FOOD ALLERGY

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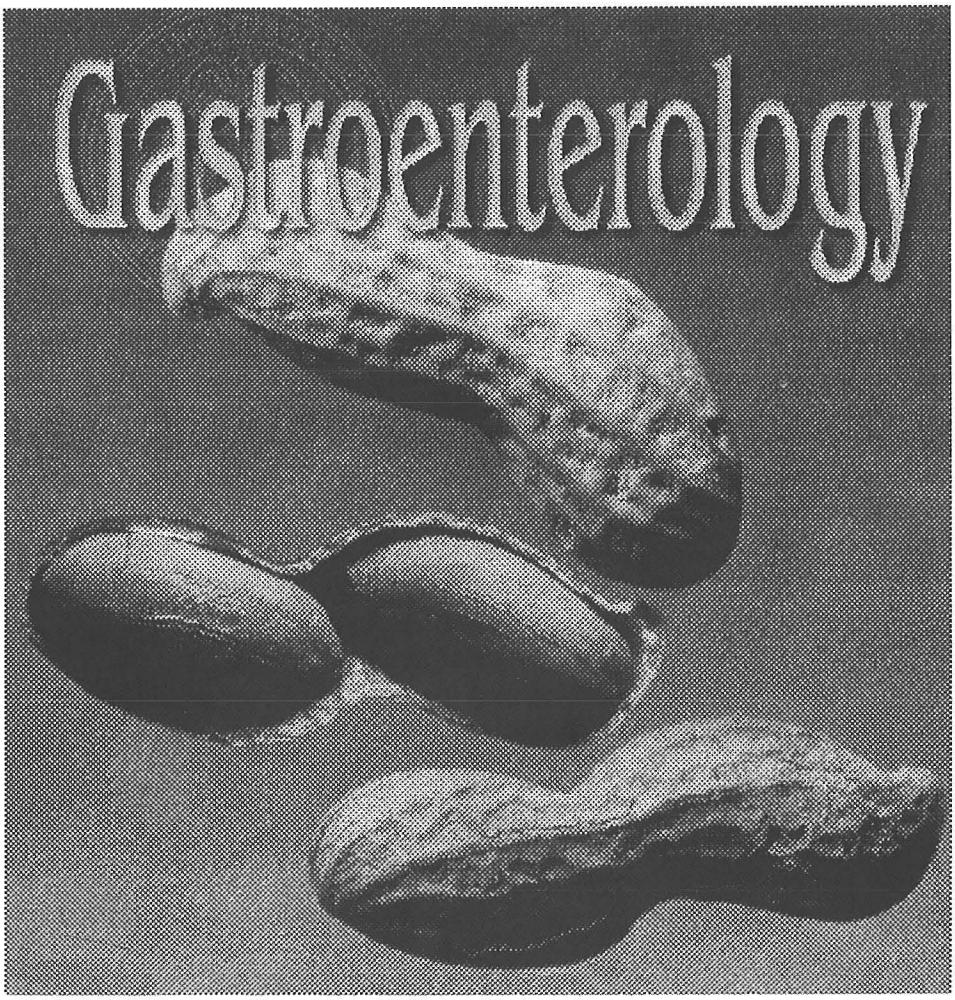

William Harford has no financial interests nor other relationships with commercial concerns related directly or indirectly to this program.

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"Gastrointestinal allergy is a diagnosis frequently entertained, occasionally evaluated, and rarely established. It offers, to its enthusiastic supporters, a reasonable explanation for many obscure abdominal complaints. To the skeptical, it frequently appears as a specious and unwarranted diagnosis. Although these conflicting views cannot be resolved on the basis of existing knowledge, the present status of gastrointestinal allergy is examined in this review with the hope of separating the well founded from the hypothetical."
Ingelfinger F, Lowell F, Franklin W. Gastrointestinal allergy. New Engl J Med. 1949;241:303-308

OUTLINE

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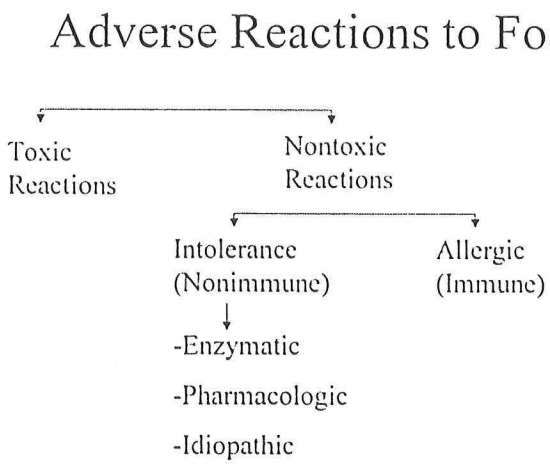
DEFINITIONS

In common usage a variety of adverse reactions to food are called food "allergies". This has lead to confusion and controversy about food allergy. The European Academy of Allergy and Clinical Immunology classifies adverse reactions to food into toxic food reactions and nontoxic food reactions.

Toxic food reactions may occur in anyone, provided a sufficient amount of food, additive, or contaminant is ingested. Histamine toxicity due to scombroid fish poisoning is an example of a toxic food reaction.

Nontoxic food reactions depend on individual susceptibilities. Nontoxic food reactions may be the result of nonimmune mechanisms (intolerance) or immune mechanisms (allergy or hypersensitivity). The majority of adverse food reactions are due to food intolerance. Food intolerance can be categorized as enzymatic, pharmacologic, and idiopathic. Diarrhea due to lactase deficiency is an example of enzymatic food intolerance. Adverse reaction to vasoactive amines normally present in some foods, such as tyramine in aged cheese, is an example of pharmacologic food intolerance. IgE-mediated peanut allergy and celiac sprue are examples of food allergies.



PREVALENCE OF FOOD ALLERGY

In a survey of U.S. households, about 15% of families reported that one or more members had food allergy [1]. The prevalence of self-reported food allergy was found to be about 17.5 % in a survey of British adults and 12.5% in a survey of Dutch adults [2,3]. There is a large discrepancy between self-reported food allergy and true food allergy as defined by positive double-blind placebo-controlled food challenge (DBPCFC). In the Dutch and British studies, a sample of respondents agreed to DBPCFC. Of these, less than 20% had confirmation of the suspected adverse reaction to food, and a substantial proportion of these were not due to food allergy but food intolerance. Thus, the overall prevalence of true food allergy in adults in the US and Europe is probably between 1% and 2 %.

The prevalence of food allergy is higher in children than in adults. In a prospective study of newborns followed for 3 years, 8% developed food allergy confirmed by DBPCFC [4]. Other prospective studies have found that the prevalence of cow's milk allergy in infants

is 2% to 3%. The prevalence of food allergy is particularly high among children with moderate to severe atopic dermatitis. In a report from a referral practice, 35% of atopic children (most of whom had atopic dermatitis) were found to have food allergies [5]. Among asthmatic children without atopic dermatitis, the prevalence of food-induced wheezing has been reported to be about 5% [6]. Many but not all childhood food allergies resolve. About 85% of children lose their milk allergy by 3 year of age [7].

THE IMPACT OF FOOD ALLERGY

Although the prevalence of confirmed food allergy is lower than that of self-reported allergy, it is still substantial among both children and adults. Food allergies are the most common cause of anaphylaxis treated in emergency rooms [8]. It is estimated that in the U.S. 100 to 200 deaths per year are due to food-related anaphylaxis [9]. In children, food allergies are responsible for some cases of gastroesophageal reflux, enterocolitis, and proctocolitis. Food allergies contribute to some cases of childhood atopic dermatitis and asthma. Adults also suffer from both IgE-mediated food allergy and other immune-mediated food reactions such as celiac sprue. The foods most often responsible for allergies (milk, eggs, peanuts, nuts, and wheat) are commonly encountered. They are used in preparing a large variety of foods. Strict avoidance is difficult and requires education, vigilance, and self-discipline.

Quality of life is affected not only by confirmed food allergy, but also by the belief that an individual is affected by a food allergy. About 25% of parents believe that one or more of their children suffer from food allergy. This belief often leads to diet modifications and restrictions [1]. In most cases diet modifications made for perceived food allergy do not seriously affect quality of life or health. However, malnutrition and failure to thrive may occur among children whose parents act on a strong and persistent belief that their child is food-allergic without confirmation of the allergies and without appropriate professional dietary advice [10]. Medical practitioners may aggravate the problem of unsubstantiated food allergy and unnecessary dietary restrictions. As discussed below, the positive predictive value of skin tests or radioallergosorbest tests (RAST) for food allergy is low. Only about 30-40% of positive tests predict clinical food allergy when DBPCFC is done. Thus, if a large number of potential food allergens are tested by skin tests or RAST and the patient is counseled to avoid all foods giving positive tests, unnecessary diet restrictions will result. There are also adults, such as those who believe that they are afflicted with the multiple chemical sensitivity (MCS) syndrome, who believe that they have immune reactions to an extremely wide variety of common substances in the environment, including a wide variety of foods. The consensus of the academic medical community is that such widespread reactivity is not immune-mediated. Many of the methods used by practitioners to evaluate and treat MCS have not been confirmed by well-designed trials. However, these beliefs are often held very strongly, even though extensive restrictions often impair quality of life and place patients at risk for malnutrition [11,12].

FEATURES OF THE GASTROINTESTINAL IMMUNE SYSTEM

The GI immune system contains more lymphocytes (10^{12}) and makes more antibodies (primarily IgA) than any other organ in the body [13]. Cells of the GI immune system are

found within the mucosa and submucosa, regional lymph nodes and the reticuloendothelial system of the liver.

Specialized epithelial cells call M cells are found over Peyer's patches and serve as antigen processing cells. Normal epithelial cells are also thought to play role in immune processing of food antigens, as discussed below.

