
Diagnosis and Management of Childhood Food Allergy

Scott H. Sicherer, MD

Food allergy appears to be increasing in prevalence and has become a common diagnostic and management issue for the general pediatrician. Studies now a decade old showed that 6% to 8% of children younger than 3 years have a food allergy.¹ Several large, prospective studies on birth cohorts of newborns have shown a prevalence of cow's milk allergy of 2.5%,²⁻⁴ and recent studies indicate that one in 150 children has a peanut allergy.⁵ The pediatrician is first-line in diagnosing these potentially life-threatening allergies. The pediatrician is not only faced with differentiating food allergy from a myriad of other disorders but must also recognize a variety of manifestations of food allergy. For example, cow's milk allergy can manifest as severe reactions, such as anaphylaxis and gastrointestinal symptoms leading to failure to thrive, or may be more subtle with symptoms such as atopic dermatitis, reflux, bloody stools, or even colic. With a working knowledge of the pathophysiology, clinical manifestations, diagnostic methods, treatment strategies, and natural history of food allergic disorders, the pediatrician can successfully treat many of these patients. The goal of this article is to provide the tools needed to rationally approach the diagnosis and management of food allergy in the pediatric office setting and to understand the indications for referral to an allergist or a gastroenterologist.

Pathophysiology

Twenty-eight percent of parents believe that their infant or young child has a food allergy, but when physician-supervised oral food challenges are performed to verify these suspicions, only up to 8% of children are proven to be sensitive.¹ Part of the confusion leading to the overestimate of food allergy arises from the variety of nonallergic adverse reactions to

foods. Food allergy is defined as an adverse immunologic response to food protein.⁶ This is in contrast to toxic reactions exemplified by food poisoning or to a number of disorders that are considered food intolerance. Food intolerance is host specific but does not involve immune mechanisms (Table 1). Although there is overlap in symptoms, particular clinical features provide clues to differentiating these disorders from allergies.

True allergies represent an aberrant immune response to foods. A general understanding of the underlying mechanisms is crucial for formulating a rational approach to the diagnosis of these disorders. The normal immunologic response to the tremendous variety and volume of ingested food protein (not fats or carbohydrates) is active tolerance with the generation of food protein-specific suppressor T cells, IgA and IgG antibodies.⁷ However, in genetically predisposed children, exposure to particular food proteins results in one of two general aberrant responses. In IgE antibody-mediated food allergy, T cells direct B cells to produce food-specific IgE antibodies that arm tissue mast cells (sensitization). Reexposure to the food is detected by these IgE antibodies on the surface of mast cells and results in the release of mediators such as histamine that cause the observed reaction (clinical allergy). This mechanism underlies most of the acute reactions to food proteins (Fig 1). The second mechanism, non-IgE-mediated food allergy, results from the generation of T cells that respond directly to the protein with the elaboration of mediators that direct allergic inflammation (eosinophilic inflammation, increased vascular permeability), leading to a variety of subacute and chronic responses.⁸

Although any food protein can potentially elicit an allergic response, it is peculiar that a number of specific foods account for 85% to 90% of food allergy in children. These foods are cow's milk, egg, soybean, wheat, peanut, nuts from trees (eg, walnut, hazelnut), fish, and shellfish.⁹⁻¹¹ This could be due to the early exposure to these foods at a time of immunologic immaturity, or there may be specific attributes of these proteins that increase their allergenicity. At least some maternally

From the Division of Allergy and Immunology, Mount Sinai Hospital, New York, New York.

Scott H. Sicherer, MD, is Assistant Professor of Pediatrics in the Division of Allergy and Immunology, Department of Pediatrics, Jaffe Food Allergy Institute, Mount Sinai School of Medicine.

Curr Probl Pediatr 2001;31:39-57.

Copyright © 2001 by Mosby, Inc.

0045-9380/2001/35.00 + 0 53/1/112814

doi:10.1067/mps.2001.112814

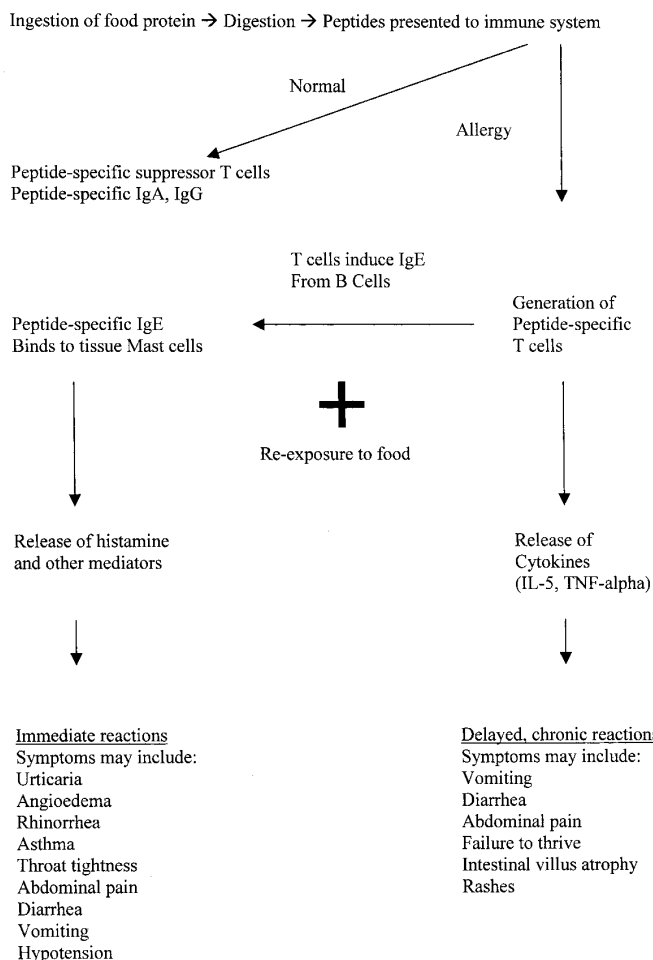


FIG 1. Immunologic mechanisms underlying food hypersensitivity disorders.

ingested food proteins are passed in small amounts in an immunologically intact form in breast milk and can also cause sensitization and clinical reactions. Corn, tomato, strawberry, citrus, chocolate, food dyes, and preservatives are often listed as common allergens, but true significant allergies to these are rare.¹²

Clinical Manifestations

Gastrointestinal Allergy Affecting Infants

A spectrum of non-IgE-mediated allergic reactions confined to the gastrointestinal tract occur in infants (Table 2). The least problematic is dietary protein-induced proctitis/proctocolitis. These infants are otherwise healthy but develop small amounts of blood mixed with mucus in otherwise normal appearing or mucousy stool (in contrast to streaks of blood on the surface of hard stool observed with fissures). The

TABLE 1. Examples of adverse reactions to foods that are not allergies (not immune mediated)

Toxic/Pharmacologic: not dependant on host factors

Bacterial food poisoning
Sudden or delayed abdominal pain, vomiting
Scombrod fish poisoning
Sudden angioedema, hives, abdominal pain, throat tightness from ingestion of histamine-like spoilage products
Caffeine

Jitteriness, increased motor activity

Intolerance: dependant on host factors

Lactase deficiency
Dose-dependant bloating, diarrhea from lactose ingestion
Pancreatic insufficiency
Malabsorption
Gallbladder/liver disease
Malabsorption
Gustatory rhinitis
Rhinorrhea induced by spicy foods

mean age at diagnosis is 2 months.¹³ Histologically, high numbers of eosinophils or eosinophilic “abscesses” in the lamina propria,¹⁴ crypt epithelium, and muscularis mucosa are observed,¹⁵ but biopsy is rarely needed to confirm the diagnosis. The dietary proteins frequently implicated include cow’s milk and soy. The condition also occurs in exclusively breast-fed infants¹⁶⁻¹⁸ because of maternally passed dietary antigens, usually cow’s milk protein. Elimination of the causal protein from the diet of the breast-feeding mother or substitution to a hypoallergenic formula resolves the bleeding within 72 hours.

Dietary (food) protein-induced enteropathy is a more severe disorder characterized by a symptom complex of malabsorption, failure to thrive, diarrhea, emesis, and hypoproteinemia.¹⁹⁻²³ The syndrome may also occur following infectious gastroenteritis in infants.^{21,24} Intestinal biopsy results reveal patchy villous atrophy with cellular infiltrates. Diagnosis is based on the combined findings from endoscopy/biopsy and allergen elimination and challenge. There are reports of similar symptoms with foods other than milk (egg, rice, poultry, seafood).

The most severe form of non-IgE-mediated gastrointestinal food allergy in infants is food protein-induced enterocolitis syndrome (FPIES).²⁵⁻²⁷ This is a symptom complex of profuse vomiting and diarrhea (usually heme positive), leading to failure to thrive, and has the potential of dehydration and shock during chronic ingestion of the causal protein. These infants may also develop acidemia and methemoglobinemia²⁸ and present with a sepsis-like picture including elevated white blood cell counts. Colonic biopsies in symptomatic

TABLE 2. Gastrointestinal food allergic disorders in infants (non-IgE-mediated)*

Disorder	Growth	Emesis	Edema	Diarrhea	Villus injury
Enterocolitis	Failure	Profuse	Mild	Present	Present
Enteropathy	Failure	Mild	Moderate	Present	Present
Proctocolitis	Normal	None	None	Bloody	None

*Other disorders: reflux, occult blood loss, colic, and constipation.

patients reveal crypt abscesses and a diffuse inflammatory cell infiltrate with prominent plasma cells; small bowel biopsies reveal edema, acute inflammation, and mild villous injury.²⁹⁻³³ However, biopsy is not required for diagnosis. Suspicion is raised when the features are present, a search for other causes (infection) is negative, and there is improvement when not ingesting the causal protein. Readministration of the causal protein, following a period of symptom resolution with avoidance, results in symptoms that include a characteristic, 1- to 2-hour delayed onset of profuse vomiting; later onset (~5 hours) of diarrhea; evidence of gastrointestinal inflammation through stool examination for heme and eosinophils; a rise in the peripheral polymorphonuclear leukocyte count of more than 3500 cells/mL; and an occurrence of shock in 20% of patients.^{25-27,34} These attributes of rechallenge form a basis for diagnostic oral challenges that may be cautiously undertaken, if warranted. The most common causal protein is cow's milk, but 50% of patients will also react to soy, and other foods and grains (such as rice) have been implicated.³⁵

Food allergy has been implicated as a potential cause of a number of other disorders in infants. Cow's milk allergy may play a role in a subset of infants (16%-41%) with gastroesophageal reflux disease.³⁶⁻⁴⁰ These prevalence estimates were determined from referral populations of infants with clear-cut, severe symptoms and esophagitis. Allergy was more likely when features of malabsorption, along with pH probes that showed a phasic reduction in pH following feeding, were present, compared with the sharp drops and rapid resolution in pH observed in nonallergic reflux disease. Although a trial excluding cow's milk-based formula from the diet may be considered in the pediatric office setting, improvement may not necessarily be based on an immunologic change. Primary gastroesophageal reflux is always a diagnosis of exclusion, once obstruction, metabolic disorders, and other inflammatory conditions are ruled out. However, many practitioners are reluctant to do the invasive testing required to exclude other conditions in the vomiting infant and resort to formula changes. A

response to a casein hydrolysate may be indicative of cow's milk allergy but may also result from altered gastrointestinal motility caused by other properties of the formula. Nonetheless, such a substitution may be a reasonable therapeutic and diagnostic maneuver.

