotherapy in patients who experienced peanut-induced anaphylaxis, Nelson and coworkers^{57,58} demonstrated that a minority of patients could tolerate larger quantities of peanuts for a prolonged period after rush therapy, but the adverse reaction rate was unacceptable for standard clinical practice. Consequently, alternative strategies to treat patients with food allergy are being explored.

Two such approaches are under investigation. One involves the mutation of IgE-binding epitopes on major peanut proteins, and the other involves the use of peanut protein cDNAs encoded within plasmid vectors. In collaboration with A. W. Burks and G. A. Bannon, 3 major peanut proteins have been identified, sequenced, mapped for IgE-binding epitopes, and cloned for full-length cDNA.⁵⁹⁻⁶² Mutational analyses of the immunodominant epitopes on these 3 proteins revealed that a single amino acid substitution dramatically reduced or eliminated IgE binding to individual epitopes.⁶⁰ T-cell epitope mapping with peanut-specific T-cell lines demonstrated 4 immunodominant T-cell regions on the Ara h 2 molecule, 3 of which mapped to different locations than the immunodominant IgE-binding epitopes. Similar findings have been reported for mutated Bet v 1.⁶³ Because the T cell and some IgG-binding epitopes on these peanut proteins differ from IgE-binding epitopes, the mutated recombinant proteins may be able to "desensitize" patients with peanut allergy in a manner similar to standard immunotherapy without the risk of inducing anaphylactic symptoms. Studies in our peanut-allergic mouse model should enable us to test this hypothesis.

In addition to using mutated recombinant proteins, DNA-based immunization protocols may prove useful for "desensitizing" patients with food allergy, as previously suggested.^{64,65} Studies in our mouse model demonstrated that the type of immune response to pDNA immunization is strain dependent.⁶⁶ These findings suggest that interindividual variation is also likely to occur in human subjects, and further studies will be necessary

before using this form of therapy in allergic patients. This will undoubtedly require further refinements in plasmid-vector constructs and potentially more "patient-friendly" means of vaccine administration (eg, oral delivery).

Oligonucleotide immunostimulatory sequences containing unmethylated palindromic CpG motifs have been shown to possess immunomodulatory properties that decrease airway hyperreactivity, lung eosinophilia, and allergen-specific IgE production when administered during allergen sensitization.⁶⁷ These nucleotide sequences activate antigen-presenting cells (primarily monocytes) to secrete IFN- α , IFN- β , IL-6, IL-12, and IL-18 and natural killer cells to secrete IFN- γ , both of which promote T_{H1} responses. The use of oligonucleotide immunostimulatory sequences as adjuvants with "engineered" recombinant proteins may provide a more effective form of immunotherapy for IgE-mediated food allergies. Other adjuvants that induce deviation of antigen-specific T_{H2} responses to T_{H1} responses also could be used and include antigen-linked cytokines (eg, IL-12 and IL-18)⁶⁸ or heat-killed *Listeria monocytogenes*.⁶⁹

A more global strategy that may be useful in treating IgE-mediated food allergy is the use of humanized anti-IgE antibody therapy. This form of therapy has the advantage of treating multiple food sensitivities regardless of allergen specificity. Early studies of anti-IgE therapy in asthma and allergic rhinitis are showing great promise.⁷⁰⁻⁷² By using "humanized" mAbs specific for the C_ε3 domain of IgE (portion of the IgE Fc region that binds to the Fc_ε receptor), investigators have shown that anti-IgE therapy leads to a dose-dependent decrease in circulating IgE and respiratory symptoms, as well as a decrease in basophil Fc_ε receptor numbers.⁷³ Nevertheless, it remains to be established whether anti-IgE therapy can reduce food-specific IgE antibody levels sufficiently over prolonged periods to prevent food-induced anaphylaxis. Although such therapy is likely to be very expensive over the long term, it is possible that anti-IgE therapy could be used to temporarily decrease a patient's allergic reactivity so that "desensitization" with more traditional allergen immunotherapy can be given without the risk of inducing severe, unwanted side effects.