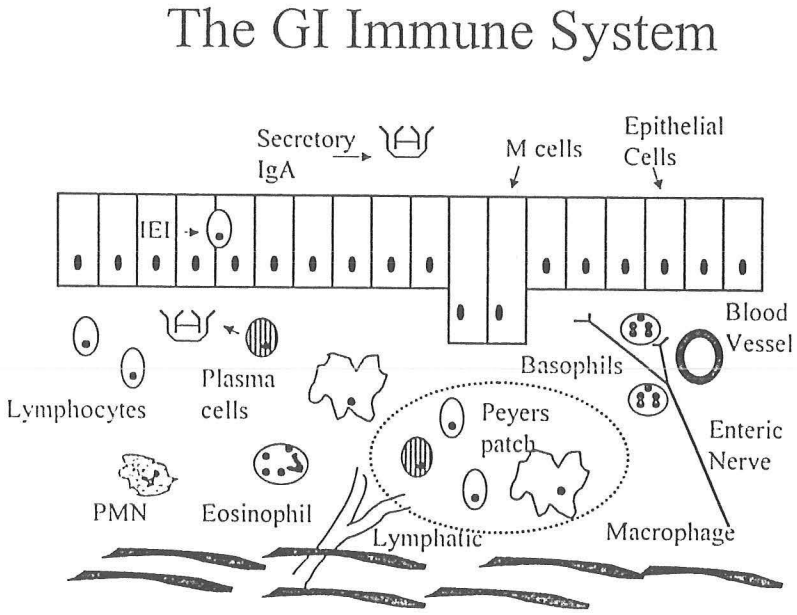
Lymphocytes are found among cells of the epithelial layer (intraepithelial lymphocytes or IELs), scattered throughout the lamina propria of the mucosa (lamina propria lymphocytes or LPLs), and in follicles or Peyer's patches, as well as in the mesenteric lymph nodes. Lymphocytes are distributed throughout the length of the GI tract, including the oropharynx and esophagus, but are concentrated in the small bowel and colon. Other immune cells are also distributed throughout the lamina propria, including macrophages, mast cells, eosinophils, and polymorphonuclear leukocytes. The function of IELs is not clear. More than 98% are CD8 + memory T cells. LPLs are heterogeneous. About 50% of LPLs are IgA-secreting plasma cells and the rest are a mixture of T and B lymphocytes.

Mast cells are scattered throughout the lamina propria of the GI tract. The normal function of GI mast cells is not clear, but they may have a function in the immune response to worms and other parasites. They are the major effector cells in immediate hypersensitivity reactions. Activated mast cells release a number of mediators, including histamine, neutral proteases such as tryptase, prostaglandins, leukotrienes (such as LTC4) and cytokines (such as TNFα, IL5, TGFβ). These mediators have a wide variety of effects in the GI tract. Mast cell activation occurs through several mechanisms. The classic immune mechanism is through cross-linking of antigen-specific membrane-bound IgE by multivalent antigen. Mast cells may be sensitized simultaneously with IgE antibodies of different specificities. There are also non-immune mechanisms of mast cell activation, including opioids, radiocontrast agents, and activated C3 complement. Some of these may play a role in GI food reactions that simulate IgE-mediated food allergic reactions. [14]. Mast cells are found close to enteric nerves, an observation that has lead to speculation about interactions between food allergy and irritable bowel syndrome [15].

Eosinophils are thought to have a major role in defense against intestinal parasitic diseases and they also play a role in some GI allergic reactions. A moderate number of eosinophils are normally found scattered throughout the lamina propria. Eosinophilic infiltration is markedly increased in eosinophilic gastroenteritis, a disease in which food allergy plays a role in some patients. Interleukin 5 (IL5), IL3 and GM CSF secreted by T cells lead to eosinophil activation. In addition to the release of factors toxic to parasites (eosinophilic cationic proteins, platelet activating factor and LTC4) eosinophils release cytokines such as IL4 that favor IgE production and other cytokines that recruit inflammatory cells. These contribute to late phase allergic reactions [14].

Macrophages are scattered throughout the lamina propria and in Peyer's patches, where they function as antigen-presenting cells. They also secrete a wide variety of cytokines.

Polymorphonuclear leukocytes may be found in the lamina propria, and are recruited in large number during some immune reactions.



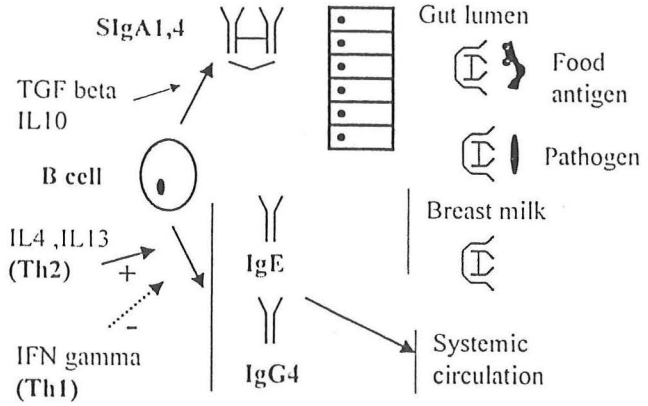
Immunoglobulin Production

IgA is the dominant immunoglobulin of the GI tract. In secretions IgA exists as a dimer, bound by the J chain, and is attached to *secretory component*, a specialized glycoprotein. Secretory component is required for transport of IgA from the lamina propria to the lumen and protects the IgA molecule from degradation by intestinal enzymes. IgA does not bind to complement or Fc receptors, although it can activate the alternative complement pathway. Secretory IgA (sIgA) is directed against bacterial and viral surface molecules, preventing their attachment to epithelial cells and also complexes with potential food allergen molecules in the lumen, limiting their uptake. Secretory IgA has an enterohepatic circulation. IgA-antigen complex is taken up in the ileum, transported to the liver, where Kuppfer cells destroy the antigen and release the free sIgA into the bile. B cells activated in the GI lamina propria acquire homing markers for breast tissue. Thus, sIgA plasma cells in the breast secrete IgA into breast milk, providing passive immunity against enteric pathogens for infants.

GI lamina propria plasma cells also produce IgE and IgG. The balance of cytokines secreted by activated T cells and other cells affects B cell isotype switching. TGFβ and IL10 induce isotype switching to IgA1 and IgA2, whereas IL4 and IL13 induce isotype switching to IgE and IgG4. IL4 and IL13 are produced by the Th2 subset of CD4+ T cells as well as by mast cells, NK cells, and basophils. IFNγ antagonizes IL4-induced switching to IgE. IFNγ is produced by the Th1 subset of CD4+ T cells [16,17]. The factors that lead to IgE production and GI allergic reactions rather oral tolerance are not well understood. Polymorphisms in the regulatory regions of the IL4 genes, for example,

might lead to a predisposition to secrete abnormally high levels of IgE-inducing cytokines in response to antigen [18].

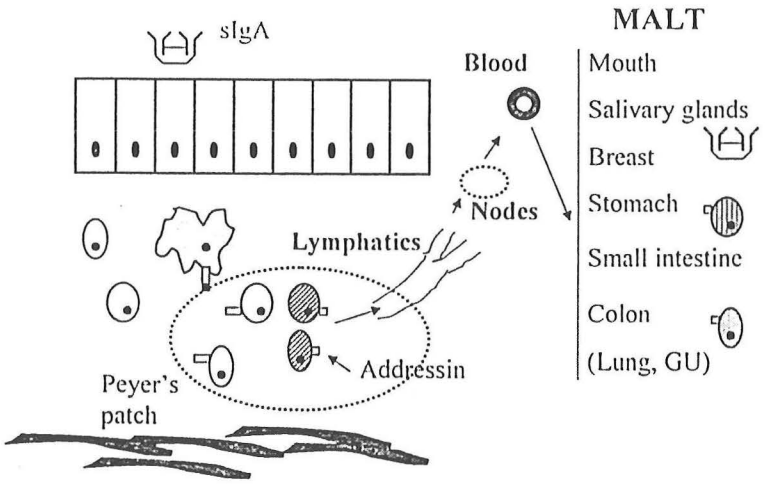
Antibody Production



Mucosa Associated Lymphoid Tissue (MALT)

There is interchange of lymphoid cells and antibodies among different areas of gastrointestinal mucosa and certain other tissues. Labeled cells from Peyer's patches can be traced from the submucosa into mesenteric lymph nodes, the thoracic duct, and vena cava. From there they are distributed into the lamina propria of various sites in the GI tract including the mouth and salivary glands, the breast of lactating females, and to a lesser extent the lung and genitourinary tract. Activated MALT T cells express the surface addressin molecule $\alpha 4\beta 7$, which functions as a homing signal for other mucosal sites.

Mucosa Associated Lymphoid Tissue



ORAL TOLERANCE AND IMMUNE DEFENSE

The GI tract is exposed to a very large antigenic load. In addition to the resident commensal bacterial population, the GI tract processes approximately 100 tons of food

during a lifetime, a large proportion of which is potential allergen. The GI immune system must be able to mount a vigorous defensive response to potentially dangerous microorganisms while avoiding the same response to normal commensal bacteria and food antigens. This is accomplished by two general mechanisms: 1) defenses against the uptake of potential allergens and 2) immune tolerance to food antigens.

