Annu. Rev. Nutr. 1996. 16:161–77

MECHANISMS OF FOOD ALLERGY

Hugh A. Sampson
Division of Immunology and Allergy, Johns Hopkins University School of Medicine, Baltimore, Maryland 21205

A. Wesley Burks
Pediatric Allergy and Immunology, University of Arkansas for Medical Sciences, Arkansas Children's Hospital, Little Rock, Arkansas 72202

KEY WORDS: food allergens, anaphylaxis, food intolerance

ABSTRACT

Our understanding of food allergy has made tremendous strides recently. With now–relatively uniform definitions of the clinical presentations of food allergy, the scientific literature is more discernible. In this progress, we have come to understand that the prevalence of food allergy is up to 8% in children and 2% in adults. Additionally, these studies have shown the role of specific allergens and mediators in the immunopathogenesis of food allergy. Much of the information available still relates to immunoglobulin E–mediated food reactions, although other immunologic mechanisms are being studied extensively. The diagnosis and treatment of food allergy is now much more standardized. Long-term studies have shown the natural history of many of these reactions.

CONTENTS

DEFINITIONS 162
PREVALENCE 162
IMMUNOPATHOGENESIS—FOOD ALLERGENS 163
MEDIATORS 165
CLINICAL PRESENTATION 166
DIAGNOSIS 169
TREATMENT 172
NATURAL HISTORY 174
SUMMARY 174

0199-9885/96/0715-0161$08.00

DEFINITIONS

Food-allergy research has made significant progress in the last 20 years. Working in an area of medicine that once relied heavily on anecdote, food-allergy researchers utilizing the model of food allergy have contributed greatly to our understanding of the immunoglobulin (Ig) E response and the human immune response in general. Multiple notable contributions to the scientific literature in this field have shed light not only on the clinical signs and symptoms, but also on the allergens and mediators that participate in this immune response.

The term allergy has been overused and abused (3). As the practice of medicine has evolved, it has become clear that many symptoms previously attributable to allergic reactions are the result of nonimmunologic mechanisms. One of the major difficulties in interpreting the medical literature has been the lack of a uniform definition of terms to define the clinical problems that are seen. These terms have now been standardized (3).

Adverse reaction is a general term applied to a clinically abnormal response attributed to an ingested food or food additive. *Food allergy* (hypersensitivity) denotes an immunologic reaction resulting from the ingestion of a food or food additive. For many, the term food allergy is synonymous with reactions that involve an IgE mechanism. Although IgE mechanisms account for the majority of immunologic reactions, in some reactions other immune mechanisms may play a part. *Food anaphylaxis* is the classic allergic, systemic hypersensitivity to a food or food additive that is mediated by IgE mechanisms and involves very specific chemical mediators. *Food intolerance* is a general term describing an abnormal physiologic response to an ingested food or food additive that is not proven to be immunologic in nature. This encompasses idiosyncratic, metabolic, pharmacologic, or toxic responses to a food or food additive. An *idiosyncratic response* is a quantitatively abnormal response to a food substance that differs from its physiologic or pharmacologic effect and resembles hypersensitivity but does not involve immune mechanisms. A *metabolic reaction* is an adverse reaction that occurs as the result of the effect of a food or food additive on the metabolism of the host recipient. A *pharmacologic reaction* is the result of a naturally derived or added chemical that produces a drug-like or pharmacologic effect in the host. *Food toxicity* implies an adverse effect caused by the direct action of a food or food additive on the host without the involvement of immune mechanisms. Toxins may be either contained within the food or released by microorganisms or parasites contaminating food products.

PREVALENCE

The actual prevalence of adverse food reactions is unknown. A consumer survey indicated that one third of American households believed that at least

one member of their family had food allergies (71). In 1983, the *Federal Register* estimated that approximately 15% of the population may be allergic to some food ingredients or ingredient (78).