NATURAL HISTORY OF FOOD HYPERSENSITIVITY

The prevalence of food hypersensitivity is greatest in the first few years of life, affecting about 6% to 8% of infants in the first year.⁷⁴ Most young children "outgrow" (become tolerant of) their food hypersensitivity within a few years, except in most cases of peanut, tree nut, and seafood allergy. In a prospective study of adverse reactions to foods in infants, 80% of confirmed symptoms developed in the first year of life.⁷⁴ In a prospective study of milk hypersensitivity in children through 3 years of age, most children lost their milk allergy by age 3 years: 50% by 1 year of age, 70% by 2 years of age, and 85% by 3 years of age.⁵¹ All children with negative PST responses to milk at 1 year of age lost their sensitivity by their

third birthday, whereas 25% of those with positive PST responses continued to have milk allergy at 3 years of age.⁷⁵ In addition, about 35% of infants with evidence of milk-specific IgE antibodies at 1 year of age had other food allergies by 3 years of age, and 25% had other food allergies at 10 years of age.^{75,76} Because young children with milk (or egg) allergy have about a 25% likelihood of having other food allergies, it is often recommended that major food allergens such as peanuts, tree nuts, fish, and shellfish be avoided until the child is at least 3 years of age. Although this recommendation seems practical, there is no evidence at the present time to demonstrate that this strategy will be successful in preventing future allergy.

Although younger children are more likely to "out-grow" their food allergies,^{77,78} it is apparent that older children^{52,77,79} and adults¹⁰ also lose their reactivity if the responsible food allergen is identified and completely eliminated from the diet. Approximately one third of children and adults will lose their clinical reactivity after 1 to 2 years of allergen avoidance.^{10,52,80,81} PST and RAST results typically remain positive and do not predict which patients will lose their clinical reactivity. The severity of the initial reaction does not appear to correlate with the likelihood of losing clinical reactivity, but the degree of compliance with the allergen avoidance diet and the food responsible for the reaction do affect the outcome. For example, patients with peanut, nut, fish, or shellfish sensitivity rarely lose their clinical reactivity.

Most non-IgE-mediated gastrointestinal food allergies occur in infants and are "outgrown" in the first 2 to 3 years of life. However, allergic eosinophilic gastroenteritis is frequently seen in adults, and the number of cases developing in young children and adolescents is believed to be increasing. Long-term studies have not been completed, and therefore the prognosis of this disorder remains to be determined. Although most cases of dietary protein-induced enteropathy are outgrown, celiac disease is a lifelong sensitivity, and gluten-containing grains must be avoided for life. No formal studies on the natural history of non-IgE-mediated cutaneous or respiratory disorders have been undertaken, but these sensitivities are believed to be longstanding.

CONCLUSION

About 2% of the population is affected by various food-induced allergic disorders. A number of well-characterized food-induced allergic disorders have been delineated. Patients afflicted with these disorders may be accurately diagnosed by using a systematic evaluation, including medical history, laboratory studies, diagnostic elimination diets, and food challenges. Once the appropriate diagnosis has been made, patients must be educated to avoid the specific food allergen or allergens and to treat allergic reactions in case of an accidental ingestion. However, many investigators are working on novel forms of immunotherapy that may provide definitive therapy for these disorders in the not-too-distant future.