GI Defenses Against Antigens
Digestion of Antigens
Physical Barriers to Antigens
- Glycocalyx
- Epithelial Cell Layer
- Tight Junctions
- Peristalsis (Migrating Motor Complex)

Immunologic Barriers
- Secretory IgA
- Intraepithelial Lymphocytes
- Kupffer Cells
- Serum Antigen-Specific IgA and IgG

The normal process of digestion destroys many potential antigens. The first physical barrier to antigens in the GI tract is the layer of mucus secreted by epithelial mucous cells. This layer contains complex glycoproteins and mucins that trap large macromolecules and pathogens. The epithelial cells and tight junctions between cells form a second barrier, but many pathogens have the capacity to bind to cells membranes and invade the mucosa. The peristaltic migrating motor complex aids in clearing antigens by sweeping them out of the GI tract. As mentioned above, secretory IgA serves as a barrier to pathogens and other antigens. The role of intraepithelial lymphocytes is not clear, but they may aid in clearing antigens that have penetrated into the superficial layer of the epithelium. The Kupffer cells bind IgA-antigen complexes before they reach the systemic circulation. Antigen-specific IgA and IgG circulating in the portal and systemic circulation bind antigen that has breached GI defenses.

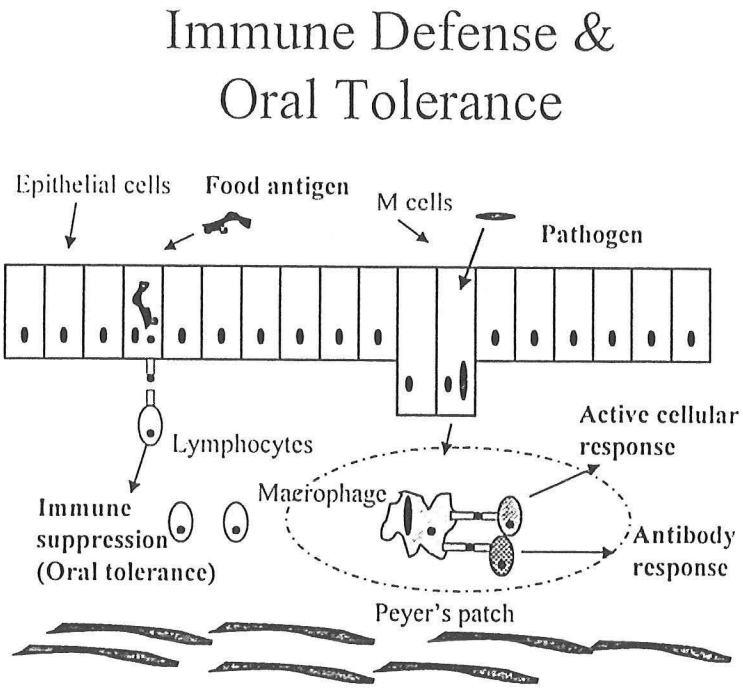
Uptake of intact food antigens
Despite barriers to the penetration of antigen, it is estimated that even in the mature GI tract about 1-2% of food proteins reaches the systemic circulation in an immunologically intact from and is transported throughout the body. The GI tract of infants is even more permeable, accounting in part for the higher incidence of food allergy [19]. When the intestinal barrier is compromised by inflammation (due to an infection, for example), the amount of antigen breaching mucosal defenses is substantially higher. If an active immune response were to be generated to all this protein, the system would be overwhelmed. However, the normal response to the absorption of food protein into the systemic circulation is immune tolerance, rather than an active immune response. The phenomenon of oral tolerance has been recognized for many years. In 1911 Wells fed guinea pigs ovalbumin and found that he was unable to elicit an immune response to it when it was later given systemically. This tolerance was found to be active, since T cells could transfer it to naïve animals.

Immune defense and oral tolerance

The mechanisms that lead to oral tolerance have not been elucidated, but models have been proposed. Evidence suggests that potential GI antigens may be processed by one of two different mechanisms: M cells or intestinal epithelial cells (IEC's).

Antigen processing by M cells has a major role in eliciting an active immune response. M cells are specialized epithelial cells often found over Peyer's patches. They have no surface microvilli, and the mucosa overlying M cells is devoid of glycocalyx, facilitating access to antigens. The cytoplasm of M cells extends into the lamina propria. M cells have lectin receptors for a number of bacteria and viruses and are efficient in taking up intact pathogens and large macromolecules. These antigens are passed intact to lamina propria macrophages that present the antigen to T cells in the Peyer's patches. T cell activation in Peyer's patches induces CD8+ T cells to differentiate into cytolytic effectors (cell-mediated response) and B cells to differentiate into plasma cells (antibody response). Thus, bacterial and viral antigen processing through M cells tends to elicit an active inflammatory response.

It has been proposed that protein processing by IEC's has a major role in generating oral tolerance to food proteins. IEC's express major histocompatibility (MHC) class II molecules. They can take up small soluble proteins from the lumen and transport them from the apical to basolateral aspect of the cell, where they are presented to LPLs. IECs appear to activate CD8 + suppressor T cells. There is evidence that nonclassical MHC I molecules, such as CD 1d, are involved in this response. Small soluble food proteins processed through IECs (in contrast to bacterial and viral antigens) generally elicit T cell suppression and oral tolerance rather than an active cellular and antibody response.



Food Allergy

The classic experiment of Prausnitz and Kűstner in 1921 was an early study of food allergy. Kűstner was known to be allergic to fish, while Prausnitz was not. Serum was taken from Kűstner and injected into the skin of Prausnitz' forearm. When Prausnitz ate fish, a wheal at developed at the site of the injection, thus demonstrating the passive transfer of food hypersensitivity [20]. IgE-mediated immediate hypersensitivity reactions to food, as illustrated by the Prausnitz/Kűstner reaction, are involved in the pathogenesis of anaphylaxis, as well as in some cases of rhinitis, asthma, urticaria, atopic dermatitis and GI symptoms. The pathogenesis of some of these syndromes has not been completely elucidated. Immunologic reactions to food also involve non IgE-mediated mechanisms, such as immune complex formation and cell-mediated immune reactions. These are less well understood than IgE mediated immediate hypersensitivity.

Food Allergens

Although there are hundreds of different foods in the normal human diet and thousands of potential antigens, a small number account for most of food-induced allergic reactions. In children, cow's milk, eggs, peanuts, soy, and wheat account for about 90% of reactions. In adolescents and adults, peanuts, tree nuts, fish, and shellfish account for about 85% of reactions. Allergies to other ingredients such as food colorings, preservatives, and spices occur, but they are rare [21].

Common Food Allergens

Children	**Adults**
Cow's milk	Peanuts
Eggs	Tree Nuts
Soy	Fish
Wheat	Shellfish
Peanuts	
Tree nuts	
Fish	

Food allergens are generally heat-stable, water-soluble glycoproteins ranging in size from 10 to 70 kd. A number of food allergens have been identified and characterized, including those from peanuts, cow milk, codfish, shrimp, soybeans, hazelnut [22]. IgE binding epitopes have been mapped on many of the protein fractions. This has improved our understanding of such observations as cross reactivity between certain pollens and fresh fruit (See Oral Allergy Syndrome below) [23].

Peanuts

Peanuts are among the most allergenic of foods. The major peanut allergens, designated Ara h1, h2, and h3, have been characterized, cloned, and sequenced. Ara h1 forms a complex that resists digestion and presents multiple epitopes that are spatially adjacent to each other in the folded protein. Single amino acid substitutions can markedly change allergenicity [24]. Patients with severe peanut allergies should be careful to avoid exposure to peanut products of any type. In a randomized study refined peanut oil caused no

reactions in peanut-allergic patients. However, less processed oil (also known as crude or pressed oil) caused reactions in 10% of patients [25].

Cow's milk

Cow's milk is among the first foods introduced to infants, and one of most common allergens in children. There are at least 30 immunogenic protein components in milk. There is no consensus regarding which components are the most allergenic.

Seafood

Seafood in general (crustaceans in particular) is a common cause of food allergy. Allergy to seafood tends to persist despite avoidance. Seafood allergy is common among workers in the industry. In one study, 16% of a group of Canadian seafood workers had occupational asthma. Even inhalation of fumes of cooking seafood can produce allergic reactions [26]. At least one of the major shrimp allergens (Pen a I) has been identified. There appear to be shared antigenic determinants among shrimp, lobster, crawfish, and crab. Patients with allergy to crustaceans rarely report cross reactivity with fish, but fish sensitive patients may report concomitant shrimp sensitivity [27].

FOOD ALLERGY SYNDROMES

Food allergy is generally characterized by specific problems in one or more organ systems in response to one or a few foods.

- Cutaneous: itching, flushing, urticaria, angioedema, atopic dermatitis
- Respiratory: nasal congestion, rhinorrhea, laryngeal edema, bronchospasm
- Gastrointestinal: perioral itching, paresthesias, and swelling; nausea and vomiting; abdominal cramping; diarrhea; enteropathy
- Cardiovascular: hypotension, shock, depressed cardiac output.

Food allergy has not been confirmed to be a cause of behavioral problems, chronic fatigue, and multiple subjective symptoms. Food allergy has been implicated as a cause of headaches and arthritis only in isolated case reports [28,29]. In many cases food-associated headaches are due to toxic reactions to food additives rather than to allergy, as discussed below (see Non-Allergic Food Reactions). It is rare to have allergies for more than a few foods.

IgE-Mediated Food Allergy Syndromes

Anaphylaxis

Anaphylaxis refers to a systemic reaction caused by IgE crosslinking and release of mast cell and basophil mediators. Symptoms occur in a number of different organ systems.

Food is one of the most common causes of outpatient anaphylactic reactions. In theory, any food protein may cause anaphylaxis. Among the most commonly implicated are peanuts and tree nuts, fish, shellfish, cow's milk, eggs, fruit, seeds and cereals such as wheat. The amount of food necessary to cause anaphylaxis varies with the individual and with the food. Some patients are sensitive to microgram quantities of peanuts, and, as mentioned above, other patients are sensitive to inhalation of fumes from cooking fish. In other cases serious reactions occur only with a relatively large portion of food. Prior

exposure and sensitization to a food must occur before an anaphylactic reaction is elicited, but patients, particularly children, often have a first reaction without known prior exposure. There are several possible explanations for this. Infants are sensitized to some antigens through maternal breast milk. Other exposures may occur through foods hidden in processed foods, or through cross-sensitization to a similar antigen.