Although the public believes the prevalence of food allergies to be quite high, many in the medical community suggest the true prevalence of food allergy is rare. Unfortunately, this difference in perception has caused numerous difficulties in the actual care of patients with possible food allergies. Only recently are there data in the medical literature that begins to address this issue.

In Colorado in a general pediatric practice, a prospective study followed 480 newborns through their third birthday (11). Of the 133 children thought to have had adverse food reactions, only 38 (or 8% overall) had symptoms confirmed by an oral food challenge. In a similar study performed in Denmark on 1759 infants, the prevalence alone of allergy to cow milk was found to be 2.2% (34). In a survey of 7500 households in the United Kingdom, approximately 20% of the sample reported a food intolerance (82). A subset of those reporting symptoms agreed to double-blind, placebo-controlled food challenges to at least one of eight foods: 19.4% had symptoms confirmed, suggesting an overall prevalence of adverse food reactions of 1.4–1.8%. A Dutch study found that although10% of a randomly selected adult population reported adverse food reactions, after blind challenges it was concluded that only about 2% were adversely affected (54).

The significant findings from these studies show that the vast majority of food allergic reactions perceived as being present in a baby's first year of life, as well as perceived food allergies in general, are much more common than proven food allergies are. In general, the consensus from the medical literature is that the prevalence of adverse food reactions is approximately 2–8% in infants and children and 1% in adulthood.

IMMUNOPATHOGENESIS—FOOD ALLERGENS

The major food allergens have been identified as water-soluble glycoproteins ranging from 10,000–60,000 daltons (47). They are generally stable to treatment with heat, acid, and proteases. The physicochemical properties that might account for their unique allergenicity are currently undergoing extensive study.

Cow milk, one of the first foreign proteins encountered by infants, is one of the most common food allergens. Its mixture of more than 20 protein components has been implicated in a number of possible immunologically mediated reactions (2). Several studies have examined the immune response to the individual milk proteins. Goldman et al skin tested patients with various milk proteins and found more patients to have a positive skin test to casein (it is known now that virtually all commercial sources of casein are contaminated with whey) (24). In oral challenges with the individual proteins, they found a

greater reaction to β-lactoglobulin. IgE antibodies to bovine gammaglobulin (10), α-lactalbumin, β-lactoglobulin, and bovine serum albumin (23) have been found in most milk-allergic patients. Immunoblotting studies, as well as other techniques, have shown significant cross-reactivity between milk proteins in cows, goats, and sheep.

Chicken egg is a common food allergen, particularly in children. Traditionally, the egg yolk has been considered less allergenic than the egg white (5). Ovalbumin, ovomucoid, and ovotransferin have been identified as the primary egg white allergens (45, 46). Recent evidence has indicated that previous studies showing ovalbumin (*Gad d* II) as the major egg white allergen were hampered by the presence of ovomucoid (*Gad d* I) in commercial ovalbumin preparations (8). After high-pressure liquid chromatography (HPLC) purification of the egg proteins, both prick skin testing and IgE- and IgG-specific ELISAs demonstrated significantly greater responses to ovomucoid in patients with challenge-positive egg hypersensitivity.

Peanuts appear to be one of the most allergenic foods for both children and adults. Unlike allergic reactions to milk and eggs, allergic reactions to peanuts typically do not abate over time. Utilizing different techniques, Bush et al identified multiple allergenic fractions (17). Recently, two major peanut allergens have been described, *Ara h* I and *Ara h* II (16, 15). Both are glycoproteins with acidic pI's and molecular weights of 63,500 and 17,500, respectively. Sequencing of the *Ara h* I gene revealed it to be a member of the vicilin family of seed storage proteins (14). The vicilin proteins are common to many legumes and other members of the plant kingdom (i.e. wheat, cotton). In general, hard-pressed peanut oils do not contain peanut protein, so patients with peanut hypersensitivity may consume these products safely (75).