REFERENCES

1. Bock SA, Sampson HA, Atkins FM, et al. Double-blind, placebo-controlled food challenge (DBPCFC) as an office procedure: a manual. *J Allergy Clin Immunol* 1988;82:986-97.
2. Sicherer SH. Manifestations of food allergy: evaluation and management. *Am Fam Physician* 1999;59:415-24.
3. Metcalfe D, Sampson H. Workshop on experimental methodology for clinical studies of adverse reactions to foods and food additives. *J Allergy Clin Immunol* 1990;86:421-42.
4. Loveless MH. Allergy for corn and its derivatives: experiments with a masked ingestion test for its diagnosis. *J Allergy* 1950;21:500-9.
5. May CD. Are confusion and controversy about food hypersensitivity really necessary? *J Allergy Clin Immunol* 1985;75:329-33.
6. May CD. Objective clinical and laboratory studies of immediate hypersensitivity reactions to food in asthmatic children. *J Allergy Clin Immunol* 1976;58:500-15.
7. Bernstein M, Day J, Welsh A. Double-blind food challenge in the diagnosis of food sensitivity in the adult. *J Allergy Clin Immunol* 1982;70:205-10.
8. Bock SA, Atkins FM. Patterns of food hypersensitivity during sixteen years of double-blind, placebo-controlled food challenges. *J Pediatr* 1990;117:561-7.
9. Sampson HA. Immunologically mediated food allergy: the importance of food challenge procedures. *Ann Allergy* 1988;60:262-9.
10. Pastorello E, Stocchi L, Pravettoni V, et al. Role of the food elimination diet in adults with food allergy. *J Allergy Clin Immunol* 1989;84:475-83.
11. Burks AW, Mallory SB, Williams LW, Shirrell MA. Atopic dermatitis: clinical relevance of food hypersensitivity reactions. *J Pediatr* 1988;113:447-51.
12. Norgaard A, Bindslev-Jensen C. Egg and milk allergy in adults. *Allergy* 1992;47:503-9.
13. Kivity S, Dunner K, Marian Y. The pattern of food hypersensitivity in patients with onset after 10 years of age. *Clin Exp Allergy* 1994;24:19-22.
14. Sampson HA. Food Allergy. Part 1: Immunopathogenesis and clinical disorders. *J Allergy Clin Immunol* 1999;103:717-28.
15. Eigenmann PA, Sicherer SH, Borkowski TA, Cohen BD, Sampson HA. Prevalence of IgE-mediated food allergy among children with atopic dermatitis. *Pediatrics* 1998;101:e8.
16. Champion R, Roberts S, Carpenter R, Roger J. Urticaria and angioedema: a review of 554 patients. *Br J Dermatol* 1969;81:588-97.
17. Steinman HA. "Hidden" allergens in foods. *J Allergy Clin Immunol* 1996;98:241-50.
18. Bock S, Buckley J, Holst A, May C. Proper use of skin tests with food extracts in diagnosis of food hypersensitivity. *Clin Allergy* 1978;8:559-64.
19. Sampson HA, Albergo R. Comparison of results of skin tests, RAST, and double-blind, placebo-controlled food challenges in children with atopic dermatitis. *J Allergy Clin Immunol* 1984;74:26-33.
20. Sampson HA. Comparative study of commercial food antigen extracts for the diagnosis of food hypersensitivity. *J Allergy Clin Immunol* 1988;82:718-26.
21. Atkins FM, Steinberg SS, Metcalfe DD. Evaluation of immediate adverse reactions to foods in adult patients. I. Correlation of demographic, laboratory, and prick skin test data with response to controlled oral food challenges. *J Allergy Clin Immunol* 1985;75:348-55.
22. Ortolani C, Spano M, Pastorello EA, Ansaloni R, Magri 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;83:683-90.
23. Pastorello E, Ortolani C, Farioli L, et al. Allergenic cross-reactivity among peach, apricot, plum, and cherry in patients with oral allergy syndrome: an in vivo and in vitro study. *J Allergy Clin Immunol* 1994;94:699-707.
24. Menardo J, Bousquet J, Rodiere M, et al. Skin test reactivity in infancy. *J Allergy Clin Immunol* 1985;74:646-51.
25. Rosen J, Selcow J, Mendelson L, Grodofsky M, Factor J, Sampson H. Skin testing with natural foods in patients suspected of having food allergies...is it necessary? *J Allergy Clin Immunol* 1994;93:1068-70.
26. Lockey RF. Adverse reactions associated with skin testing and immunotherapy. *Allergy Proc* 1995;16:293-6.
27. Sampson H, Ho D. Relationship between food-specific IgE concentration and the risk of positive food challenges in children and adolescents. *J Allergy Clin Immunol* 1997;100:444-51.
28. Sicherer SH, Sampson HA. Cow's milk protein-specific IgE concentrations in two age groups of milk-allergic children and in children achieving clinical tolerance. *Clin Exp Allergy* 1999. In press.