Ingestion of whole cow's milk by infants younger than 6 months may lead to occult blood loss from the gastrointestinal tract and iron deficiency anemia.⁴¹ The use of infant formulas generally results in resolution of symptoms. Evidence exists that infantile colic is associated with cow's milk allergy in a subset of patients (sometimes on an IgE-mediated basis), but more studies are needed to define the relationship.⁴²⁻⁴⁴ Cow's milk intolerance has also been suggested as a cause of chronic constipation in older infants and toddlers.^{45,46}

Gastrointestinal Allergy Affecting Children

Many of the gastrointestinal food allergies affecting older children are caused by IgE-mediated mechanisms. Sudden onset of gastrointestinal symptoms, such as pain, nausea, and vomiting, developing minutes after ingestion of a particular food and dependent on IgE antibody to the food protein, is termed gastrointestinal anaphylaxis.⁸ The rapidity and consistency of the reaction belies the immunopathophysiology.

The oral allergy syndrome (OAS) is characterized by pruritus and edema of the oral mucosa occurring during and immediately following ingestion of certain fresh fruits and vegetables.⁴⁷ The symptoms rarely progress beyond the mouth. The reaction occurs primarily in patients with allergic sensitivity to pollens and is caused by IgE antibodies directed toward cross-reacting proteins found in the pollens and in the fruits and vegetables.⁴⁸ Patients with birch-pollen hay fever may experience the OAS with the ingestion of peach, apple, plum, and almond, whereas patients with IgE sensitivity to ragweed pollen may experience reactions to melons (eg, watermelon, cantaloupe) and banana. Interestingly, patients are usually able to ingest cooked forms of the foods (eg, apple juice, peach pie) without symptoms because the responsible allergens are usually destroyed in the heating process.

Presumably, the proteins are similarly inactivated by stomach acid, hence preventing systemic reactions. It is interesting to note that the causal proteins, although distributed throughout the fruit, are concentrated in the peel.⁴⁹ This may lead some patients to assume that a topically sprayed pesticide is at fault because ingestion of the fruit after peeling may allay the symptoms. It is crucial to differentiate the symptoms of OAS from the early symptoms of a systemic reaction to food (anaphylaxis), and because this may be impossible in the younger child, a strict avoidance of the foods causing symptoms may be a prudent alternative. A small subset of individuals with OAS may experience progression to systemic reactions.

Allergic eosinophilic gastroenteritis/esophagitis is an IgE-mediated disease in some patients but also has a non-IgE-mediated basis. Patients with the disease have severe reflux, postprandial abdominal pain, vomiting, early satiety, and diarrhea.^{50,51} The presence of inflammation and significant eosinophilic infiltration of the esophagus, stomach, and/or small intestine suggests the diagnosis. The location of the inflammation also determines symptoms (ie, dysphagia from esophageal involvement). Treatment with a strict avoidance diet utilizing an elemental formula is efficacious in some patients,^{51,52} but other treatment modalities have included steroids and fundoplication. Unfortunately, the disorder is associated with multiple food allergies and the results of allergy tests may not be helpful in identifying particular offending foods. Celiac disease may also be considered a food allergy because an immune response to gluten causes the disease. Patients present over a period of months with steatorrhea, flatulence, and weight loss, and biopsy of the jejunal mucosa reveals extensive flattening of villi.⁵³

Skin Manifestations

The skin is a common target organ for allergic responses to food. Acute urticaria is characterized by pruritic, transient, erythematous raised lesions, sometimes accompanied by localized swelling (angioedema). Food allergy accounts for up to 20% of acute urticaria⁵⁴ and is mediated by specific IgE to food protein. Lesions usually occur within minutes and only rarely beyond an hour of ingestion. In young children, urticaria may develop primarily on the face at sites of direct contact with the food and this is termed contact urticaria. Although this may occur in the absence of any systemic symptoms, it is difficult to determine the risk for systemic reactions and avoidance is preferred.

Because only 1.4% of chronic/persistent urticaria (lasting over 6 weeks) is caused by food allergy,⁵⁵ a search for a causative food in the initial evaluation of this illness is not generally warranted.

Atopic dermatitis (AD) usually begins in early infancy and is characterized by a typical distribution, extreme pruritus, and a chronic and relapsing course.⁵⁶ AD is frequently associated with allergic disorders (asthma, allergic rhinitis) and with a family history of allergy.⁵⁷ Although numerous nonallergic factors may exacerbate AD (infection, irritants), there is evidence to suggest that, particularly in children, IgE-mediated food allergy plays a pathogenic role.^{57,58} Non-IgE-mediated food allergy has also been implicated.⁵⁹ The foods most commonly implicated in young children are egg, cow's milk, wheat, soy, and peanut. Clinical studies utilizing double-blind, placebo-controlled, oral food challenges have shown a prevalence rate of food allergy of 37% in young children with moderate to severe AD.^{60,61} The more severe the rash, the more likely food allergy is the identified cause.⁶²

Dermatitis herpetiformis is a chronic papulovesicular skin disorder in which lesions are distributed over the extensor surfaces of the elbows, knees, and buttocks.⁶³ Like celiac disease, the disorder is associated with a specific non-IgE-mediated immune reaction to gluten.

Respiratory Manifestations

The upper respiratory tract can be a target of IgE-mediated food allergy in the form of food-induced allergic rhinitis with nasal congestion, rhinorrhea, sneezing, and pruritus. The prevalence of this illness, even among patients referred to allergy clinics, appears to be lower than 1%.⁶⁴ That is, isolated rhinitis is a rare manifestation of food allergy; however, 25% to 80% of patients with documented IgE-mediated food allergy experience nasal symptoms during oral food challenges that elicit symptoms in other organ systems.⁶⁴ Gustatory rhinitis refers to rhinorrhea caused by spicy foods. This is not an immunologic reaction and is mediated by neurologic mechanisms.⁶⁵

The lower respiratory tract is also affected by food allergy but, like food allergy-induced rhinitis, is rarely an isolated response.⁶⁶ Food-induced asthma is an IgE-mediated response from ingestion of the causative food or from inhalation of vapors released during cooking.^{67,68} The prevalence of asthma related to ingestion of causal food(s), as verified by physician-supervised, oral food challenges, depends on the referral base in

which it is studied: the prevalence is 5.7% among unselected children with asthma,⁶⁹ 11% among children with AD,⁶⁷ and 24% among children whose parents give a history of food-induced wheezing.⁶⁸

An example of a non-IgE-mediated adverse pulmonary response to food is Heiner's syndrome. This uncommon syndrome of infancy is characterized by an immune reaction to cow's milk proteins with precipitating antibodies (IgG) to cow's milk protein resulting in pulmonary infiltrates, pulmonary hemosiderosis, anemia, recurrent pneumonia, and failure to thrive.⁷⁰

Anaphylaxis

Technically, anaphylaxis refers to a manifestation of allergic activation at a site distant from direct contact with the triggering agent; clinically, it refers to a severe multi-organ reaction associated with IgE-mediated hypersensitivity.⁷¹ Reactions can be triggered by minute amounts of causal proteins. Food allergy is the most common cause of outpatient anaphylaxis (34%-52% of cases).⁷²⁻⁷⁴ Symptoms that characterize a severe reaction can include throat tightness, hoarse voice (laryngeal edema), wheezing, loss of consciousness (hypotension, hypoxemia), and a feeling of "impending doom."

Several series have shown that adolescents are at high risk for fatal outcomes, and particular risk factors and features of fatal food-induced anaphylaxis are shown in Table 3.^{75,76} The fact that in about half of the cases there were initial symptoms followed by a period of quiescence and then recurrence of a severe respiratory decompensation one to two hours later (a biphasic response) underscores the importance of continued observation of the patient for at least 4 hours following a reaction.^{75,76} Rarely, anaphylaxis may be prolonged with symptoms lasting for days. The foods most often responsible for food-induced anaphylaxis are peanut, tree nuts, fish, and shellfish.⁷⁵⁻⁷⁷

Food-associated, exercise-induced anaphylaxis occurs in 2 forms.⁷⁸ Anaphylaxis may occur when exercise follows the ingestion of a particular food to which IgE-mediated sensitivity is usually demonstrable (eg, celery or wheat) or, less commonly, after the ingestion of any food. Ingestion of the incriminated food, or exercise in isolation, does not provoke symptoms.

Diagnosis

General Considerations

An evaluation for food allergy is warranted in patients who experience the common clinical mani-

TABLE 3. Features of fatal food-induced anaphylaxis

High-risk group

Adolescent
Underlying asthma
Known allergy to peanut, tree nut, or seafood

Features of fatal episode

Delay in treatment
Biphasic response
Absence of skin symptoms

festations of food allergy or syndromic associations as described previously. The initial evaluation, beginning with a thorough history and physical examination, must consider a broad differential diagnosis, including metabolic disorders, anatomic abnormalities, malignancy, pancreatic insufficiency, and nonimmunologic adverse reactions to foods, as well as many other disorders that could lead to similar symptoms. Allergic reactions to substances other than foods (eg, animal dander, molds, dust) must also be considered. Once food allergy is identified as a likely cause of symptoms, confirmation of the diagnosis and identification of the implicated food(s) can proceed.