Several cereal grains cause allergic reactions. An α-amylase-trypsin inhibitor from wheat, a glycoprotein with a molecular weight of less than 17,000, has been identified as a significant allergen in patients with Baker's asthma (6). In another study, highly degenerate profilin-specific primers were used to amplify by polymerase chain reaction the profilin-coding sequence of wheat complementary DNA (60). IgE binding to this protein revealed it to be a potential plant allergen with sequence similarity to the birch pollen allergen.

Profilins constitute a ubiquitous family of proteins that control actin polymerization in eukaryotic cells. In particular, profilin participates in the acrosomal reaction in animal sperm cells. Work from Valenta et al (79) has shown that profilins are prominent allergens that can be isolated from birch tree, timothy grass, and mugwort weed pollen. Approximately 20% of all pollen allergic patients tested displayed IgE reactivity to a recombinant birch profilin. The presence of profilin and possibly related proteins as cross-reacting allergenic components in various plants could provide an explanation as to why

certain allergic patients display IgE-mediated reactions to pollens and even to food from distantly related plants.

MEDIATORS

The role of specific cells and their mediators continues to be a much-debated topic with regard to food hypersensitivity reactions. Sampson and colleagues (62, 65) have completed several studies examining the cell type and mediators involved in such reactions. They have shown, following a positive food challenge, a rise in plasma histamine without a change in complement activity, basophil number, or total basophil content. In patients with atopic dermatitis and food hypersensitivity, skin biopsies obtained 4 and 14 h after challenge revealed eosinophil infiltrate and deposition of the eosinophilic protein major basic protein.

IgE molecules have also been found to participate in the inflammatory response via mechanisms other than direct mast cell activation. Children with atopic dermatitis and food hypersensitivity have high spontaneous basophil histamine release in vitro when compared with normal controls or atopic dermatitis patients without food hypersensitivity. Mononuclear cells from these patients also secreted high levels of histamine-releasing factor (HRF) (64, 66). After an appropriate food-elimination diet was implemented for approximately one year, spontaneous basophil histamine releasability and production of HRF fell to baseline levels and correlated clinically to less cutaneous hyperreactivity. In addition, passive transfer of this releasing factor could be demonstrated in nonatopic controls. Basophils from nonatopic individuals were stripped of all IgE molecules and sensitized with IgE from food-allergic patients. This rendered the normal basophils capable of secreting histamine in response to HRF. Previous studies have not detected a rise in serum tryptase in children experiencing food-induced anaphylaxis (67). As opposed to the mast cell's central role in anaphylactic reactions following insect stings, basophils, macrophages, endothelial cells, and their mediators may have a more active role in anaphylactic reactions following food ingestion.

Findings of alterations in lymphocyte function and cytokine production related to the pathogenesis of food allergy have recently been published. Mitogen-stimulated T cells from food-allergic patients with eosinophilic gastroenteritis produced less interferon gamma than did similarly stimulated T cells from normal individuals (36). Interleukin (IL)-4 and IL-5 production was markedly elevated in similar cultures (35). Compared with that of normal pediatric patients, in the challenge-proven, cow milk–allergic children, the maturation of interferon gamma-producing T cells and the function of suppresser T cells both appear to be delayed, and to normalize when oral tolerance is demonstrated (72, 73). The authors did not compare these responses in

children with immediate or delayed reactions to cow milk ingestion. Others have reported that interferon gamma production was significantly lower in children with late reactions following the ingestion of cow milk (low total IgE, cow milk–specific IgE) compared with children experiencing immediate anaphylactic reactions to cow milk (high total IgE, cow milk–specific IgE) (28).