29. Nolte H, Schiøtz PO, Kruse A, Stahl Skov P. Comparison of intestinal mast cell and basophil histamine release in children with food allergic reactions. *Allergy* 1989;44:554-65.
30. Sampson H. In vitro diagnosis and mediator assays for food allergies. *Allergy Proc* 1993;14:259-61.
31. 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;321:228-32.
32. Min K-U, Metcalfe D. Eosinophilic gastroenteritis. *Immunol Allergy Clin North Am* 1991;11:799-813.
33. Powell G. Food protein-induced enterocolitis of infancy: differential diagnosis and management. *Comp Ther* 1986;12:28-37.
34. May CD, Remigio L, Feldman J, Bock S, Carr R. A study of serum antibodies to isolated milk proteins and ovalbumin in infants and children. *Clin Allergy* 1977;7:583-95.
35. Kelly KJ, Lazenby AJ, Rowe PC, Yardley JH, Perman JA, Sampson HA. Eosinophilic esophagitis attributed to gastroesophageal reflux: improvement with an amino-acid based formula. *Gastroenterology* 1995;109:1503-12.
36. Sampson HA. The role of food allergy and mediator release in atopic dermatitis. *J Allergy Clin Immunol* 1988;81:635-45.
37. James JM, Eigenmann PA, Eggleston PA, Sampson HA. Airway reactivity changes in food-allergic, asthmatic children undergoing double-blind placebo-controlled food challenges. *Am J Respir Crit Care Med* 1996;153:597-603.
38. Hansen T, Bindslev-Jensen C. Codfish allergy in adults. *Allergy* 1992;47:610-7.
39. Sicherer SH, Eigenmann PA, Sampson HA. Clinical features of food protein-induced enterocolitis syndrome. *J Pediatr* 1998;133:214-9.
40. Sampson HA, Mendelson LM, Rosen JP. Fatal and near-fatal anaphylactic reactions to food in children and adolescents. *N Engl J Med* 1992;327:380-4.
41. Schwartz L, Yunginger J, Miller J, et al. The time course of appearance and disappearance of human mast cell tryptase in the circulation after anaphylaxis. *J Clin Invest* 1989;83:1551-5.
42. Executive Committee AAA&I. Personnel and equipment to treat systemic reactions caused by immunotherapy with allergic extracts. *J Allergy Clin Immunol* 1986;77:271-3.
43. Sampson HA. Diagnosing food allergy. In: Spector SL, editor. *Provocation testing in clinical practice*. New York: Marcel Dekker, Inc; 1995. p. 623-46.
44. Bierman CW, Shapiro GG, Christie DL, et al. Eczema, rickets, and food allergy. *J Allergy Clin Immunol* 1978;61:119-27.
45. David TJ, Waddington E, Stanton RHJ. Nutritional hazards of elimination diets in children with atopic dermatitis. *Arch Dis Child* 1984;59:323-5.
46. Barnes Koerner C, Sampson HA. Diets and nutrition. In: Metcalfe DD, Sampson HA, Simon RA, editors. *Food allergy: adverse reactions to foods and food additives*. Boston: Blackwell Scientific Publications; 1991. p. 332-54.
47. Bock SA, Atkins FM. The natural history of peanut allergy. *J Allergy Clin Immunol* 1989;83:900-4.
48. Jones SM, Sampson HA. The role of allergens in atopic dermatitis. In: Leung DYM, editor. *Atopic dermatitis: from pathogenesis to treatment*. Georgetown (TX): R.G. Landes Company; 1996. p. 41-65.
49. Bernhisel-Broadbent J, Scanlon SM, Sampson HA. Fish hypersensitivity. I. In vitro and oral challenge results in fish-allergic patients. *J Allergy Clin Immunol* 1992;89:730-7.
50. Werfel S, Cooke S, Sampson HA. Clinical reactivity to beef in cow milk allergic children. *J Allergy Clin Immunol* 1997;99:293-300.
51. Host A. Cow's milk protein allergy and intolerance in infancy. *Pediatr Allergy Immunol* 1994;5:5-36.
52. Sampson HA, Scanlon SM. Natural history of food hypersensitivity in children with atopic dermatitis. *J Pediatr* 1989;115:23-7.
53. Hourihane JO'B, Roberts SA, Warner JO. Resolution of peanut allergy: case-control study. *Br Med J* 1998;316:1271-5.
54. Bindslev-Jensen C, Vibits A, Stahl Skov P, Weeke B. Oral allergy syndrome: the effect of astemizole. *Allergy* 1991;46:610-3.
55. Burks AW, Sampson HA. Double-blind placebo-controlled trial of oral cromolyn in children with atopic dermatitis and documented food hypersensitivity. *J Allergy Clin Immunol* 1988;81:417-23.
56. Sicherer SH, Munoz-Furlong A, Burks AW, Sampson HA. Prevalence of peanut and tree nut allergy in the US as determined by a random digit dial telephone survey. *J Allergy Clin Immunol* 1999;103:559-62.
57. Oppenheimer JJ, Nelson HS, Bock SA, Christensen F, Leung DYM. Treatment of peanut allergy with rush immunotherapy. *J Allergy Clin Immunol* 1992;90:256-62.