Frequency of Symptoms Associated with Anaphylaxis

Symptoms	Percentage
Urticaria or angioedema	90
Upper airway edema	55
Dyspnea/wheezing	50
Flushing	45
Dizziness, hypotension, syncope	33
GI symptoms	30
Rhinitis	15
Headache	15
Itching without rash	5

(Modified from [30])

PN and TN allergies are among the most common food allergies. In a recent telephone survey, the self-reported prevalence of allergies to peanuts and tree nuts among U.S. adults was found to be about 0.5% to 1% [31]. PN and TN allergies may be life threatening, and are rarely outgrown. In a careful study of 122 children with PN and/or TN allergies it was found that these allergic reactions occurred early in life, at a median age of 2 years for PN and 5 years for TN. In 70% of cases there was no previous known exposure at the time of the first reaction. Subsequent accidental exposures were common, occurring in about half of the children over a 5-year follow-up. Many of these accidental ingestions occurred outside the home [32].

The features of food-induced anaphylaxis have been reviewed in several studies. In a careful review of 13 cases of fatal or near-fatal anaphylaxis in children and adolescents, all the patients had known food allergies prior to the episode of anaphylaxis. In no case did the patients knowingly ingest allergen. Twelve of the 13 had asthma. Peanuts or nuts were responsible for 10 cases, milk for 2 cases, and eggs for 1 case. Six of the 7 who survived received epinephrine within 30 minutes of the onset of symptoms, compared to 2 of the 6 that died [33]. Other studies have confirmed that many patients have had a previous immediate hypersensitivity reaction, that asthma is a risk factor for severe anaphylactic reactions, that ingestion often involved hidden allergens served in schools or restaurants, and that a major factor contributing to survival is the early use of epinephrine [8,34].

Mouse models of both peanut anaphylaxis and IgE-mediated cow's milk hypersensitivity have been developed that may be useful in exploring the pathophysiology and developing new therapeutic approaches for these allergies [35,36].

Food-dependent exercise-induced anaphylaxis

In some individuals exercise can precipitate reactions ranging from pruritus and urticaria to life-threatening anaphylaxis-like reactions. These reactions are thought to be due to mediators that stimulate mast cell degranulation and release of histamine [37]. Some of these patients have exercise-induced symptoms only after eating and some after eating only specific foods. In a few such patients, particularly those developing symptoms before the age of 20, skin testing or RAST has been used to detect food-specific IgE [38].

Oral Allergy Syndrome

Oral allergy syndrome (OAS) is a form of IgE-mediated contact allergy confined to the mouth and throat. Patients with OAS who eat certain fresh fruits and vegetables experience the rapid onset of itching, tingling, and swelling of the lips, tongue, palate, and throat. OAS most often occurs among patients with pollen allergies. There is cross-reactivity between certain pollen and fruit antigens. For example, patients with allergic rhinitis due to ragweed may experience OAS with watermelon, cantaloupe, honeydew melon, and bananas. Patients allergic to birch pollen (most common in Scandinavia) may react to apples. Cooked foods do not generally cause symptoms. The diagnosis is based on the history and a positive skin test. However, these patients usually have negative skin tests when the tests are done with conventional commercial antigens, presumably because the relevant antigen is labile, and only present in fresh food. Skin tests should be done by pricking the suspected food and then pricking the skin with the same lancet [39].

Latex-fruit allergy

Allergy to natural rubber latex causes a variety of symptoms, ranging to urticaria to anaphylaxis. The prevalence of latex allergy in the general population is less than 1%, but higher in those with frequent exposure to inhaled latex allergens from powdered rubber gloves and wound or mucosal exposure to latex products. Healthcare workers have been found to have a 5% to10% prevalence of latex allergy. The highest prevalence, reported to be between 18 and 37%, has been reported in children with spina bifida and urogenital abnormalities. [40,41]. The diagnosis is made by history and skin or serum tests for latex-specific IgE. In the U.S. several serum tests are available that have moderately good predictive value [40].

A substantial number of persons with latex allergy also have food allergies, particularly to fruit. Studies have shown fruit allergy in 20 to 50% of patients with latex allergy. The most common foods implicated are avocado, banana, kiwi, and papaya. Allergy to a variety of other fruit, chestnuts, and fish has also been reported [42,43]. Conversely, the prevalence of latex allergy seems to be increased among patients with fruit allergy [44].

Latex allergy is IgE mediated. Natural latex is a complex material with many components capable of eliciting an IgE response, but evidence suggests that heveins are the major antigens. Hev b is an endochitinase that is also present in fruit. Thus, heveins may be the shared antigens that explain the cross-reaction between latex and certain fruits.

Non IgE-Mediated Food Allergy Syndromes and Food Allergy Syndromes of Uncertain Pathophysiology

Urticaria and Atopic Dermatitis

Urticaria is a skin disease presenting as raised, red, and intensely pruritic lesions, which may change in shape or location within a period of hours. It is mediated by mast cell degranulation in the superficial dermis. Some drugs, such as opiates and anesthetic muscle relaxants, cause mast cell degranulation and urticaria by non-IgE mediated mechanisms. Urticaria affects up to 25% of the population. About 70% of cases of urticaria are acute and self-limited, with rapid onset and resolution within several hours, while 30% are chronic, lasting for weeks or months. Causes of urticaria include drugs, plant products or metals, stinging insects, latex, infections and autoimmune conditions. Some cases develop in response to cold or other physical stimuli. Cholinergic urticaria is noted after exercise, sweating, or hot showers. However, a definite cause is found in only occasional cases of acute urticaria and rarely in cases of chronic urticaria. Urticaria is one of the most common manifestations of acute, IgE-mediated food allergy.
Up to 50% of adult patients with chronic urticaria attribute their condition to food allergy. However, in one study only 10% of these patients developed reactions with DBPCFC [45]. Urticarial reactions to food generally occur within 30 minutes of ingestion.

Atopic dermatitis (AD) is a form of eczema that often begins in infancy and is often associated with allergic rhinitis and asthma. Skin lesions are pruritic, red, and scaly. The skin may become thickened and lichenified. Distribution varies with age. AD is often familial. It may be related to a maternal gene located on chromosome 11 [46]. Food allergies can be documented by DBPCFC in 30 to 40% of children with moderate to severe AD. Among children with AD and documented food allergies, food allergen avoidance often results in substantial improvement [5,47]. Food allergies are much less common among adults with AD. The pathogenesis of the relationship of AD to food allergy is not well understood.

Allergic Rhinitis and Asthma

During acute IgE-mediated allergic food reactions, upper respiratory symptoms such as rhinitis and lower respiratory symptoms such as bronchospasm commonly occur in conjunction with other symptoms such as urticaria. However, food allergy uncommonly causes isolated bronchospasm in children and does so very rarely in adults. In studies of children followed in asthma clinics, 2 to 6% were found to have wheezing provoked during blinded food challenges [6,48]. In another study of asthmatic children selected for histories of adverse reactions to food, 24% had positive blinded food challenge with wheezing as one of the symptoms, but only 2% had wheezing as an isolated symptom [49]. Children with asthma who have symptoms related to food allergy most often are highly atopic. Concomitant allergic rhinitis, atopic dermatitis and high serum IgE levels are common. Among a group of such atopic children with asthma, 15% developed wheezing during blinded food challenge, although only about ½ of these patients had a significant fall in $FEV_{1.0}$ [50]. It is possible that the contribution of food allergy to asthma has been underestimated in some studies. Many of the children studied had severe asthma

requiring daily medication, thus minimizing the effect of food challenge on $FEV_{1.0}$. In a study that measured airway hyper-responsiveness by methacholine challenge before and after blinded food challenge, significant changes were noted in 7 of 12 patients who developed symptoms after challenge [51]. It is reasonable to conclude that food hypersensitivity plays a significant role in a subset of children with asthma, specifically those who have other atopic conditions such as atopic dermatitis.

GASTROINTESTINAL FOOD ALLERGIC REACTIONS

Pathophysiology

The pathophysiology of gastrointestinal food allergic reactions is not well understood. Some gastrointestinal food allergic reactions are IgE mediated in children, but evidence for IgE mediated mechanisms is much weaker among adults [52,53]. Gastrointestinal food allergic reactions in adults verified by DBPCFC do not correlate with skin or RAST testing for IgE antibodies [54]. It is possible that only local GI IgE- mediated reactions are involved. Increased IgE levels have been found in the feces of patients with documented food allergies who have negative skin tests and/or RAST [55,56]. Endoscopic studies have explored the local effects of food allergens. In one study investigators applied solutions of antigens or placebo controls directly to the gastric mucosa at endoscopy in 30 patients with DBPCFC confirmed food allergy and in 20 normal subjects. Only ½ of the allergic patients had positive skin tests or RAST. They observed the mucosal reaction over 10 to 20 minutes and obtained biopsies. They noted macroscopic reactions such as swelling, erosions, and bleeding. Tissue examination showed decreases in tissue histamine and mast cell counts [57]. An uncontrolled and unblinded colonoscopic allergen provocation study showed similar results [58].

There are several possible mechanisms for non-IgE mediated GI allergic reactions, such as antibody mediated cellular cytotoxicity. One group of investigators found a correlation between antibody against beta lactoglobulin coated RBCs and cow's milk allergy in children [59]. Other investigators have postulated that immune complexes may play a role [60]. Cellular immune mechanisms may be important but have not been well-established.