A general scheme for the diagnosis of food allergy is given in Fig 2. The history is truly paramount and the aim is to identify the likelihood of food allergy, the potential mechanism of the disorder (IgE or non-IgE-mediated), and the potential causal foods. These initial determinations will guide the selection of specific diagnostic tests and treatment modalities. One may first expect that acute, IgE-mediated reactions are relatively simple to diagnose; however, a number of nuances must be considered. Children ingest food frequently throughout the day so virtually any symptoms attributable to allergy may occur proximate to an ingestion. Of course, questions must focus on the timing from ingestion to symptoms for acute reactions and the amount ingested but must also focus on consistency of reactions. It is unlikely that a previously tolerated food would trigger a reaction compared with a food that is not frequently encountered. In a child with an established allergy to particular food(s) who experiences subsequent reactions despite avoidance, occult ingestion of the previously identified causal protein is more likely than occurrence of a new allergy. The physician and family may need to undertake considerable investigation into specific ingredients when a prepared food or restaurant meal triggered a reaction, and no assumptions should be made (eg, an almond bakery cookie may have contained peanut, processed food may

HISTORY AND PHYSICAL EXAMINATION

Consider alternative causes, consider acute or chronic reactions, decide upon likely underlying pathophysiology



PRICK SKIN TEST or LABORATORY TESTS

RAST selected to confirm non-IgE mediated allergy or to identify possible causal foods in IgE-mediated allergy, consider ancillary tests as needed (endoscopy, heme-occult test, etc.)



ELIMINATION OF SUSPECT FOOD

May represent treatment if specific causal food(s) identified or formula changed in infant, otherwise may represent a diagnostic trial to observe for amelioration of chronic symptoms



FOOD CHALLENGES

Physician-supervised challenges if multiple food were eliminated during diagnostic trials, or if suspected foods not yet confirmed by history and test results.



EDUCATION ABOUT AVOIDANCE AND EMERGENCY PROCEDURES

As indicated for the type of allergy and age of patient.



PERIODIC RE-ASSESSMENT FOR DEVELOPMENT OF TOLERANCE

Yearly for allergy to egg, milk, wheat and soy in young children, less frequently for other allergens.

FIG 2. A general scheme for the diagnosis of food allergy (see text for details).

have been in contact with an unlabeled contaminant in the production line).

When dealing with chronic disorders that may be associated with multiple food allergies (eg, atopic dermatitis or eosinophilic esophagitis), the family's suspicions concerning particular foods are notoriously inaccurate. Diet records and symptom diaries may be helpful but are rarely diagnostic. In some cases, confirmation of a diagnosis requires invasive testing, such as endoscopy for potential eosinophilic gastroenteritis or enteropathy; however, in most cases, the diagnosis of food allergy rests on determination of food-specific IgE antibodies, results of elimination diets, and responses to oral food challenges.⁷⁹ In many cases, evaluation will require the assistance of an allergist familiar with these methodologies.

Diagnostic Tests for IgE Antibody

The primary in vitro test used for guidance in the diagnosis of food allergy is determination of the specific IgE antibody (not total IgE) directed toward the food protein

in question. Allergists use prick skin tests (scratch tests) for this purpose. While the patient is not taking antihistamines, a device such as a bifurcated needle, lancet, or tip of a small gauge needle is used to puncture the skin through a glycerinated extract of a food commercially available for this purpose. This relatively painless procedure allows the protein in question to interact with the food-specific IgE antibody on the surface of skin mast cells. If the antibody is present, mast cells will release mediators leading to immediate, localized angioedema and reflex vasodilation resulting in a typical wheal and flare. The patient must have avoided antihistamines for 5 half-lives of the particular antihistamine before testing. Appropriate positive (histamine) and negative (saline-glycerine) controls are also placed; the former are used to establish that the response is not blocked and the latter to determine whether there is a dermatographism, a nonspecific wheal and flare response to local skin trauma. There is no age limit for skin testing: even infants can be tested.

Allergists compare the skin response to the specific food with the positive and negative controls and report

TABLE 4. Features of prick skin tests and RASTs

	Prick skin test	RAST
Sensitivity	Usually higher	—
Speed of result	10 minutes	Days
Availability	Allergist	Primary care pediatrician
Affected by drugs	Yes	No (may use antihistamines)
Affected by skin disease	Yes, if widespread	No
Cost	~1/4 to 1/10 of RAST	May be high if multiple tests
Negative test reliable	Yes	Yes
Positive test equates to clinical reactivity	No	No

the results in one of a variety of reporting schemes (usually on a scale of 1 to 5) to reflect relative sizes of the response. The protein in commercial extracts of some fruits and vegetables are prone to degradation, so fresh extracts of these foods are more reliable and may be used by the allergist.⁸⁰ For food allergy, a positive response is generally defined as a mean wheal diameter of 3 mm or greater after subtraction of the saline control.⁸¹ Intradermal allergy skin tests with food extracts give an unacceptably high false-positive rate and can elicit systemic reactions (almost not an issue for prick tests) and should not be used.⁸²

Maintenance of extracts and performance and interpretation of prick skin tests are beyond the diagnostic armamentarium of the primary care pediatrician. However, the pediatrician has available the option of determining the presence and concentration of food-specific IgE antibody through a serum test, the radioallergosorbent test (RAST). The methodology of this test involves binding the protein in question to a solid matrix (paper or gel) and exposing this substrate to the patient's serum. The IgE antibody, specific for the bound protein, binds to the protein matrix, and a second labeled antibody is used to detect the food specific IgE antibody. Tests are now available for a wide variety of foods. There are a variety of manufacturers and manners of reporting results: classes (class 1 to 5 or 6), counts, percent, or standard units per liter. Increasing amounts of specific antibody will give higher measures but, despite what some manufacturers may indicate, there is no uniform point at which the results indicate a true or severe allergy to the food. Table 4 compares the features of prick skin tests and RASTs. The cost of performing a modest number of RASTs can exceed the cost of an allergy referral that includes skin tests.

Both the prick skin tests and RASTs merely show the presence of IgE antibody to the food. That is, they reflect sensitization, not necessarily clinical reactivity,

so they cannot be used in isolation to diagnose food allergy. Further, the RASTs are less sensitive than prick skin tests and may sometimes "miss" sensitization (there can be RAST negative, prick skin test positive individuals with severe reactions). The tests are most valuable when they report negative results because the high sensitivity makes them perfect for ruling out IgE-mediated reactions to the food tested.^{82,83} Unfortunately, a positive test result is associated with true clinical reactions only about 50% of the time.^{82,83} In fact, the test results will also remain positive even after clinical reactivity has resolved.

How can the pediatrician best utilize the RAST in the office setting? The most valuable use is to confirm an acute reaction that appears by history to be IgE mediated. For example, hives after ingestion of a peanut-containing cookie would be expected to be associated with a positive test result. If the test results are negative, alternative diagnoses (a different food or nonfood trigger) would be considered more likely and referral to an allergist indicated. If there was ingestion of a mixture of several potential offenders, the RAST may assist in determining which food was causal. Because IgE-mediated allergies can be long-lived and severe, it is essential to confirm that the correct food has been identified. Because of the high sensitivity, a negative RAST result is useful in confirming that a reaction is not mediated by IgE antibody when a non-IgE-mediated mechanism is already suspected. This can be especially important when symptoms overlap a subacute and chronic time course.

The limitations of the tests must be fully appreciated. The primary confusion arises from the high false-positive rate, especially in highly atopic children. Ordering "panels" of food allergy tests can be disastrous when one is then faced with multiple false-positive results and the child is falsely labeled as "allergic to everything." Tests should only be performed based on potential triggers from the history or

a priori reasoning about common causal foods in particular disorders. There are a number of other nuances in interpreting these tests. The size of a skin test reaction or level of RAST does not reflect severity of reactions. Thus, a person who is "RAST class 5, skin test 4+" to peanut may have a milder reaction than someone who is "RAST class 2, skin test 2+." In fact, these test results might be found in a person who eats peanuts without any reaction! To further complicate matters, some of the test results may be positive because there are clinically irrelevant, cross-reacting proteins among foods. For example, most people with peanut (a legume) allergy will also have a positive test result to soybean, peas, and other legumes,⁸⁴ but most can ingest these foods without a clinical reaction.^{85,86} Grass pollen-allergic individuals may have positive test results to ingested grains for similar reasons. Lastly, false-negative results do occur, so if unexpected results are seen it is important to repeat the test and/or refer.

The development of more specific and predictive tests is an area being aggressively researched. The level of specific IgE antibody measured by using a particular method of RAST test (CAP-RAST FEIA or UniCap [Pharmacia, Uppsala, Sweden], reported in arbitrary units called kU_A/L) was reported to be useful in determining the chance of true reactivity to a few foods in children with AD at a mean age of 5 years.⁸⁷ For example, IgE antibody levels of more than 6 kU_A/L to egg, over 32 kU_A/L to milk, over 15 kU_A/L to peanut, and over 20 kU_A/L to codfish were 95% predictive for producing a reaction and would indicate that the food should be avoided. Because the study population was highly atopic, these positive predictive cut-off values are generous and may give a margin of safety when applied to a less selected group. Unfortunately, lower values, unless virtually undetectable, may still indicate a potential for having an allergic reaction. In using these values, it must be emphasized that such cut-off numbers are not determined, as yet, for any other foods and that these numbers only apply to AD in this age group of children. It would be expected that the predictive cut-off values would be lower in children with acute reactions without eczema or in younger children. Also, values below these levels in these children may still be associated with clinical reactions (even anaphylaxis). It is worth pointing out that the predictive values were different for different foods and that the blanket statements made by various manufacturers concerning

positives ("class 2 and above") are not necessarily clinically relevant.