A group of Japanese investigators has published a series of related articles examining proliferative responses of lymphocytes to food antigens in food-allergic atopic dermatitis patients. They reported that cell-mediated immune responses involving CD4+ lymphocytes and their secreted products, IL-2 and interferon gamma, are involved in late-onset food allergic reactions observed during food challenges in these patients (41). Additionally, proliferative responses of peripheral blood mononuclear cells (PBMC) from these patients increased following incubation of the PBMCs with the respective food allergen (1). The same investigators reported that decreased lymphocyte proliferative responses following appropriate food elimination may be useful in assessing the success of a particular elimination diet (70). This group has advocated the use of proliferative responses of PBMCs to heat-denatured food allergens in counseling food-allergic patients experiencing allergic symptoms with certain raw but not boiled or cooked forms of the same food (40). Recent studies by Sampson and others (4, 32) have not confirmed that lymphocyte proliferative responses are significantly increased in a group of patients with immediate food hypersensitivity reactions. Future studies will need to enroll patients only after blinded, placebo-controlled food challenges have taken place and other factors are adequately controlled.

Evidence that immunologic mechanisms (and presentations) other than IgE cause significant clinical food sensitivity is scant, though multiple studies have been published with many of the anecdotal variety. Food antigen-antibody complexes have been demonstrated in food-allergic individuals, but they also have been demonstrated in normal individuals. Although cell-mediated immunologic mechanisms contribute to several forms of adverse food reactions, no clear and objective demonstration has shown a cell-mediated food hypersensitivity disorder.

CLINICAL PRESENTATION

Hypersensitivity reactions to foods commonly provoke cutaneous, respiratory, and gastrointestinal symptoms. Cutaneous symptoms can include urticaria, angioedema, pruritus, and an erythematous macular rash. Respiratory symptoms may be evidenced by coughing, wheezing, profuse nasal rhinorrhea, sneezing, and laryngeal edema. Gastrointestinal symptoms can be nausea, cramping, vomiting, flatulence, and diarrhea. Some patients may experience generalized anaphylaxis following a specific food ingestion (67, 83). Risk

factors for fatal or near-fatal food hypersensitivity reactions include patients with asthma, adolescent patients, patients who do not receive epinephrine immediately after the reaction begins, and patients with a previous serious anaphylactic reaction. A brief report emphasized that a generalized anaphylactic reaction to a food in an infant or child can present with acute respiratory distress, mimicking a foreign body aspiration (31). Exercise-induced anaphylaxis may follow the ingestion of any meal or the ingestion of a specific food for which the patient has specific IgE antibodies (55). Children with severe IgE-mediated cow milk allergy have been shown to have more specific allergic sensitizations, atopic dermatitis, episodes of severe anaphylaxis, and hospitalizations than other atopic children (38).

The oral allergy syndrome is considered a form of contact urticaria that is confined almost exclusively to the oropharynx and rarely involves other target organs. The symptoms include rapid onset of pruritus and angioedema of the lips, tongue, palate, and throat. The symptoms generally resolve rapidly. This syndrome is most commonly associated with the ingestion of fresh fruits and vegetables (2).

Infantile colic is an ill-defined syndrome of paroxysmal fussiness characterized by inconsolable crying, drawing up of the legs, abdominal distention, and excessive gas. A variety of factors, including psychosocial and dietary, have been implicated in this syndrome. A blinded, cross-over study in bottle-fed and nursing infants suggested that IgE-mediated hypersensitivity may play a role in some infants with colic (48). It is likely though that this mechanism accounts for only 10–15% of colicky infants.

Food-induced colitis generally presents in the first few months of life; it is most often secondary to cow milk or soy protein hypersensitivity (26, 57, 59) but has also been reported secondary to egg, wheat, corn, fish, shellfish, and nuts (56). Exclusively breast-fed infants may develop colitis secondary to food allergens passed in their mothers' breast milk (44). In a series of patients, 45% of those infants diagnosed with food protein-induced colitis were exclusively breast fed (56). These infants generally do not appear ill, often have normally formed stools, and generally come to attention because of the presence of blood (gross or occult) in their stools. Lesions are confined to the large bowel and consist of mucosal edema with infiltration of eosinophils in the epithelium and lamina propria. In severe lesions with crypt destruction, polymorphonuclear leukocytes are also prominent (49). Over 50% of infants diagnosed with this disorder are sensitive to both cow milk and soy protein (13). The disorder tends to be outgrown by 18–24 months of age.