Benign Food Protein-Induced Eosinophilic Proctocolitis

Dietary protein-induced eosinophilic proctocolitis is a mild disorder that occurs in infants fed with cow's milk, soy formula or even, in a few cases, hydrolysate. About 50% of cases have been reported in exclusively breast-fed infants. Rectal bleeding is noted, generally gradual in onset, usually as a small amount of blood in the diaper or streaks of blood on stools. Other than bleeding, the infants appear well. They do not develop colic, abdominal distention, or diarrhea. Weight gain is normal. The stool may contain increased polymorphonuclear leukocytes. A mild to moderate distal colitis is found, often with erosions. Biopsies show an eosinophilic infiltrate and, occasionally, crypt abscesses. This syndrome is likely due to an immune reaction to food proteins that in many cases are transported antigenically intact in breast milk. It is not clear why the inflammatory response is limited to the distal colon or what role the eosinophilic infiltrate plays. Treatment consists of use of a hydrolyzed casein-based formula. It may be necessary for breastfeeding mothers to completely eliminate their intake of cow's milk and soy protein. With treatment, bleeding and fecal leukocytes generally resolve within several days,

although the histologic changes may persist longer. The prognosis is very good. Chronic colitis does not develop. Reintroduction of allergen within the first months often leads to relapse, but infants generally lose their sensitivity and are able to tolerate a normal diet by the end of their first year [39,61].

Food Protein-Induced Enterocolitis Syndrome (FPIES)

Food protein-induced enterocolitis syndrome (FPIES) is an uncommon immune-mediated syndrome involving the small bowel and colon, most often presenting within the first several months of life. Symptoms usually develop between 45 and 90 minutes after feeding, and include irritability, vomiting, and diarrhea. FPIES often leads to failure to thrive, poor weight gain, and malabsorption. Infants may appear acutely ill and have leukocytosis [39,62-64].

The responsible allergen is usually cow milk, but 50% also have reactions to soy formulas, and some have reactions to proteins in maternal breast milk. Similar reactions to other foods, such as egg, wheat, rice, oats, peanuts, nuts, chicken, turkey, and fish have been reported, particularly in older children and rarely in adults [39]

The differential diagnosis includes giardiasis, C. dificile colitis, cystic fibrosis, and malrotation. Stools may have blood, polymorphonuclear leukocytes and eosinophils. Jejunal biopsies show patchy villous atrophy and infiltration with lymphocytes, plasma cells, eosinophils, and mast cells. Colon biopsies show a diffuse inflammatory cell infiltrate and crypt abscesses [65]. The diagnosis is usually made on the basis of the history, exclusion of other causes, and response to a hydolysate formula. Elimination of the responsible foods leads to improvement rapidly, usually within 72 hours. The diagnosis can be confirmed with oral challenge.

Most children lose their sensitivity by the age of 3. Rechallenge can be used to confirm loss of sensitivity, but should be done under medical supervision. In children who have not lost their sensitivity, reactions may be severe. Vomiting and diarrhea lead to serious volume depletion and even shock in up to 15% of cases. Peripheral WBC counts typically rise by at least 3500.

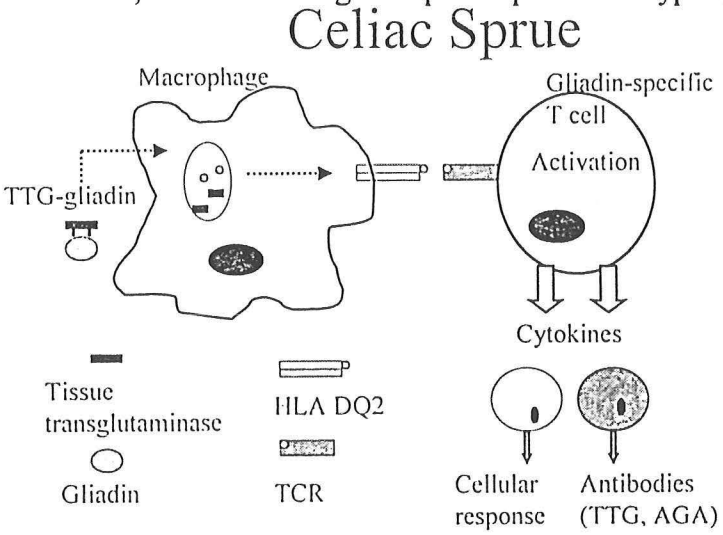
FPDIES is not IgE mediated. IgE antibodies to cow milk or other foods are not found. The immunopathogenic mechanism is unknown, but is thought to be T cell mediated. Cytokines secreted by activated T cells may impair the integrity of the mucosa on exposure to antigen. Secretion of TNF γ by cells isolated from intestinal biopsies is increased. Milk protein specific T cells secreting TNF γ have been demonstrated, and fecal TNF γ has been found in increased concentrations after positive milk challenge [62,63]. Antibody-dependent cell-mediated cytotoxicity may also play a role [59].

Allergic Eosinophilic Esophagitis

Cow's milk allergy may contribute to gastroesophageal reflux (GER) in a significant proportion of young children. In a series of 204 children (mean age 6 months, range 1-12 months) with GER, 85 were found to have cow's milk allergy by elimination diet and 2 blind challenges. Children with GER and cow's milk allergy had higher prevalence of atopic dermatitis and diarrhea [66]. Esophageal biopsies showed an eosinophilic infiltrate. It seems reasonable to consider cow's milk allergy among infants with GER who do not respond readily to antisecretory therapy, particularly among atopic infants with diarrhea.

Celiac Sprue/ Dermatitis Herpetiformis

Celiac sprue (CS) and dermatitis herpetiformis are due to an immune reaction to proteins present in wheat and other grains. These conditions were reviewed in my Internal Medicine Grand Rounds in June, 1999. The allergen in CS is gliadin, a component of the storage proteins of wheat and other related grains. Among patients with CS, ingestion of gliadin leads to damage to the small bowel mucosa. A dense inflammatory infiltrate in the lamina propria is associated with damage to the epithelial cells, villous atrophy, and crypt hyperplasia, leading to a variable degree of malabsorption. CS is strongly associated with specific HLA class II D region genes. The specific HLA II DQ alleles DQA1*0501 and DQB1*0201 are present in more than 95% of CS patients. This haplotype codes for an antigen presenting surface molecule termed DQ2. A complex immune reaction seems to take place in these patients. Tissue transglutaminase (TTG) is an enzyme located in the lamina propria ordinarily involved in response to injury. TTG deaminates proteins, including gliadin. TTG is thought to form a complex with gliadin. The TTG-gliadin complex is taken up and processed by antigen presenting cells, which then activate gliadin-specific T lymphocytes. In response to T cell stimulation, mucosal B cells produce both IgA and IgG antibodies to gliadin (AGA). Autoantibodies are also produced to TTG. The role of AGA and TTG antibodies in mucosal injury has not been determined. It is the cellular immune response rather than the antibody response that causes mucosal damage in CS. In response to gluten challenge there is a dense infiltration of the lamina propria with CD4 + T lymphocytes. Cytokine production leads to recruitment of a number of inflammatory cells, including mast cells, basophils, and eosinophils. Several cytokines have complex effects on the epithelium. TGF, for example, stimulates proliferation of crypt cells and interferes with epithelial cell differentiation, effects that might help to explain the crypt hyperplasia seen in CS.



Eosinophilic Gastroenteritis

Eosinophilic gastroenteritis is an uncommon disease characterized by dense eosinophilic infiltration of the GI tract in the absence of parasites, vasculitis, or other systemic causes of eosinophilia. Peripheral eosinophilia is commonly but not invariably present. It has been reported in all age groups. Any part of the GI tract may be involved, but the stomach and small bowel are the most common sites. The infiltration may involve the

serosal surfaces, the muscularis, the mucosa, or a combination of sites. The number of eosinophils exceeds 20 per high power field. A wide variety of symptoms may be seen, depending on the site predominantly affected, and include abdominal pain, ascites, obstruction, bleeding, perforation, diarrhea, protein-losing enteropathy, and malabsorption. The diagnosis is made on the basis of the clinical presentation and biopsies. The pathophysiology is not understood. The presence of the eosinophilic infiltrate suggests an allergic basis. About ½ of patients have allergic disease such as asthma. Some patients have elevated serum IgE levels, and others may have food-allergen specific IgE antibodies. A substantial number of patients have food intolerances. In a subset of such patients a specific food allergen can be identified. Improvement may occur on an elimination diet, but is often temporary. Symptomatic patients are usually treated with steroids [67-70].

EVALUATION OF FOOD ALLERGIES

The evaluation of food allergies is straightforward in cases where a dramatic and objective symptom follows closely on the ingestion of a specific food. It is more difficult if the symptoms are not dramatic or objective, the onset is delayed, or if a variety of foods seem to cause the reaction.

History

The goals of taking a history among patients with adverse food reactions are to:

1) determine whether the pattern of the symptoms coincides with previously described syndromes and
2) define the problem accurately so that a diagnostic plan can be designed.

Items that should be explored include:

- Risk factors- atopy, asthma; age of exposure of foods (cow's milk, solid foods);
- Age at first occurrence and most recent occurrence;
- Description of symptoms, including severity;
- Timing from food ingestion and onset of symptoms;
- Quantity of food required to produce symptoms;
- Number of occasions that food has caused symptoms, and
- Association with exercise.