In summary, tests for IgE antibody are an adjunct in the diagnosis of food allergy but are not, in themselves, proof of clinical reactivity. There are a host of tests that have been touted to be useful in the diagnosis of food allergy but have never been shown to be useful in blinded studies. These include measurement of IgG₄ antibody, provocation-neutralization (drops placed under the tongue or injected to diagnose and treat various symptoms), cytotoxicity testing (cell death observed subjectively on a glass slide containing foods), and applied kinesiology (muscle strength testing), among other unproved methods.⁸⁸

Elimination Diets

In the case of a patient who exhibits chronic symptoms consistent with a food allergy, elimination of potentially causal food protein(s) with resolution of symptoms provides presumptive evidence of causality. Conversely, nonresolution of symptoms may reflect that the causal protein has yet to be eliminated, a new protein was introduced to which the child is sensitive, or the symptoms were not related to food allergy. For the gastrointestinal manifestations of food allergy in infants, elimination usually involves a simple formula switch. The process is more complicated in older children.⁷⁹ There are 3 types of elimination diets: elimination of one or several foods suspected to be causing symptoms, elimination of all but a defined group of "allowed" foods (oligoantigenic diet), and an elemental diet consisting of a hydrolyzed formula or an amino acid-based formula.

The type of elimination diet selected will depend on the clinical scenario being evaluated, a priori reasoning concerning frequent offenders in particular disorders (eg, egg, cow's milk, wheat, and soy in infants with AD), and the results of tests for IgE antibody. The first type of diet involves the elimination of one or several suspect foods. If symptoms persist, the eliminated food(s) is (are) excluded as a cause of symptoms. The length of trial depends on the type of symptoms, but 1 to 6 weeks is usually the range required.

The second type of elimination diet consists of eliminating a large number of foods suspected to cause a chronic problem (usually including those that are common causes of food-allergic reactions as described previously) and giving a list of allowed foods. This oligoantigenic diet is useful for evaluation of chronic disorders when a larger number of foods are suspect-

ed. This may be the case, for example, with severe AD. An example of such a diet may be one that allows lamb, rice (all forms), cooked apple, broccoli, asparagus, spinach, lettuce, sweet potato, salt, sugar, vinegar, and olive oil. Individualization for this type of elimination diet is almost always needed. The advantage of this diet is that a nutritionally balanced, palatable diet is maintained while most of the potentially causal foods are removed. The primary disadvantage is that, if symptoms persist, the cause could still be attributed to foods remaining in the diet.

The third type of elimination diet is an elemental diet in which calories are obtained from a hydrolyzed formula or from an amino acid-based formula. A variation of this diet includes a few foods likely to be tolerated (but, again, this adds the possibility that persistent symptoms could still be attributed to foods remaining in the diet). This diet is extremely difficult to maintain in patients beyond infancy. In extreme cases, nasogastric feeding of an amino acid-based formula can be achieved, although some patients can tolerate the taste of these formulas with the use of flavoring agents provided by the manufacturers. This diet may be required when the diets mentioned previously fail to resolve symptoms but suspicion for food-related illness remains high. It is also required in disorders associated with multiple food allergies such as allergic eosinophilic gastroenteritis (AEG). With AEG, prolonged elimination of 3 to 6 weeks is typically needed to achieve resolution of symptoms.⁵²

Except for infants switched to an alternative formula or children undergoing elimination of just a few foods, these diets are very tricky to manage and require the expert advice of allergists and dietitians who can ensure nutritional adequacy, accurate avoidance, and interpretation of the results. For breast-fed infants, maternal dietary elimination would be required. When a food to which IgE antibodies has been demonstrated is removed from the diet during a chronic disorder, it is possible that reintroduction could result in more acute, severe reactions. It is clear that these more complicated scenarios require referral.

Oral Food Challenges

Oral food challenges are performed by feeding the patient gradually increasing amounts of the suspected food under physician observation and are usually undertaken by allergists.⁷⁹ Allergists undertake oral food challenges either by performing "open" feedings or by blinding through hiding the food in a carrier food

and using placebo challenges to reduce the risk of bias in the interpretation of results. The least biased manner for performing these tests is double-blind and placebo-controlled, which is considered the gold standard for diagnosing food allergy. The underlying pathophysiology is not an issue in oral challenges and the methodology can be applied to any suspected adverse response to foods, including suspected behavioral changes and reactions to food dyes/preservatives.

There are several settings in which physician-supervised oral food challenges are required for diagnosis of food-allergic disease. In general, when several foods are under consideration as a cause of symptoms, test results for specific IgE are positive, and elimination resulted in resolution of symptoms, then oral challenge testing for each food eliminated would be indicated to allow expansion of the diet. For acute anaphylactic-type reactions without evidence of food-specific IgE for a food highly suspected to have caused a significant reaction, a physician-supervised challenge would be indicated to safely reintroduce the food (in case of a false-negative skin test/RAST). If suspicion concerning particular food(s) remains high despite elimination without resolution of symptoms, challenge(s) may be required. If one is dealing with a non-IgE-mediated reaction, oral challenges may be the only means of diagnosis. Oral challenges are also an integral part of following patients likely to lose their clinical reactivity to the food in question.

There are settings in which oral challenges may be optional or contraindicated. Severe anaphylaxis to an isolated ingestion, with a positive test result for specific IgE antibody to the causal food, is one clear example of a relative contraindication for oral challenge because this scenario defines confirmation of a convincing history and elimination is undertaken as treatment. If the food being eliminated is not a major part of the diet (eg, kiwi), then challenge is not usually warranted. If several members of a food family are being eliminated, but the food family is not a major part of the diet (eg, tree nuts), these same rules may apply.

Pediatricians should feel comfortable in performing oral food challenges, even blinded challenges, in the office setting in a select set of circumstances when the symptoms of a reaction were not severe and there is no evidence of IgE antibody. For example, introduction of cow's milk to a child with a history of isolated proctocolitis or of a food thought by the family to result in behavioral changes or mild gastrointestinal symptoms

TABLE 5. Technique for administration of self-injectable epinephrine
Epi-Pen/Epi-Pen Jr

Store at room temperature, monitor for expiration date
Remove gray safety cap from back end of device
Press narrow end firmly into lateral thigh (arrows point in this direction)
Act of pressing against leg will activate spring-loaded needle
May go through thin clothing, avoid seams of clothing
Hold in place (do not "punch" and pull back)
Wait about 10 seconds (for medication to pass into muscle)
Remove device from leg
Needle should be exposed if successful

Ana-Kit

Remove cap from needle
Press plunger till stops with needle pointing up to expel air/extra epinephrine
Turn plunger 1/4 turn to the right
Inject straight into lateral thigh (intramuscular)
Press plunger until it stops (injects 0.3 mg for weight over 45 lbs [20 kg])
(alternatively, follow 0.1 mL gradations on barrel to individualize pediatric dose)
Remove from thigh
2nd dose, if needed: Turn plunger 1/4 turn to the right
Inject straight into lateral thigh
Press plunger (press to stop gives 0.3 mg)
Remove from thigh

can be performed. Conversely, oral food challenge for enterocolitis syndrome, although not an IgE-mediated disorder, can result in severe, delayed reactions and these patients should be referred for challenge.

Treatment

Medications

In terms of acute reactions, patients calling from the field with more than minimal symptoms should be directed to emergency services. If a patient arrives in the office with symptoms of anaphylaxis, a prompt assessment is needed. For patients presenting with mild symptoms of an acute allergic reaction, antihistamines may be the only required medication to reduce itching/rash caused by the release of histamine. However, for patients experiencing more significant symptoms of anaphylaxis, with respiratory and/or cardiovascular symptoms, additional therapies are required.⁷¹ A complete review of the therapeutic armamentarium available to the physician for the treatment of the patient in extremis is beyond the scope of this review. The initial assessment of the patient suspected of acute anaphylaxis includes evaluation of the airway, breathing, and circulation. Emergency care includes the rapid administration of epinephrine and antihistamines with consideration for administering corticosteroids, oxygen, intravenous fluids, inhaled bronchodilators, and med-

ications to support blood pressure and to stabilize the patient for transport for advanced care.

Epinephrine is the drug of choice for treatment of anaphylaxis. Intramuscular injection allows for more immediate and efficient absorption compared with the subcutaneous route.⁸⁹ The dose of 0.01 mL/kg of 1:1000 dilution of aqueous epinephrine (maximum dose, 0.3-0.5 mL, 0.3-0.5 mg) should be delivered promptly. Intravenous epinephrine carries the risk of dysrhythmias and should be reserved for refractory hypotension. H₁ antihistamines such as diphenhydramine may be given orally, intramuscularly, or by slow intravenous infusion. The use of adjunctive H₂ antihistamines (cimetidine) may increase effectiveness. Oral prednisone or intravenous or intramuscular methylprednisolone may be given to modulate the late-phase responses in moderate to severe reactions. Aerosolized beta-agonists may be required as supplemental therapy for wheezing. Hypotension is treated with large volumes of crystalloid and vasopressors, as needed. As mentioned previously, severe reactions may occur even after a period of clinical improvement, so prolonged observation (> 4 hours) is needed even if symptoms have resolved.

Because the prompt administration of epinephrine is crucial for the treatment of severe allergic reactions, children at risk for these reactions should have self-administered epinephrine available at all times. Candidates for having this medication include children with previous severe reactions, allergy to foods commonly causing severe reactions (peanuts, tree nuts, seafood), and children with food allergy and underlying asthma. Premeasured doses of epinephrine are available by prescription in the form of Epi-Pen (Dey, Napa, Calif) and Ana-Kit (Bayer Corp, Spokane, Wash). The Epi-Pen is a disposable, single-dose, drug delivery system with a spring-activated, concealed needle. It is available in 2 doses: Epi-Pen 0.3 mg for older children and adults and Epi-Pen Jr 0.15 mg for children up to 45 lbs. The Ana-Kit package includes antihistamines and a prefilled syringe with 2 doses (0.3 mg each) of epinephrine. Indications for administering the medication generally include signs of respiratory or cardiovascular allergic symptoms following a known or possible exposure, but this must be individualized for particular patients who may deserve, based on prior history of severe reactions, treatment even for minimal or no symptoms following a known ingestion of causal food.