58. Nelson HS, Lahr J, Rule R, Bock SA, Leung DYM. Treatment of anaphylactic sensitivity to peanuts by immunotherapy with injections of aqueous peanut extract. *J Allergy Clin Immunol* 1997;99:744-51.
59. Eigenmann PA, Burks AW, Bannon GA, Sampson HA. Identification of unique peanut and soy allergens in sera adsorbed with cross-reacting antibodies. *J Allergy Clin Immunol* 1996;98:969-78.
60. Shin D, Compadre CM, Sampson HA, et al. Identification and analysis of the critical amino acids and structures necessary for specific IgE binding to Ara h 1, a major peanut allergen. *J Biol Chem* 1998;273:13753-9.
61. Stanley JS, King N, Burks AW, et al. Identification and mutational analysis of the immunodominant IgE binding epitopes of the major peanut allergen Ara h 2. *Arch Biochem Biophys* 1997;342:244-53.
62. Rabjohn P, Helm R, Stanley J, et al. Molecular cloning and epitope analysis of the peanut allergen, Ara h3. *J Clin Invest* 1999;103:535-42.
63. Ferreira F, Ebner C, Kramer B, et al. Modulation of IgE reactivity of allergens by site-directed mutagenesis: potential use of hypoallergenic variants for immunotherapy. *FASEB J* 1998;12:231-42.
64. Hsu C, Chua K, Tao M, et al. Immunoprophylaxis of allergen-induced immunoglobulin E synthesis and airway hyperresponsiveness in vivo by genetic immunization. *Nature Med* 1996;2:540-4.
65. Spiegelberg H, Orozco ER, Roman M, Raz E. DNA immunization: a novel approach to allergen-specific immunotherapy. *Allergy* 1997;52:964-8.
66. Li XM, Huang CK, Schofield B, et al. Strain-dependent induction of allergic sensitization caused by peanut allergen DNA immunization in mice. *J Immunol* 1999;162:3045-52.
67. Broide D, Schwarze J, Tighe H, et al. Immunostimulatory DNA sequences inhibit IL-5, eosinophilic inflammation, and airway hyperresponsiveness in mice. *J Immunol* 1998;161:7054-62.
68. Kim TS, DeKruyff RH, Rupper R, Maecker HT, Levy S, Umetsu DT. An ovalbumin-IL-12 fusion protein is more effective than ovalbumin plus free recombinant IL-12 in inducing a T helper cell type-dominated immune response and inhibiting antigen-specific IgE production. *J Immunol* 1997;158:4137-44.
69. Yeung VP, Gieni RS, Umetsu DT, DeKruyff RH. Heat-killed *Listeria monocytogenes* as an adjuvant converts established murine Th2-dominated immune responses into Th1-dominated responses. *J Immunol* 1998;161:4146-52.
70. Fahy JV, Fleming E, Wong HH, et al. The effect of an anti-IgE monoclonal antibody on the early- and late-phase responses to allergen inhalation in asthmatic subjects. *Am J Respir Crit Care Med* 1997;155:1828-34.
71. Boulet LP, Chapman KR, Cote J, et al. Inhibitory effects of an anti-IgE antibody E25 on allergen-induced early asthmatic response. 1997;155:1835-40.
72. Casale TB, Bernstein IL, Busse W, et al. Use of anti-IgE humanized monoclonal antibody in ragweed-induced allergic rhinitis. *J Allergy Clin Immunol* 1997;100:100-10.
73. MacGlashan-DWJ, Bochner BS, Adelman DC, et al. Down-regulation of Fc(epsilon)RI expression on human basophils during in vivo treatment of atopic patients with anti-IgE antibody. *J Immunol* 1997;158:1438-45.
74. Bock SA. Prospective appraisal of complaints of adverse reactions to foods in children during the first 3 years of life. *Pediatrics* 1987;79:683-8.
75. Host A, Halken S. A prospective study of cow milk allergy in Danish infants during the first 3 years of life. *Allergy* 1990;45:587-96.
76. Host A, Halken S, Jacobsen HP, Eastmann A, Mortensen S, Mygil S. The natural course of cow's milk protein allergy/intolerance [abstract]. *J Allergy Clin Immunol* 1997;99:S490.
77. Bock SA. The natural history of food sensitivity. *J Allergy Clin Immunol* 1982;69:173-7.
78. Hill DJ, Firer MA, Ball G, Hosking CS. Recovery from milk allergy in early childhood: antibody study. *J Pediatr* 1989;114:761-6.
79. Burks AW, James JM, Hiegel A, et al. Atopic dermatitis and food hypersensitivity reactions. *J Pediatr* 1998;132:132-6.
80. Hill DJ, Firer MA, Shelton MJ, Hosking CS. Manifestations of milk allergy in infancy: clinical and immunological findings. *J Pediatr* 1986;109:270-6.
81. Businco L, Benincori N, Cantani A, et al. Chronic diarrhea due to cow's milk allergy. A 4- to 10-year follow-up study. *Ann Allergy* 1985;55:844-7.