Malabsorption syndromes (excluding celiac disease) may present in the first several months of life with diarrhea (not infrequently steatorrhea) and poor weight gain (43). Symptoms may include protracted diarrhea, vomiting in up to two thirds of patients, failure to thrive, and carbohydrate malabsorption,

demonstrated by the presence of reducing substances in the stools. Increased fecal fat and abnormal D-xylose absorption are generally present. Cow milk sensitivity is the most frequent cause of this syndrome, but sensitivity to soy, egg, and wheat (transient celiac disease) have also been reported (52). In cow milk–induced malabsorption, serum IgA and IgG antibodies specific to cow milk proteins are elevated, but this is not specific to the malabsorption syndrome.

Celiac disease is a more extensive enteropathy leading to malabsorption. Total villous atrophy and extensive cellular infiltrate are associated with sensitivity to gliadin, the alcohol-soluble portion of gluten found in wheat, rye, barley, and oat. The incidence is reported as 1:4000 but is as high as 1:300 in Sweden (19). Approximately 90% of patients with celiac disease are histocompatibility antigen (HLA)-B8-positive and nearly 80% (compared with 20% or fewer in normal patients) have the HLA-DW3 antigen (76), supporting the genetic predisposition theory of the disease. Patients often present with diarrhea or frank steatorrhea, abdominal distention and flatulence, weight loss, and occasionally nausea and vomiting. Villous atrophy of the small bowel is a characteristic feature of celiac patients ingesting gluten, with increased lymphocytes, predominantly of the CD8 cytotoxic/suppresser phenotype, in the peripheral space (69). IgA antibodies to gluten are present in over 80% of adults and children with untreated celiac disease, and IgG antibodies to a variety of foods are elevated, presumably secondary to increased food antigen absorption. The immunopathogenesis of this disorder remains unclear, although a cell-mediated mechanism appears to be involved (77).

Allergic eosinophilic gastroenteritis is characterized by pronounced infiltration of the stomach and/or small intestinal mucosa, muscular layer, and/or serosa with eosinophils; clinical symptoms generally correlate with the degree of eosinophil infiltration of the small bowel wall (51). A syndrome of malabsorption generally is due to infiltration of the mucosal layer, whereas a picture of obstruction may follow infiltration of the muscular layer. Subserosal disease generally is characterized by eosinophilic ascites. The immunopathogenic mechanism(s) responsible for this disorder is not known, but peripheral blood T cells from these patients secrete excessive IL-4 and IL-5 (35), a finding consistent with the elevated IgE and eosinophilia seen in this disorder. In children, especially with gastroesophageal reflux, food hypersensitivity may be a more common cause of allergic eosinophilic gastroenteritis than was previously appreciated. A group of ten children with postprandial abdominal pain (colic), early satiety (or food refusal), vomiting (frequently with thick stringy mucus), occasionally diarrhea, and failure to thrive were reported (39). These children were refractory to all standard medical therapy; six of the ten children had undergone Nissen fundoplication and continued to have symptoms (retching instead of vomiting) and failure to thrive. Endoscopy and

biopsies of the esophagus, stomach, and proximal intestine were consistent with a diagnosis of allergic eosinophilic gastroenteritis. Following six to eight weeks of an amino acid-based elemental diet (Neocate® plus rice), symptoms completely resolved in eight of ten children, and biopsies revealed marked reduction or clearing of the eosinophilic infiltrate in the esophagus and significant improvement in the grade of basal zone hyperplasia and the lengths of the vascular papillae (39). Symptoms promptly recurred following challenges with specific foods.

DIAGNOSIS

As with all medical disorders, the diagnostic approach to the patient with a suspected adverse food reaction begins with a medical history and physical examination. Then to establish that a food allergic reaction has occurred, the following information is necessary: (*a*) the food suspected to have provoked the reaction; (*b*) the quantity ingested; (*c*) the length of time between ingestion and the development of symptoms; (*d*) a description of the symptoms provoked; (*e*) whether or not similar symptoms developed on other occasions when the food was eaten; (*f*) whether or not other factors (i.e. exercise) are involved; and (*g*) the length of time since the last reaction.