Proper technique among patients using devices for self-administered epinephrine is lacking.^{90,91} Thus, it

TABLE 6. Pitfalls in avoiding particular food proteins

Pitfall	Examples
Nonstandard terms on food labels	Various terms indicating particular food proteins such as casein (milk), whey (milk), ovalbumin (egg)
Ambiguous terms on food labels	"Natural flavoring" may indicate cow's milk or other allergens, "spices" may indicate garlic or other allergens
Religious labels	"Pareve" may indicate nondairy but does not guarantee absence of milk protein
Cross-contamination	In processing lines (eg, milk protein found in juice boxes), in the home setting (shared utensils), or in restaurants
Nonfood items	Fish food has fish protein, some shampoos may have nut oils
Ingredient switching	Large size of a product may have different ingredients than a small size, despite similar packaging design
Hidden ingredients	Egg whites to make a pretzel shiny, peanut butter to seal the end of egg rolls, peanut butter to thicken sauces

is absolutely essential that prescribing physicians periodically review with patients the indications for, and technique of, administering the medications from these devices (Table 5). Patients must be instructed that after the administration of these medications, prompt transportation (ie, ambulance) to an emergency facility should be sought because recurrence of symptoms can occur. After emergency care has been provided, the family must be reminded to refill prescriptions for the expended devices. Lastly, patients should be provided with information for obtaining medical emergency bracelets identifying their allergy.

Diet

Dietary management of food allergy in infants is relatively straightforward for formula-fed infants. At least 86% of young children with IgE-mediated cow's milk allergy will tolerate soy,⁹² so for these disorders, evaluation for soy allergy and use of soy formula should be considered. However, approximately 50% of infants with non-IgE-mediated reactions will react to soy,^{25,34,93} and in this case, substitution of an extensively hydrolyzed formula should be considered. A small percentage of children (1%-5%) may react to the residual protein in these formulas, necessitating treatment with an amino acid-based formula.^{94,95} For the breast-fed infant, maternal dietary restriction is advised, but the mother may require the aid of a dietitian for instruction and avoidance of malnutrition. Maternally ingested protein persists in the breast milk for several days following ingestion.

Dietary avoidance is more complex in the older child, especially with multiple food allergies. The elimination of even a single dietary food protein is not a simple task. Table 6 lists a variety of possible pitfalls in dietary management of food allergy. A primary issue in avoidance is the ambiguity of food labeling practices. In a cow's milk-free diet, for example, patients must be instructed not only to avoid all cow's milk products but

also to read ingredient labels for key words that may indicate the presence of cow's milk protein. Terms such as casein, whey, lactalbumin, caramel color, "natural flavoring," and nougat may, for example, signify the presence of cow's milk protein. In many cases, the allergic individual must query companies for further product information, although product labeling is improving. Patients and parents must also be made aware that the food protein, as opposed to sugar or fat, is the ingredient being eliminated. For example, lactose-free cow's milk contains cow's milk protein and many egg substitutes contain chicken egg proteins. Conversely, peanut oil and soy oil do not generally contain the food protein, unless the processing method is one in which the protein is not completely eliminated (as with cold-pressed or extruded oil). The Food Allergy Network (800-929-4040; www.foodallergy.org) assists families and physicians in the difficult task of eliminating the allergenic foods. When reactions are severe or multiple foods are eliminated from the diet, it is prudent to enlist the aid of an allergist and dietitian in formulating a nutritionally balanced, safe diet.

Another issue that arises in elimination diets is the role of botanically related foods (eg, legumes such as peanut, soy, other beans) and animal proteins (eg, various fish). In general, elimination of a whole family of foods is not warranted based on allergy to one member.⁹⁶ However, there are some exceptions. Many fish allergic individuals react to several species,^{86,97} and tree nut allergic children may have several nuts to which they react.⁹⁸ Legume allergy in peanut allergic children is relatively uncommon,⁸⁵ but reports of allergy to specific beans among those with peanut allergy (namely, lentil, garbanzo, and lupine) appear to be more common.^{99,100} The nuances of cross-reactivity among foods is beyond the scope of this review, but evaluation for tolerance to members of food groups is usually warranted and no assumptions about allergy to particular foods should be made.

TABLE 7. Suggestions for managing food allergy in schools

Avoidance
Increased supervision during meals/snacks, “allergy table”
No food, container, or utensil sharing
Cleaning of tables, toys
Substitution of causal food during craft, cooking, science projects
Handwashing before/after food handling and eating
Avoidance of exposure to food during preparation/cooking
Provision of safe substitute foods
Foods brought in should have ingredient labels
Instruction of staff on issues, such as:
Careful label reading
Cross-contamination
Technical/scientific word(s) for the food(s)
Treatment
Physician-prescribed treatment protocols in place, periodic review of protocols
Epinephrine available for potentially life-threatening reactions (readily available, not locked)
Education of supervising personnel on:
Recognizing signs of an allergic reaction, activating emergency services
Technique of medication administration
Basic first aid and resuscitation

Special Considerations for School

In a review of 6 fatal allergic reactions to foods in children and adolescents,⁷⁵ 5 were caused by peanut or tree nuts and 4 of these occurred in school. An important issue was that delayed recognition of the symptoms and delayed treatment led to the fatal outcomes. It is crucial for the pediatrician to support the school and family in providing a safe environment for food allergic children. The American Academy of Pediatrics,¹⁰¹ the American Academy of Allergy Asthma and Immunology,¹⁰² and a number of health care experts¹⁰³⁻¹⁰⁵ have addressed the need for emergency preparedness in the school setting. A summary of their recommendations and other recommendations gleaned from the results of our study¹⁰⁶ is summarized in Table 7.

This author and colleagues¹⁰⁶ recently reviewed 124 episodes of peanut or tree nut allergic reactions occurring in school or day care. A disproportionate percentage of reactions (64%) occurred in preschool or daycare and the school reaction represented the first reaction for 25% of the children (primarily those younger than 4 years). The affected children generally had displayed previous features of atopy and this indicates that care should be taken in introducing new, allergenic foods in the day care setting to such children. Accidental ingestions occurred primarily from food sharing or accidents, but craft projects with peanut butter (eg, bird feeders) were a major source of reactions by skin contact and ingestion. Most peanut allergic children are unaffected

by casual exposure to peanut butter, and skin contact generally leads to local reactions at the point of contact. However, these exposures presumably also increase the risk of ingestion of small amounts of the allergenic food. Some schools have decided to ban peanuts. This may be a useful approach in the day care setting when supervision is difficult. Arguments for school bans include reducing the overall “burden” of the allergen. Arguments against banning include producing a false sense of security, impracticality, burden on unaffected families, slippery slope (are egg, milk, wheat, soy, etc, also to be banned?), and legal issues. In our study, following the guidelines in Table 7 would have avoided most reactions.

An important component of the school management of food allergy is to have a clear emergency plan in place, medications readily available, and school personnel trained in recognizing a reaction and using the medications appropriately (including training on administration of the medication). An example of a school emergency plan is shown in Fig 3. Educational materials for schools, camps, and daycare are available through the Food Allergy Network.

Natural History

Fortunately, most (~90%) children lose their sensitivity to most of the common allergenic foods (egg, milk, wheat, soy) within the first 3 years of life.^{11,107} Resolution occurs for both the IgE and non-IgE-mediated reactions to these foods and even children with multiple, severe allergies achieve tolerance.¹⁰⁸ There are some children, however, in whom these allergies persist. There have not been any long-term studies on these food allergies, but series of food allergy in adults rarely report allergies to these foods.¹⁰⁹ Positive skin test reactions may persist despite the development of clinical tolerance. Recent studies have indicated that food-specific IgE antibody does decline with tolerance in most individuals,¹¹⁰ but specific diagnostic concentrations are undefined. Serial diagnostic food challenges over time are helpful in managing these food allergic children.

Unfortunately, sensitivity to certain foods, such as peanut, tree nuts, fish, and shellfish, is rarely lost, with sensitivity persisting into adulthood. The notion that peanut and tree nut allergy is permanent derives, in part, from the observation that it is an allergy that affects adults; indeed, it is seen at a rate similar to that seen in children.^{5,111} Specific proof that peanut allergy

EMERGENCY HEALTH CARE PLAN			
ALLERGY TO: _____			Place Child's Picture Here
Student's Name: _____ D.O.B: _____ Teacher: _____			
Asthmatic Yes ☐ * No ☐ *High risk for severe reaction			
SIGNS OF AN ALLERGIC REACTION INCLUDE:			
Systems:		Symptoms:	
• MOUTH itching & swelling of the lips, tongue, or mouth			
• THROAT* itching and/or a sense of tightness in the throat, hoarseness, and hacking cough			
• SKIN hives, itchy rash, and/or swelling about the face or extremities			
• GUT nausea, abdominal cramps, vomiting, and/or diarrhea			
• LUNG* shortness of breath, repetitive coughing, and/or wheezing			
• HEART* "thready" pulse, "passing-out"			
The severity of symptoms can quickly change. *All above symptoms can potentially progress to a life-threatening situation!			
ACTION:			
1. If ingestion is suspected, give _____ medication/dose/route _____ immediately!			
2. CALL RESCUE SQUAD: _____			
3. CALL: Mother _____ Father _____ or emergency contacts			
4. CALL: Dr. _____ at _____			
DO NOT HESITATE TO ADMINISTER MEDICATION OR CALL RESCUE SQUAD EVEN IF PARENTS OR DOCTOR CANNOT BE REACHED!			
_____ Parent Signature		_____ M.D. Date	
_____ Date		_____ Doctor's Signature	
EMERGENCY CONTACTS		TRAINED STAFF MEMBERS	
1. _____ Relation: _____ Phone: _____		1. _____ Room _____	
2. _____ Relation: _____ Phone: _____		2. _____ Room _____	
3. _____ Relation: _____ Phone: _____		3. _____ Room _____	

For children with multiple food allergies, use one form for each food.



FIG 3. Example of an emergency care plan for schools (courtesy of the Food Allergy Network, Fairfax, VA, with permission).

persists was shown in a study by Bock and Atkins.¹¹² They reported a follow-up of 32 peanut allergic children (confirmed by double-blind, placebo-controlled oral food challenges at early school age or beyond), followed over 2 to 14 years (mean, 7 years), and none experienced resolution of the allergy. However, several subsequent epidemiologic and case-control studies that followed children younger than 2 years with peanut allergy found a resolution rate by age 4 of up to

18%.^{113,114} The features of children who outgrew the peanut allergy compared with matched control patients who did not included small or negative prick skin test reactions, a longer interval since their last reaction (median 40 months vs 12 months), and fewer additional food allergies. Severity of initial reactions did not influence the outcome. Taken together, these studies indicate that peanut allergic infants may become tolerant but that once the allergy is established

TABLE 8. The roles of the pediatrician and allergist in managing food allergy

	Pediatrician	Allergist
Initial recognition of allergy	Integral	Ancillary
Definitive diagnosis		
Anaphylaxis to one food	Yes (uncomplicated)	Yes
Mild infantile allergies	Yes (mild gastrointestinal)	Yes
Other food allergies	No	Yes
Elimination of one food	Yes	Yes
Elimination of multiple foods	No	Yes
Determination of resolution	Not usually	Yes
Prevention	Yes	Yes

in early childhood, resolution is rare. The importance of reevaluation of the allergy, including physician-supervised food challenges, is evident.