A diet diary may be helpful if the history is not clear. A diary is most helpful when symptoms occur intermittently, when suspect foods are eaten infrequently, and when the symptoms occur shortly after exposure

Tests for Food Allergen-Specific IgE

Skin tests

Skin tests should be done by experienced practitioners. The choice of allegens to be tested, the reagents to be used, and the interpretation of the results requires training and experience. In addition, severe and unexpected anaphylactic reactions may occur, and the practitioner must be trained and equipped to deal with these emergencies. Skin tests are commonly used to test for food allergen-specific IgE. A small quantity of dilute (usually 1/10 to 1/20) glycerinated extract of allergen is placed on the skin. The allergen is

delivered to the dermis by pricking the skin through the solution with a bifurcated lancet. Intradermal injection has been shown to be inaccurate [71]. Saline-glycerine negative controls and histamine positive controls are applied at the same time. The reaction is measured after about 15 to 20 minutes. A wheal and flare reaction of at least 3 mm larger than the negative control or at least the same size as the histamine control indicates the presence of antigen-specific IgE [72]. Antigen solutions for many common foods are commercially available. Commercial available antigen solutions do not always give valid results. In cases of allergy to fruits and vegetables, the antigen used for testing must be fresh. Cooking and processing degrades relevant antigens. In such cases the antigen can be delivered by first pricking the unprocessed fresh food and then pricking the skin with the same lancet. Allergy medications should be withheld before testing, if possible. Skin tests must be done with caution among patients with a history of anaphylaxis. Reliable skin tests may not be possible among patients on medication and in those with dermatographism or extensive atopic dermatitis. In children younger than 2 years old, the negative predictive accuracy of skin tests is not as good as in older children.

"Provocation-neutralization" is a variation of skin testing which has no place in the evaluation and management of allergy. In this procedure, symptoms are produced by giving an intracutaneous dose of food allergen, then relieved by giving successive injections of other dilutions of the same allergen until a neutralizing dose is found. This procedure was found to be invalid by a rigorous double-blind, placebo-controlled clinical trial [73].

In Vitro Tests

Food allergen-specific IgE can be detected by radioallergosorbent tests (RAST). This technique uses food allergens bound to a solid support medium. Patient IgE attaching to the medium is detected by radiolabeled anti-IgE. The reliability of RAST varies from one food to another. It is useful among patients for whom skin testing is contraindicated or difficult. In vitro tests can be done while the patient is on antihistamines. RAST is semi-quantitative, and reported as Class 1 through 4, with 4 being the highest titer. The CAP System Fluorescent Enzyme ImmunoAssay (CAP FEIA) (Pharmacia Diagnostic, Sweden) is a relatively new in vitro assay that allows more accurate quantitative determination of IgE over a range of 0.35 to 100,000 kU/L.

The negative predictive value of skin tests and RAST is excellent. A patient with a negative skin test or RAST to a particular food allergen generally has less than a 5% chance of reacting to that food. However, the positive predictive value is much lower. Patients often have IgE to a number of food allergens without clinical allergy to those foods. The positive predictive value of both skin and RAST tests for clinical food allergy is about 30 to 40% in populations with a prevalence of about 10% [72,74]. Thus, confirmation by food challenge is often necessary. Foods to be tested should be carefully selected to include only those suspected to be of clinical importance, in order to avoid a large number of false positive tests.

The CAP FEIA offers advantages over standard RAST. In a recent study CAP FEIA was used to measure the concentrations of food-specific IgE in a group of 196 atopic children and adolescents previously evaluated by history, skin test, and DBPCFC. By using

receiver operating characteristic curves, the investigators found that they could set diagnostic levels of IgE (15 kU/L for peanut, for example) that predicted clinical allergy with greater than 95% certainty for egg, milk, peanut, and fish in populations with a prevalence of about 10%. Thus, the CAP FEIA test may eliminate the need to perform DBPCFC for confirmation of IgE-mediated allergies to these foods. The negative predictive value for these foods was less than 90%, however, and the positive predictive value for soy and wheat were found to be poor [74].

Although RAST and CAP FEIA tests are convenient, decisions regarding when they should be obtained, which allergens should be tested, and interpretation of the results require training and experience. It is prudent to refer patients who need these tests to specialists for evaluation.

Other In-Vitro Tests

A number of other in-vitro tests have been explored. Basophil histamine release has no better predictive value than skin testing or RAST and is used only as a research tool. Levels of other allergen-specific immunoglobulins, such as IgG4, IgM, IgA, and immune complexes do not correlate with clinical food allergy. IgG food-allergen specific antibodies are commonly found in asymptomatic normal individuals. Leukocytoclastic testing involves mixing white blood cells from patients with allergenic food extracts on microscopic slides and observing the cells for various toxic effects. This procedure has never been validated [75,76]. Serum tryptase is often for several hours elevated after episodes of anaphylaxis to insect stings, but is not as reliably elevated after food-induced anaphylaxis [77].

Elimination Diets

Elimination diets followed by oral food challenges are an important diagnostic tool. If the suspected food allergy is not IgE-mediated, skin tests and RAST will not be helpful. Elimination diets are most practical when only a few foods are suspected. The elimination of many foods simultaneously requires very strict or elemental diets that are difficult to follow. Even elimination of single food groups such as milk, eggs, or soy may be difficult, since they are used in a large number of prepared foods. Patients must be well informed and careful to avoid inadvertent ingestion. An experienced dietitian should be enlisted help to educate the patient or parents about reading labels and making sure the diet is balanced. The elimination diet is followed until there is resolution or definite improvement in the symptoms, usually one or two weeks. Suspect foods are then re-introduced one at a time.

Elimination diets may be unsuccessful if the responsible food allergen is not considered or if the patient does not completely avoid it during the trial period. Obviously, if the symptoms are not due to food allergy or intolerance, they will not improve during the trial. Elimination diets can substantiate an adverse reaction to food, but cannot establish that the reaction is due to an immune mechanism. An example of an oligoantigenic diet is given below.

Oligoantigenic Diet [77]
Rice or corn
Two to four vegetable chosen by the patient and physician
Two to four types of fruit chosen by the patient and physician
Chicken
White vinegar, olive oils, honey, sugar, salt

Oral Food Challenges
Oral food challenges are an important tool for substantiating suspected food reactions. Only a minority of suspected food intolerances are confirmed by blinded oral food challenges. As mentioned above, positive skin tests and RAST predict clinical allergy in less than ½ of cases. Therefore, food challenges help to avoid unnecessary and potentially harmful diet restrictions. As mentioned above, the new CAP FEIA can accurately predict a clinical reaction to certain foods (egg, milk, peanut, and fish) if the IgE level is above certain levels. In these cases, confirmation by oral food challenge can be avoided. Among patients with a history of severe anaphylaxis, the diagnosis of food allergy is often accepted without confirmatory oral challenge if the food was ingested alone or with other tolerated foods, and if a skin test or in vitro test for the specific IgE is positive. If the clinical history is convincing and the suspected food is not an important part of the diet (kiwi, for example), oral food challenge is usually not warranted. When multiple foods are suspected or when chronic diseases such as atopic dermatitis are being evaluated, confirmation of food allergy is important. Many childhood food allergies are outgrown, especially those to milk, egg, and soy, but skin tests may remain positive for years after the patient has become tolerant. Thus, periodic oral food challenges are often the only means to determine if an allergy has resolved [72].

Oral food challenges can be open, single-blind or double-blind placebo-controlled. Prior to food challenge, suspect foods are eliminated from the diet for at least 2 weeks, antihistamines are stopped according to their elimination ½ life, and asthma medications are reduced as much as possible. Patients should fast for 2 to 3 hours prior to the challenge. They should be examined carefully prior to the challenge to establish their baseline. For example, if bronchospasm is one of the symptoms, spirometry should be done prior to the challenge. Only experienced practitioners should do oral food challenges if there is any possibility of a severe reaction (for example, young children suspected of egg, milk, or peanut allergy). Patients should be observed in the medical setting for at least 2 hours after the last dose of the challenge, or longer if there is a history of delayed reactions.

Open Food Challenge
Open food challenges are appropriate when the likelihood of a positive reaction is judged to be low, based on the history, and when there is little risk of a severe reaction. Open challenge under medical supervision is useful method to refute an unlikely history of food reaction. For an open challenge, any form of the food the patient will eventually eat is acceptable. The food is given in gradually increasing amounts until a typical full serving has been given.

Single-blind food challenge eliminates the bias of the subject, and may be a practical technique for determining which foods from a long list might be causing symptoms.

Double-Blind Placebo-Controlled Food Challenge (DBPCFC)
The DBPCFC was introduced by Charles May in 1976 [78]. It has been accepted as the gold standard for the diagnosis of adverse food reactions, and has been used in both clinical and research settings. It will work for any physiological mechanism or timing if the challenge is designed correctly. The challenge is designed to reproduce the patient's history, including the amount of antigen required and the timing of the reaction. Guidelines for DBPCFC have been published [71,79,80].

A variety of mechanisms have been used to provide the food in a blinded fashion. Many common foods (such as milk, soy, and egg) can be obtained in dehydrated, powdered form and placed in opaque gelatin capsules. Test foods may also be placed in vehicles that disguise flavor and appearance, such as applesauce, grape juice, or tuna fish. Food and placebo should be prepared by someone other than the physician who will be observing the patient for reactions. The starting dose is usually about ½ the amount thought to be likely to produce a reaction. A typical dose might be 100 to 400 mg of dried food. For peanuts this would be the equivalent of about ¼ of 1 peanut, for milk about 3 mL. The timing of subsequent doses is scheduled so that the interval between challenges is slightly longer than the time predicted for a reaction to occur by the history. If the challenge is negative up to a total ingestion of 8 to 10 gm of dried food (or 60 to 100 mg of wet food) the challenge is stopped. Placebo trials are done in the same fashion. Negative trials should be confirmed by an open trial with a normal portion size of the food prepared in the usual fashion, to make certain that the blinded trial was not falsely negative because of differences in processing, for example.