Why do some children outgrow these allergies yet others do not? Why are children more likely to become tolerant of some foods and not others? The exact mechanisms are unknown but probably reflect maturation of the gut (improved digestion, less absorption) with less systemic circulation of immunologically intact protein. There also appears to be a change in the immune responses, since IgE levels often fall with tolerance. The biochemical nature of the food also appears to play a role in that IgE antibodies directed to particular structures seem to be more resilient to the induction of tolerance.

Prevention

Dietary modification with the goal of allergy prevention has been studied during pregnancy, lactation, and early feeding of infants who are at risk for atopic disease based on strong family histories of allergy. In several series, infants from atopic families whose mothers excluded highly allergenic foods from their diets during lactation had significantly less AD and food allergy compared with infants whose mothers' diets were unrestricted.¹¹⁵⁻¹¹⁸ However, the differences may not extend beyond early childhood.¹¹⁹

The delayed introduction of solid foods has also been associated with reduction in allergic disease. In a study of 1265 unselected neonates, the effect of solid food introduction was evaluated over a 10-year period.^{120,121} A significant linear relationship was found between the number of solid foods introduced into the diet by 4 months of age and subsequent AD, with a 3-fold increase in recurrent eczema at 10 years of age in infants receiving 4 or more solid foods compared with

infants receiving no solid foods before 4 months of age. A prospective, nonrandomized study comparing breast-fed infants who first received solid foods at 3 months versus at 6 months of age revealed reduced AD and food allergy at 1 year of age in the group avoiding solids for the 6-month period,¹²² but no significant difference in these parameters was found at 5 years.¹²³ Because these series did not randomize patients, these studies must be considered suggestive until further randomized trials confirm the findings.

The Committee on Nutrition of the American Academy of Pediatrics recently published suggestions based on the available literature with the goal of preventing childhood allergy.¹²⁴ At-risk pregnancies were defined as a child being born into a family with biparental atopy or if there was one atopic parent and a sibling with atopy. The severity or type of atopic disease was not defined. The recommendations included exclusive breast-feeding for the first year of life; supplementation, if needed, using partial or complete hydrolysate formula; and maternal elimination during the breast-feeding period of peanut and nuts, with consideration for elimination of egg, milk, fish, and possibly other foods. No specific restrictions, except perhaps of peanut, were recommended during pregnancy. For food introduction, the following was suggested: withholding solids to 6 months; milk to 12 months; egg to 24 months; and peanut, nuts, and fish to 36 months. There is literature to support the notion that atopic mother's breast milk may contain cytokines that direct immune responses in the infant toward allergic reactions,¹²⁵⁻¹²⁷ so further prospective blinded studies are needed to determine the best practices.

It is imperative to appreciate that food allergy is generally the first manifestation of the "atopic march" and such children often develop environmental allergies, asthma, and rhinitis in later childhood and adulthood.¹²⁸ Caution should be exercised in these children for identification of these atopic disorders, and environmental controls to reduce sensitization to dust mites, molds, and pet danders may be considered. In terms of additional food allergies, 35% of children with cow's milk allergy go on to have additional food allergies.¹²⁹ In a highly atopic referral population with peanut allergy, we noted that 34% developed an allergy to tree nuts.⁹⁸ There are no cross-reacting proteins between peanut and tree nuts so this observation likely represents the development of new allergies to highly allergenic foods in food allergy-disposed individuals. In such atopic individ-

uals, caution should be exercised in introducing other highly allergenic foods.

Referral

As has been indicated, referral to an allergist, dietitian, and other subspecialists is important in evaluating and treating patients with food allergy. Table 8 delineates the role of the primary care pediatrician and allergist in the care of the food allergic child. Of course, the pediatrician's personal comfort level with the management of the specific child will dictate the specific division of responsibilities.

Future Therapies

Currently, strict avoidance of causal foods and treatment of accidental ingestions are the only available therapies for food allergy. Immunotherapy (allergy shots) has not proven practical for treatment because the injection of food protein results in anaphylaxis.¹³⁰ With the goal of more definitive therapies for food allergic disorders in mind, a multitude of experimental therapies are under investigation.

Humanized anti-IgE antibodies for injection into patients have been developed that are able to bind and remove free-floating IgE antibodies from the bloodstream and may reduce or abolish allergic responses. Anti-IgE may, therefore, provide treatment for many IgE-mediated allergic disorders (not just food allergy). Allergen-specific novel therapies include vaccination with proteins altered such that the epitopes that bind IgE are removed while areas of the protein are left intact so that T cells can still mount a response, potentially leading to tolerance.¹³¹⁻¹³⁴ Another approach to induce tolerance to specific food allergen is vaccination with DNA sequences that code for the production of food allergens^{135,136} and the use of immune modulators (cytokines, specific DNA sequences) that can direct the immune system away from allergic responses and toward tolerance of the proteins. It is hoped that these novel approaches will provide relief from chronic disease and prevent anaphylaxis for food allergic individuals.

Summary

The pediatrician plays a pivotal role in the initial diagnosis of food allergy. Alternative diagnoses are considered as a careful history, physical examination,

and directed laboratory tests determine the type of adverse reaction and the responsible food. Through elimination diets in infants, appropriately selected tests for specific IgE, and, in some cases, supervised oral food challenges, a diagnosis is secured. Treatment consists of strict dietary elimination with provisions for emergency management of accidental ingestions. Referral to an allergist and dietitian is made as warranted by the severity and type of allergy and for follow-up for possible resolution of the allergy. The pediatrician also provides information to the family for the prevention of allergy in at-risk newborns. Future diagnostic tests and treatment modalities are likely to simplify the management of the food allergic child.

Dr Sicherer is supported, in part, by K23 AI 01709-01 and the Food Allergy Initiative.

References

1. 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.
2. Jakobsson I, Lindberg T. A prospective study of cow's milk protein intolerance in Swedish infants. *Acta Paediatr Scand* 1979;68:853-9.
3. Schrandt JJP, van den Bogart JPH, Forget PP, Schrandt-Stumpel CTRM, Kuijten RH, Kester ADM. Cow's milk protein intolerance in infants under 1 year of age: a prospective epidemiological study. *Eur J Pediatr* 1993;152:640-4.
4. 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.
5. Sicherer SH, Muñoz-Furlong A, Burks AW, Sampson HA. Prevalence of peanut and tree nut allergy in the United States of America determined by a random digit dial telephone survey. *J Allergy Clin Immunol* 1999;103:559-62.
6. Brujinzeel-Koomen C, Ortolani C, Aas K, Bindslev-Jensen C, Bjorksten B, Noneret-Vautrin D. Adverse reactions to food. Position paper. *Allergy* 1995;50:623-35.
7. Mayer L. Mucosal immunity and gastrointestinal antigen processing. *J Pediatr Gastroenterol Nutr* 2000;30:S4-12.
8. Sampson HA, Anderson JA. Summary and recommendations: classification of gastrointestinal manifestations due to immunologic reactions to foods in infants and young children. *J Pediatr Gastroenterol Nutr* 2000;30:S87-S94.
9. Bock SA, Atkins FM. Patterns of food hypersensitivity during sixteen years of double-blind, placebo-controlled food challenges. *J Pediatr* 1990;117:561-7.
10. Burks AW, James JM, Hiegel A, Wilson G, Wheeler JG, Jones SM, et al. Atopic dermatitis and food hypersensitivity reactions. *J Pediatr* 1998;132:132-6.
11. Sampson HA, Scanlon SM. Natural history of food hypersensitivity in children with atopic dermatitis. *J Pediatr* 1989;115:23-7.
12. Young E, Patel S, Stoneham MD, Rona R, Wilkinson JD.

- The prevalence of reactions to food additives in a survey population. *J R Coll Physicians Lond* 1987;21:241-71.
13. Odze RD, Bines J, Leichtner AM, Goldman H, Antonioli DA. Allergic proctocolitis in infants: a prospective clinicopathologic biopsy study. *Hum Pathol* 1993;24:668-74.
 14. Winter HS, Antonioli DA, Fukagawa N, Marcial M, Goldman H. Allergy-related proctocolitis in infants: diagnostic usefulness of rectal biopsy. *Mod Pathol* 1990;3:5-10.
 15. Goldman H, Proujansky R. Allergic proctitis and gastroenteritis in children. Clinical and mucosal biopsy features in 53 cases. *Am J Surg Pathol* 1986;10:75-86.
 16. Lake AM, Whittington PF, Hamilton SR. Dietary protein-induced colitis in breast-fed infants. *J Pediatr* 1982;101:906-10.
 17. Anveden HL, Finkel Y, Sandstedt B, Karpe B. Proctocolitis in exclusively breast-fed infants. *Eur J Pediatr* 1996;155:464-7.
 18. Pittschieler K. Cow's milk protein-induced colitis in the breast-fed infant. *J Pediatr Gastroenterol Nutr* 1990;10:548-9.
 19. Kuitunen P, Visakorpi J, Savilahti E, Pelkonen P. Malabsorption syndrome with cow's milk intolerance: clinical findings and course in 54 cases. *Arch Dis Child* 1975;50:351-6.
 20. Iyngkaran N, Yadav M, Boey C, Lam K. Severity and extent of upper small bowel mucosal damage in cow's milk protein-sensitive enteropathy. *J Pediatr Gastroenterol Nutr* 1988;8:667-74.
 21. Walker-Smith JA. Cow milk-sensitive enteropathy: predisposing factors and treatment. *J Pediatr* 1992;121:S111-S115.
 22. Iyngkaran N, Robinson MJ, Prathap K, Sumithran E, Yadav M. Cows' milk protein-sensitive enteropathy. Combined clinical and histological criteria for diagnosis. *Arch Dis Child* 1978;53:20-6.
 23. Yssing M, Jensen H, Jarnum S. Dietary treatment of protein-losing enteropathy. *Acta Paediatr Scand* 1967;56:173-81.
 24. Kleinman RE. Milk protein enteropathy after acute infectious gastroenteritis: experimental and clinical observations. *J Pediatr* 1991;118:S111-S115.
 25. Sicherer SH, Eigenmann PA, Sampson HA. Clinical features of food protein-induced enterocolitis syndrome. *J Pediatr* 1998;133:214-9.
 26. Powell GK. Milk- and soy-induced enterocolitis of infancy. *J Pediatr* 1978;93:553-60.
 27. Powell G. Food protein-induced enterocolitis of infancy: differential diagnosis and management. *Compr Ther* 1986;12:28-37.
 28. Murray K, Christie D. Dietary protein intolerance in infants with transient methemoglobinemia and diarrhea. *J Pediatr* 1993;122:90-2.
 29. Gryboski J. Gastrointestinal milk allergy in infancy. *Pediatrics* 1967;40:354-62.
 30. Goldman H, Provjansky R. Allergic proctitis and gastroenteritis in children. *Am J Surg Pathol* 1986;10:75-86.
 31. Lake AM. Food protein-induced colitis and gastroenteropathy in infants and children. In: Metcalfe DD, Sampson HA, Simon RA, editors. *Food allergy: adverse reactions to foods and food additives*. Boston: Blackwell Scientific Publications; 1997. p. 277-86.
 32. Halpin TC, Byrne WJ, Ament ME. Colitis, persistent diarrhea, and soy protein intolerance. *J Pediatr* 1977;91:404-7.
 33. Jenkins H, Pincott J, Soothill J, Milla P, Harries J. Food allergy: the major cause of infantile colitis. *Arch Dis Child* 1984;59:326-9.
 34. Burks AW, Casteel HB, Fiedorek SC, Williams LW, Pumphrey CL. Prospective oral food challenge study of two soybean protein isolates in patients with possible milk or soy protein enterocolitis. *Pediatr Allergy Immunol* 1994;5:40-5.
 35. Sicherer SH. Food protein-induced enterocolitis syndrome: clinical perspectives. *J Pediatr Gastroenterol Nutr* 2000;30:S45-S49.
 36. Forget PP, Arenda JW. Cow's milk protein allergy and gastroesophageal reflux. *Eur J Pediatr* 1985;144:298-300.
 37. Staiano A, Troncone R, Simeone D, Mayer M, Finelli E, Cella A, et al. Differentiation of cows' milk intolerance and gastro-oesophageal reflux. *Arch Dis Child* 1995;73:439-42.
 38. Cavataio F, Iacono G, Montalto G, Soresi M, Tumminello M, Campagna P, et al. Gastroesophageal reflux associated with cow's milk allergy in infants: which diagnostic examinations are useful? *Am J Gastroenterol* 1996;91:1215-20.
 39. Cavataio F, Iacono G, Montalto G, Soresi M, Tumminello M, Carroccio A. Clinical and pH-metric characteristics of gastro-oesophageal reflux secondary to cows' milk protein allergy. *Arch Dis Child* 1996;75:51-6.
 40. Iacono G, Carroccio A, Cavataio F, Montalto G, Kazmierska I, Lorello D, et al. Gastroesophageal reflux and cow's milk allergy in infants: a prospective study. *J Allergy Clin Immunol* 1996;97:822-7.
 41. Zeigler RE, Fomon SJ, Nelson SE, Rebouche CJ, Edwards BB, Rogers RR, et al. Cow milk feeding in infancy: further observations on blood loss from the gastrointestinal tract. *J Pediatr* 1990;116:11-8.
 42. Jakobsson I, Lindberg T. Cow's milk proteins cause infantile colic in breast-fed infants: a double-blind cross-over study. *Pediatrics* 1983;71:268-71.
 43. Gerrard JW, MacKenzie JWA, Goluboff N, Garson JZ, Maningas CS. Cow's milk allergy: prevalence and manifestations in an unselected series of newborns. *Acta Paediatr Scand* 1973;S234:1-21.
 44. Lothe L, Lindberg T. Cow's milk whey protein elicits symptoms of infantile colic in colicky formula-fed infants: a double-blind crossover study. *Pediatrics* 1989;83:262-6.
 45. Iacono G, Carroccio A, Cavataio F, Montalto G, Cantarero MD, Notarbartolo A. Chronic constipation as a symptom of cow milk allergy. *J Pediatr* 1995;126:34-9.
 46. Iacono G, Cavataio F, Montalto G, Florena A, Tumminello M, Soresi M, et al. Intolerance of cow's milk and chronic constipation in children. *N Engl J Med* 1998;339:1100-4.
 47. Ortolani C, Pastorello EA, Farioli L, Ispano M, Pravettoni V, Berti C, et al. IgE-mediated allergy from vegetable allergens. *Ann Allergy* 1993;71:470-6.
 48. Ortolani C, Ispano M, Pastorello E, Bigi A, Ansaloni R. The oral allergy syndrome. *Ann Allergy* 1988;61:47-52.
 49. Fernandez-Rivas M, Cuevas M. Peels of Rosaceae fruits have a higher allergenicity than pulps. *Clin Exp Allergy* 1999;29:1239-47.
 50. Naylor AR. Eosinophilic gastroenteritis. *Scott Med J* 1990;35:163-5.
 51. Orenstein SR, Shalaby TM, Di Lorenzo C, Putnam PE,

- Sigurdsson L, Kocoshis SA. The spectrum of pediatric eosinophilic esophagitis beyond infancy: a clinical series of 30 children. *Am J Gastroenterol* 2000;95:1422-30.
52. Kelly KJ, Lazenby AJ, Rowe PC, Yardley JH, Perman JA, Sampson HA. Eosinophilic esophagitis attributed to gastro-esophageal reflux: improvement with an amino acid-based formula. *Gastroenterol* 1995;109:1503-12.
53. Trier JS. Celiac sprue. *N Engl J Med* 1991;325:1709-19.
54. Sehgal VN, Rege VL. An interrogative study of 158 urticaria patients. *Ann Allergy* 1973;31:279-83.
55. Champion RH. Urticaria: then and now. *Br J Dermatol* 1988;119:427-36.
56. Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. *Acta Derm Venereol* 1980;92:44-7.
57. Sampson HA. Atopic dermatitis [review]. *Ann Allergy* 1992;69:469-79.
58. Sicherer SH, Sampson HA. Food hypersensitivity and atopic dermatitis: pathophysiology, epidemiology, diagnosis, and management. *J Allergy Clin Immunol* 1999;104:S114-S122.
59. Isolauri E, Turjanmaa K. Combined skin prick and patch testing enhances identification of food allergy in infants with atopic dermatitis. *J Allergy Clin Immunol* 1996;97:9-15.
60. Eigenmann PA, Sicherer SH, Borkowski TA, Cohen BA, Sampson HA. Prevalence of IgE-mediated food allergy among children with atopic dermatitis. *Pediatrics* 1998;101:E8.
61. Burks AW, Mallory SB, Williams LW, Shirrell MA. Atopic dermatitis: clinical relevance of food hypersensitivity reactions. *J Pediatr* 1988;113:447-51.
62. Guillet MH, Guillet G. Allergologic survey in 251 patients with moderate or severe dermatitis. Incidence and value of the detection of contact eczema, food allergy or sensitization to air-borne allergens. *Ann Derm Venereol* 1996;123:157-64.
63. Fry L, Seah PP. Dermatitis herpetiformis: an evaluation of diagnostic criteria. *Br J Dermatol* 1974;90:137-46.
64. Sampson H, Eigenmann PA. Food allergy and intolerance. In: Naclerio R, Durham SR, Mygind N, editors. *Rhinitis: mechanisms and management*. New York: Marcel Dekker, Inc; 1999. p. 95-108.
65. Raphael G, Raphael M, Kaliner M. Gustatory rhinitis: a syndrome of food-induced rhinorrhea. *J Allergy Clin Immunol* 1989;83:110-5.
66. Sicherer SH, Sampson HA. The role of food allergy in childhood asthma. *Immunol Allergy Clin N Amer* 1998;18:49-60.
67. James JM, Bernhisel-Broadbent J, Sampson HA. Respiratory reactions provoked by double-blind food challenges in children. *Am J Respir Crit Care Med* 1994;149:59-64.
68. Bock SA. Respiratory reactions induced by food challenges in children with pulmonary disease. *Pediatr Allergy Immunol* 1992;3:188-94.
69. Novembre E, de Martino M, Vierucci A. Foods and respiratory allergy. *J Allergy Clin Immunol* 1988;81:1059-65.
70. Heiner DC, Sears JW. Chronic respiratory disease associated with multiple circulating precipitins to cow's milk. *Am J Dis Child* 1960;100:500-2.
71. Joint Task Force on Practice Parameters, American Academy of Allergy, Asthma and Immunology, American College of Allergy, Asthma and Immunology, and the Joint Council of Allergy, Asthma and Immunology. The diagnosis and management of anaphylaxis. *J Allergy Clin Immunol* 1999;103:958-65.
72. Pumphrey RSH, Stanworth SJ. The clinical spectrum of anaphylaxis in north-west England. *Clin Exp Allergy* 1996;26:1364-70.
73. Yocum MW, Khan DA. Assessment of patients who have experienced anaphylaxis: a 3-year survey. *Mayo Clin Proc* 1994;69:16-23.
74. Kemp SF, Lockey RF, Wolf BL, Lieberman P. Anaphylaxis: a review of 266 cases. *Arch Intern Med* 1995;155:1749-54.
75. 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.
76. Yunginger JW, Sweeney KG, Sturmer WQ, Giannandra LA, Teigland JD, Bray M, et al. Fatal food-induced anaphylaxis. *JAMA* 1988;260:1450-2.
77. Settupane G. Anaphylactic deaths in asthmatic patients. *Allergy Proc* 1989;10:271-4.
78. Romano A, Fonso M, Giuffreda F, Quarantino D, Papa G, Palmieri V. Diagnostic work-up for food-dependent, exercise-induced anaphylaxis. *Allergy* 1995;50:817-24.
79. Sicherer SH. Food allergy: when and how to perform oral food challenges. *Pediatr Allergy Immunol* 1999;10:226-34.
80. Ortolani C, Ispano 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.
81. Eigenmann PA, Sampson HA. Interpreting skin prick tests in the evaluation of food allergy in children. *Pediatr Allergy Immunol* 1998;9:186-91.
82. 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.
83. 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.
84. Barnett D, Bonham B, Howden ME. Allergenic cross-reactions among legume foods—an in vitro study. *J Allergy Clin Immunol* 1987;79:433-8.
85. Bernhisel-Broadbent J, Taylor S, Sampson HA. Cross-allergenicity in the legume botanical family in children with food hypersensitivity. *J Allergy Clin Immunol* 1989;84:701-9.
86. Bernhisel-Broadbent J, Strause D, Sampson HA. Fish hypersensitivity. II: Clinical relevance of altered fish allergenicity caused by various preparation methods. *J Allergy Clin Immunol* 1992;90:622-9.
87. Sampson HA, Ho DG. Relationship between food-specific IgE concentrations and the risk of positive food challenges in children and adolescents. *J Allergy Clin Immunol* 1997;100:444-51.
88. Terr AI, Salvaggio JE. Controversial concepts in allergy and clinical immunology. In: Bierman CW, Pearlman DS, Shapiro GG, Busse WW, editors. *Allergy, asthma, and immunology from infancy to adulthood*. Philadelphia: WB Saunders; 1996. p. 749-60.
89. Simons FE, Roberts JR, Gu X, Simons KJ. Epinephrine absorption in children with a history of anaphylaxis. *J Allergy Clin Immunol* 1998;101:33-7.