MANAGEMENT OF FOOD ALLERGY

The mainstay of food allergy management is avoidance. Immunotherapy has been successful in the management of inhaled allergens, but not in food allergy.
Avoiding food allergens may be very difficult. Many common food allergens are ubiquitous, particularly in prepared foods, and are often hidden. The level of education about food allergy is generally inadequate. Children with food allergies are not sophisticated about allergen avoidance. Many inadvertent ingestions occur outside the home, in schools or restaurants. Even schools who have identified pupils with food allergies are often not prepared to help affected children avoid their allergens or to cope with a food allergic reactions. As illustrated by the case presentation, many restaurants have a limited understanding of food allergy.

The Problem of Inadvertent Food Allergen Ingestion

Inadvertent food allergen ingestion is common. This is a critical problem for patients who have had anaphylactic reactions. There are a variety of reasons for allergens being hidden in foods. The same utensils may be used to serve or process different foods. For example, a delicatessen slicer may be used to slice both meat and cheese. A wok used to prepare one dish using peanuts may be inadequately cleaned before preparing another dish, contaminating the second dish with peanut allergens. Reactions can occur to very small

quantities of food allergens. Even inhalation of allergens carried in air or cooking fumes has been reported to cause reactions, for example to fumes from steamed shrimp [81]. Peanut allergic patients have reported reactions to airborne allergens when peanut snacks are simultaneously opened by a number of passengers [82].

It may be difficult to discern from food labels whether a particular allergen is contained in the product. The labels may be inaccurate. Ingredients may be switched without a change in the labeling. For example, one type of oil may be switched for another if a shortage of the listed oil occurs. The omission of some ingredients may be permitted by regulation if they are present in less than a specific percentage. Labeling regulations vary in different countries, so that imported foods may not have the same information as foods packaged in this country. A major source of difficulty for patients is that a food may be listed on the label by an uncommon term. This is common for egg, milk and soy.
A glaze of egg white may be used to give pretzels, bagels, and other baked goods a shiny appearance. Egg products may be found in cosmetics, shampoos, and pharmaceuticals.
Milk proteins may be found in a large variety of processed foods. Lactose may contain residual milk protein. Lactose is sometimes used as filler for the manufacture of medications. Products listed as produced from soy may also contain milk protein.
Soy is used in many ways for a large variety of processed foods. Soybean flour is used extensively in baking and is often added to cereal products. It is also used in the manufacture of processed meats. Soy protein may be used to emulsify fat and thus may be found in such products as mayonnaise and ice cream. Soybean oil may contain soy protein, and soybean oil is used for many products, such as magarine, baby foods, and salad dressings.
Peanuts are added to a large variety of processed foods, such as ice cream, marinades, and biscuits. Peanuts are often used for flavoring or seasoning. Peanuts are sometimes used for the manufacture of vegetable burgers or health foods.

<u>Labels that may indicate milk protein</u>

Butter/butter fat	Caramel color/flavoring	Casein
Curds	Whey	Caseinate
Lactalbumin	Milk solids	Rennet casein
Lactose		

<u>Labels that may indicate soy protein</u>

Gum arabic	Guar gum	Carob
Emulsifier	Thickener	Stabilizer
Bulking agent	Lecithin	Starch
Vegetable protein	Vegetable gum	Vegetable starch
Vegetable broth	Protein	Protein extender
Tofu	MSG	Miso

<u>Prevention of food allergies</u>

It is appealing to speculate that food allergies in children could be reduced by breastfeeding and by avoiding early exposure to antigens, particularly in children with a family history of atopy. In theory, breastfeeding would reduce antigen exposure through

forming complexes with maternal IgA. Exclusive breastfeeding would reduce exposure to other antigens, such as cow milk antigens, while the infant GI immune system is maturing. The benefit of exclusive breastfeeding might be improved by maternal allergen avoidance, since many antigens are secreted in breast milk. Delaying the introduction of any solid food for 6 months and particularly allergenic foods such as peanuts during the first year might be expected to help.

There are several studies of breastfeeding and maternal allergen avoidance. In one study, breastfed infants of mothers who avoided eggs, cow milk, and wheat during first 3 months had 11% incidence of atopic dermatitis at 6 months compared to 28% of infants whose mothers did not avoid these foods [83]. In another study two groups of breast-fed children with family history of atopy were followed to age 4. In one group the mothers followed a diet free from cow milk, eggs, fish for first 3 months. In the other group, the mothers followed a regular diet. In the group in which the mothers followed a low allergen diet, the incidence of atopic dermatitis in the infants was 29%, compared to 56% in the control group [84].
Neither of the above studies was placebo-controlled. In a randomized, prospective study of combined maternal and infant food-allergen avoidance, breastfed infants with a family history of atopy were chosen. In one group mothers avoided cow milk, eggs, and peanuts during late pregnancy and breastfeeding. Infants were given a casein hydrolysate formula for supplement or weaning. Solid food was avoided for 6 months, and eggs, peanuts, and fish for 12 months. In the second group, maternal diets were unrestricted and infants were fed according to the guidelines published by the American Academy of Pediatrics. At one year there was a lower cumulative incidence of urticaria, atopic dermatitis, and/or GI disease among the infants in the intervention group. There was no difference in the incidence of allergic rhinitis or asthma. By the age of 2 years there was no differences at all between the groups [85]. It seems reasonable to conclude that in infants with a family history of atopy, these measures have a modest benefit, primarily by delaying, but not necessarily preventing, the onset of some allergic conditions in some infants.

Management of Acute IgE-Mediated Food Reactions

The best treatment for IgE-mediated food reactions is avoidance, but many patients will ingest allergen inadvertently despite their best efforts.

Epinephrine is the mainstay of the treatment of anaphylaxis. Patients with previous systemic food allergy reactions should carry self-injectable epinephrine. Two brands are available Anakit (Bayer) contains a syringe with 2 doses of 0.3 mL of 1/1000 epinephrine each as well as four 2 mg chewable tablets of chlorpheniramine. Epipen Autoinjector (Dey) comes in 2 strengths, "Jr" with 0.15 mL of 1/1000 epinephrine and the regular strength, with 0.30 mL. For mild to moderate symptoms 0.3 to 0.5 mL of 1:1000 epinephrine should be given subcutaneously or intramuscularly and can be repeated every 10 to 15 minutes up to a total of 3 doses. For severe reactions the recommended dose 0.5 to 1.0 mL of 1:1000 epinephrine IV every 5-10 minutes. Epinephrine can also be given as a continuous infusion of 1.0 to 10.0 micrograms/min titrated to effect. If IV access is not available epinephrine can be given by endotracheal tube.

Large volumes of intravenous fluids may be required in severe cases in order to counteract massive volume redistribution.

Patients on beta-blockers may be resistent to epinephrine. In such cases glucagon can be used since it has non beta-receptor mediated ionotropic and chronotropic effects. The dose of glucagon is 1 to 5 mg by IV bolus, followed by and an infusion of 5 to 15 micrograms per minute. Other vasopressors, such as dopamine, norepinephrine, or phenylephrine may be also used for patients with refractory hypotension.

Anithistamines may also reduce the severity of anaphylactic reactions. A combination of H1 and H2 blockers is recommended, such as diphenhydramine 25-50 mg IV every 4-6 hours along with cimetidine 300 mg IV every 8 –12 hours.

Although their onset of action takes several hours, corticosteroids may reduce the frequency and severity of late phase reactions. Their effectiveness has not been conclusively proven.

It is important for practitioners to remember that some patients with even a mild early anaphylactic reaction will have a late recrudescence of symptoms that can be very severe. For this reason, patients with anaphylactic reactions must be observed for 4 to 8 hours [30].

Future Research

Animal models

The recent development of animal models to peanut anaphylaxis and IgE-mediated cow's milk allergy is likely to improve our understanding of food allergy.

Hypoallergenic foods

Continued advances in the understanding of food allergen epitopes may lead to several future benefits. It may be possible to create hypoallergenic food through genetic engineering. In Japan rice is a common allergen. Japanese investigators have isolated allergenic proteins from rice based on reactivity with IgE Ab from rice-allergic patients. cDNA clones encoding the proteins were isolated from a cDNA library used to deduce the amino acid sequences. Using this information it has been possible to create transgenic rice strains with reduced allergen content [86,87]. It may be possible to make similar modifications in strains of peanuts.

Immune modulation

A better understanding of the factors that lead some patients to react to antigen with IgE production and other active inflammatory responses rather than with immune tolerance may lead to the development of new pharmaceutical interventions. For example, inhibition of IgE production by modulation of cytokines may be feasible. Better understanding of allergenic epitopes may lead to the development of modified epitopes that could be used in immunotherapy [88].

NON-ALLERGIC TOXIC FOOD REACTIONS

Seafood Poisonings

Scombroid poisoning

Tuna, mackerel, jacks, dolphin, mahimahi, and bluefish contain large amounts of tissue histidine. Improper refrigeration may lead to proliferation of Proteus or other bacterial species that contaminate the fish. These bacteria decarboxylate histidine to histamine at temperatures between 20^0 and 30^0 C. However, orally ingested histamine is digested and produces no effects. Other histamine-like substances, such as saurine, may be responsible for the clinical effects. Cooking does not destroy the toxin. Histamine concentrations above 50 mg/100 gram fish are considered to be hazardous. A bitter, peppery taste may be noted, but there is often no change in the taste of smell of the fish. Symptoms begin minutes to several hours after ingestion. They include flushing and a hot sensation (especially of the face and neck), headache, dizziness, a burning sensation in the mouth and throat, and palpitations, Nausea, abdominal pain, and diarrhea are common. Bronchospasm may occur in severe cases. Symptoms generally resolve in 12 to 24 hours. Death has not been reported [89-91]. The syndrome resembles an IgE-mediated immediate hypersensitivity reaction, and can be mistaken for an allergy.