90. Sicherer SH, Forman JA, Noone S. Use assessment of self-administered epinephrine among food-allergic children and pediatricians. *Pediatrics* 2000;105:359-62.
91. Huang SW. A survey of Epi-PEN use in patients with a history of anaphylaxis. *J Allergy Clin Immunol* 1998;102:525-6.
92. Zeiger RS, Sampson HA, Bock SA, Burks AWJ, Harden K, Noone S, et al. Soy allergy in infants and children with IgE-associated cow's milk allergy. *J Pediatr* 1999;134:614-22.
93. Van Sickle GJ, Powell GK, McDonald PJ, Goldblum RM. Milk- and soy protein-induced enterocolitis: evidence for lymphocyte sensitization to specific food proteins. *Gastroenterology* 1985;88:1915-21.
94. Vanderhoof JA, Murray ND, Kaufman SS, Mack DR, Antonson DL, Corkins MR, et al. Intolerance to protein hydrolysate infant formulas: an underrecognized cause of gastrointestinal symptoms in infants. *J Pediatr* 1997;131:741-4.
95. de Boijjieu D, Matarazzo P, Dupont C. Allergy to extensively hydrolyzed cow milk proteins in infants: identification and treatment with an amino acid-based formula. *J Pediatr* 1997;131:744-7.
96. Bernhisel-Broadbent J. Allergenic cross-reactivity of foods and characterization of food allergens and extracts. *Ann Allergy Asthma Immunol* 1995;75:295-303.
97. 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.
98. Sicherer SH, Burks AW, Sampson HA. Clinical features of acute allergic reactions to peanut and tree nuts in children. *Pediatrics* 1998;102:E6.
99. Moneret-Vautrin DA, Guerin L, Kanny G, Flabbee J, Fremont S, Morisset M. Cross-allergenicity of peanut and lupine: the risk of lupine allergy in patients allergic to peanuts. *J Allergy Clin Immunol* 1999;104:883-8.
100. Kalogeromitros D, Armenaka M, Galatas I, Capellou O, Katsarou A. Anaphylaxis induced by lentils. *Ann Allergy Asthma Immunol* 1996;77:480-2.
101. Emergency preparedness for children with special health care needs. Committee on Pediatric Emergency Medicine. American Academy of Pediatrics. *Pediatrics* 1999;104:e53.
102. Anaphylaxis in schools and other childcare settings. AAAAI Board of Directors. American Academy of Allergy, Asthma and Immunology. *J Allergy Clin Immunol* 1998;102:173-6.
103. Mudd KE, Noone SA. Management of severe food allergy in the school setting. *J Sch Nurs* 1995;11:30-2.
104. Hay GH, Harper TB, Courson FH. Preparing school personnel to assist students with life-threatening food allergies. *J Sch Health* 1994;64:119-21.
105. Frazier CA, Wynn SR, Munoz-Furlong A, Ostrom NK, Sampson HA, Yunginger JW. Anaphylaxis at school: etiologic factors, prevalence, and treatment [letter]. *Pediatrics* 1993;91:516.
106. Sicherer SH, Furlong TJ, DeSimone J, Sampson HA. The US peanut and tree nut allergy registry: characteristics of reactions in schools and day care. *J Pediatr*. In press.
107. Bock SA. The natural history of food sensitivity. *J Allergy Clin Immunol* 1982;69:173-7.
108. Hill DJ, Heine RG, Cameron DJ, Francis DE, Bines JE. The natural history of intolerance to soy and extensively hydrolyzed formula in infants with multiple food protein intolerance. *J Pediatr* 1999;135:118-21.
109. Young E, Stoneham MD, Petrukevitch A, Barton J, Rona R. A population study of food intolerance. *Lancet* 1994;343:1127-30.
110. 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;29:507-12.
111. Emmett SE, Angus FJ, Fry JS, Lee PN. Perceived prevalence of peanut allergy in Great Britain and its association with other atopic conditions and with peanut allergy in other household members. *Allergy* 1999;54:380-5.
112. Bock SA, Atkins FM. The natural history of peanut allergy. *J Allergy Clin Immunol* 1989;83:900-4.
113. Tariq SM, Stevens M, Matthews S, Ridout S, Twiselton R, Hide DW. Cohort study of peanut and tree nut sensitisation by age of 4 years. *BMJ* 1996;313:514-7.
114. Hourihane JO, Roberts SA, Warner JO. Resolution of peanut allergy: case-control study. *BMJ* 1998;316:1271-5.
115. Zeiger R, Heller S, Mellon M, Forsythe A, O'Connor R, Hamburger R. Effect of combined maternal and infant food-allergen avoidance on development of atopy in early infancy: a randomized study. *J Allergy Clin Immunol* 1989;84:72-89.
116. Zeiger RS. Dietary manipulations in infants and their mothers and the natural course of atopic disease. *Pediatr Allergy Immunol* 1994;5:S33-S43.
117. Hattevig G, Kjellman B, Bjorksten B, Kjellman N. Effect of maternal avoidance of eggs, cow's milk and fish during lactation upon allergic manifestations in infants. *Clin Exp Allergy* 1989;19:27-32.
118. Sigurs N, Hattevig G, Kjellman B. Maternal avoidance of eggs, cow's milk, and fish during lactation: effect on allergic manifestation, skin-prick tests, and specific IgE antibodies in children at age 4 years. *Pediatrics* 1992;89:735-9.
119. Zeiger R, Heller S. The development and prediction of atopy in high-risk children: follow-up at seven years in a prospective randomized study of combined maternal and infant food allergen avoidance. *J Allergy Clin Immunol* 1995;95:1179-90.
120. Fergusson DM, Horwood LJ, Shannon FT. Early solid feeding and recurrent eczema: a 10-year longitudinal study. *Pediatrics* 1990;86:541-6.
121. Fergusson D, Horwood L, Shannon F. Asthma and infant diet. *Arch Dis Child* 1983;58:48-51.
122. Kajosaari M, Saarinen UM. Prophylaxis of atopic disease by six months; total solid food elimination. *Arch Paediatr Scand* 1983;72:411-4.
123. Kajosaari M. Atopy prophylaxis in high-risk infants: prospective 5-year follow-up study of children with six months exclusive breast-feeding and solid food elimination. *Adv Exp Med Biol* 1991;310:453-8.
124. American Academy of Pediatrics. Committee on Nutrition. Hypoallergenic infant formulas. *Pediatrics* 2000;106:346-9.
125. Rudloff S, Niehues T, Rutsch M, Kunz C, Schroten H. Inflammation markers and cytokines in breast milk of atopic and nonatopic women. *Allergy* 1999;54:206-11.
126. Jevinen KM, Laine ST, Jevence AL, Suomalainen HK. Does low IgA in human milk predispose the infant to development of cow's milk allergy? *Pediatr Res* 2000;48:457-62.

127. Jarvinen KM, Laine S, Suomalainen H. Defective tumour necrosis factor-alpha production in mother's milk is related to cow's milk allergy in suckling infants. *Clin Exp Allergy* 2000;30:637-43.
128. Nickel R, Kulig M, Forster G, Bergmann R, Bauer C, Lau S, et al. Sensitization to hen's egg at the age of twelve months is predictive for allergic sensitization to common indoor and outdoor allergens at the age of three years. *J Allergy Clin Immunol* 1997;99:613-7.
129. Host A. Cow's milk allergy. *J R Soc Med* 1997; 90 Suppl 30:S34-S39.
130. Nelson HS, Lahr J, Rule R, Bock A, Leung D. Treatment of anaphylactic sensitivity to peanuts by immunotherapy with injections of aqueous peanut extract. *J Allergy Clin Immunol* 1997;99:744-51.
131. Bannon GA, Li X-M, Rabjohn P, Stanley JS, Burks AW, Huang SK, et al. Ara h 3, a peanut allergen identified by using peanut sensitive patient sera absorbed with soy proteins. *J Allergy Clin Immunol* 1998;99:S141.
132. Burks AW, Bannon GA, Sicherer SH, Sampson HA. Peanut-induced anaphylactic reactions. *Int Arch Allergy Immunol* 1999;119:165-72.
133. Burks AW, King N, Bannon GA. Modification of a major peanut allergen leads to loss of IgE binding. *Int Arch Allergy Immunol* 1999;118:313-4.
134. Rabjohn P, Helm EM, Stanley JS, West CM, Sampson HA, Burks AW, et al. Molecular cloning and epitope analysis of the peanut allergen Ara h 3. *J Clin Invest* 1999;103:535-42.
135. Li X, Huang CK, Schofield BH, Burks AW, Bannon GA, Kim KH, et al. Strain-dependent induction of allergic sensitization caused by peanut allergen DNA immunization in mice. *J Immunol* 1999;162:3045-52.
136. Roy K, Mao HQ, Huang SK, Leong KW. Oral gene delivery with chitosan—DNA nanoparticles generates immunologic protection in a murine model of peanut allergy. *Nat Med* 1999;5:387-91.