Ciguatera poisoning

Ciguatera is the most common fish-borne illness worldwide and a common cause of nonbacterial food poisoning in the U.S. A toxin produced by dinoflagellates is concentrated up the food chain from small to large carnivorous reef fish. The toxin has no taste or smell, and is not destroyed by freezing or cooking. Ciguatoxin is believed to interfere with calcium regulation of passive sodium channels. Symptoms usually begin within 6 hours after ingestion. GI symptoms are a common presenting complaint, including nausea, vomiting, abdominal cramps and watery diarrhea. Neurological symptoms may present early in the course or days after the gastrointestinal symptoms resolve. These include sensory disturbance such as paresthesias of the lips and extremities, reversal of hot-cold sensation, and tooth pain. Other symptoms include hypersalivation, vertigo, ataxia, and blurred vision. Neurological symptoms may persist for months. Hypotension, bradycardia, shock and coma have been reported but death is very rare [91].

Paralytic shellfish poisoning

Paralytic shellfish poisoning may occur with ingestion of mussels, clams, oysters and scallops that have concentrated toxins produced by dinoflagellates. The toxins, including saxitoxin and other neurotoxins, are heat-stable and not destroyed by cooking. Saxitoxin inhibits the fast sodium channel, blocking nerve and muscle action potentials. A single mussel may contain many times the lethal dose of toxin. Symptoms occur within 30 minutes of ingestion. The primary symptoms are neurological. Gastrointestinal symptoms are less common. Neurological symptoms include paresthesias, headaches, vertigo, ataxia, cranial nerve paralysis, and muscle paralysis. The fatality rate is 5 to 10%, with most deaths due to respiratory failure within the first 12 hours. Muscle weakness may persist for several weeks [91].

Neurotoxic shellfish poisoning

Neurotoxic shellfish poisoning is due to the toxin of a species of dinoflagellate found along the coast of Florida. Symptoms are milder than those of paralytic shellfish poisoning and consist of paresthesias with hot/cold sensation reversal, ataxia, vomiting and diarrhea. Muscle weakness and respiratory paralysis do not occur, and recovery occurs within a few days [91].

Puffer fish poisoning
Puffer fish, considered a delicacy in Japan, may be contaminated with tetrodotoxin, which is chemically related to saxitoxin, and causes a similar clinical syndrome. The mortality rate is high, but the prognosis is good if the patient survives the first 24 hours [91].

Adverse Reactions to Food additives

Sulfites include bisulfites, metabisulfates, and sulfur dioxide. These compounds are used to inhibit browning of fresh fruits and vegetables as well as dried potatoes. They inhibit growth of microorganisms in fermented foods such as wine or beer. They are also commonly used in seafood, tea mixes, dried fruit, and prescription drugs. About 4% to 10% of asthmatics may be sensitive to sulfites. Symptoms include bronchoconstriction, GI upset, tingling, and hypotension within 2-15 min after ingestion. Reactions can be mild to life threatening. The pathophysiology is unclear, but is not immune [75,92].

Monosodium glutamate (MSG) is a flavor-enhancing amino acid often used in Chinese food. A syndrome consisting of headache, a tight sensation of face, neck, and chest, palpitations, bronchospasm, sweating, and GI upset has been attributed to MSG. However, a number of studies have suggested that MSG does not cause symptoms more often than placebo, and expert review panels have concluded that MSG is safe [75,93-96].

Tartrazine (FD&C Yellow No. 5) is an azo dye very commonly used in foods such as soft drinks, ice cream, gelatins, salad dressings, cheese, and colored deserts. In some patients, particularly those who have aspirin intolerance, it may produce urticaria and bronchospasm [75].

Aspartame is a commonly used sweetener which has been implicated as a cause of headaches, neurological, and behavioral symptoms, but this has not been confirmed by controlled studies [75,97].

Headaches and food additives
A substantial number of patients who suffer from migraines relate their headaches at least in part to food additives. Nitrates and nitrites have been widely used as preservatives, colorings, and flavoring agents, particularly in processed meats. They have been reported to cause headaches and pseudoallergic reactions [98]. A number of other substances are suspected (but not conclusively proved) to be related to migraines. These include tyrosine (cheese and chocolate), histamine (red wine), benzoic acid (preservatives), and tyramine, an amino acid with sympathomimetic activty (aged cheese, overripe bananas, avocados, peanuts, pickled herring, chicken livers) [75].

THE FOOD ALLERGY AND ANAPHYLAXIS NETWORK

The Food Allergy and Anaphylaxis Network (FAAN) is a non-profit organization whose mission is to "increase public awareness of food allergies and anaphylaxis, to provide education, and to advance research on behalf of all those affected by food allergies." The FAAN website features items such as alerts on prepared food products found to contain allergens, recipes for food allergic persons, topic discussions, and essays about current research. Publications on the website are checked for scientific accuracy by a medical advisory board that includes many of the prominent leaders in food allergy research.

Website: http://www.foodallergy.org/
Address: The Food Allergy & Anaphylaxis Network
1040 Eaton Place, Suite 107
Fairfax, VA 22030-2208
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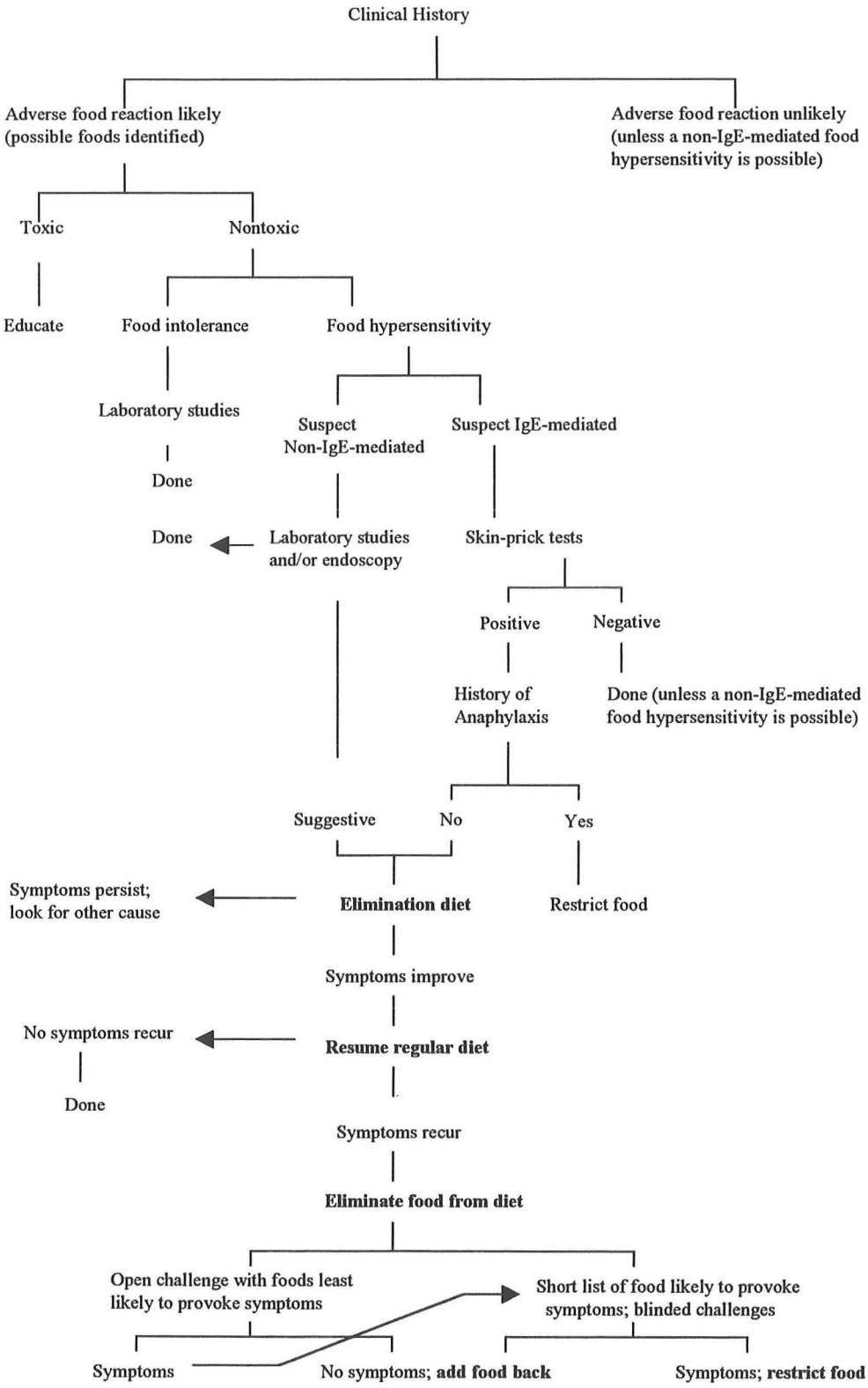
SUMMARY AND KEY POINTS

1) Food allergies occur in 2-8% of children and about 1% of adults. Children outgrow many food allergies.
2) A small number of foods account for most food allergies.
3) Many cases of suspected food allergy are not confirmed by blinded challenge.
4) Food allergies may be IgE mediated or non-IgE mediated. The pathophysiology of non-IgE mediated food allergy is not well understood.
5) Evaluation of suspected food allergies includes careful history, skin or serum tests for food-specific IgE, elimination diets, and food challenge.
6) The treatment of food allergen is avoidance, but this is difficult because many food allergens are ubiquitous and hidden.
7) Patients with a history of anaphylactic reactions to food should carry self-injectable epinephrine.

Algorithm For Evaluation And Management Of Food Reactions



From: Sampson HA. Food Allergies. In: Feldman M, Scharschmidt B, Sleisenger M, editors. Gastrointestinal Disease. Pathophysiology, Diagnosis, and Management. 7th ed. Philadelphia: W.B. Saunders, 2001:in press.

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