A diet diary has frequently been utilized as an adjunct to the medical history. Rarely, however, will this method detect an unrecognized association between a food and a patient's symptoms. In both diagnosis and management of adverse reactions, an elimination diet is used: The food or foods suspected of provoking the reaction are eliminated from the diet completely. Elimination diets are rarely diagnostic of food allergy, particularly in chronic disorders such as atopic dermatitis. Allergy prick skin tests (PST) are highly reproducible (74) and often are utilized to screen patients with suspected IgE-mediated food allergies. A food allergen (1:10 or 1:20 glycerinated food extract) eliciting a wheal (not including erythema) at least 3 mm greater than the negative control is considered positive; anything else is considered negative. A negative PST confirms the absence of an IgE-mediated reaction (overall negative predictive accuracy is greater than 95%). A positive PST indicates the possibility the patient has symptomatic reactivity to that specific food (overall the positive predictive accuracy is less than 50%). An intradermal skin test is a more sensitive tool than the PST is, but it is much less specific when compared with a blinded, placebo-controlled food challenge (12). In this study, no patient who had a negative PST but a positive intradermal skin test to a specific food had a positive food challenge to that food.

Radioallergosorbent tests (RAST) and similar in vitro assays (including enzyme-linked immunosorbent assays) are utilized for the identification of food-specific IgE antibodies. Although generally considered slightly less sen-

sitive than PSTs, one study comparing Phadebas RAST with blinded, placebo-controlled food challenges found PSTs and RASTs to have similar sensitivity and specificity when a Phadebas score of three or greater was considered positive (63). Overall, in vitro measurements of serum food-specific IgE performed in high-quality laboratories provide information similar to PSTs.

The clinical utility of basophil histamine release assays in the diagnosis of food allergy remains controversial. One review of this test summarized the use of basophil histamine release assays to food allergens and compared the results with standard RAST, PSTs, and actual oral challenges with the same food allergens (21). The concordance rate of the basophil histamine release assay with the RAST and PST were 87 and 74%, respectively, but only 50% when compared with actual food challenges. In general, the basophil histamine release assays have not been conclusively shown to be a reproducible diagnostic test for food hypersensitivity and have mainly been limited to research settings.

A prospective study evaluated the diagnostic value of intestinal mucosal IgE plasma cells, serum IgE level, and specific serum anti-cow milk IgE (RASTs) in cow milk allergy confirmed by elimination and challenge tests (68). A significantly greater number of children with cow milk allergy had intestinal mucosal IgE plasma cells when compared with a control group of children. Interestingly, these plasma cells were also found in some children with cow milk allergy even in the absence of abnormal RASTs to cow milk protein and elevated serum IgE concentrations. The authors concluded that using intestinal mucosal biopsies for the presence of IgE plasma cells in conjunction with standard measures of specific IgE plasma cells to cow milk proteins may aid in the diagnosis of cow milk protein allergy in some children. These results have implications for the food-induced enterocolitis syndrome where PSTs and serologic evidence of protein-specific IgE are usually negative, suggesting that the enterocolitis syndrome may be the result of an isolated intestinal hypersensitivity reaction.

One study proposed that specific IgG antibody concentrations for a major cow milk protein were predictive of the clinical response to an exclusion diet (18). Infants with atopic dermatitis as their only manifestation of cow milk allergy were studied. Graded oral challenges with cow milk over a one- to three-day period were used to confirm cow milk allergy. Total IgE and specific IgG antibody concentrations against the cow milk protein β-lactoglobulin were measured. As expected, the infants with positive cow milk challenges and with a positive response to an exclusion diet had significantly higher total IgE concentrations when compared with those infants with negative challenges and poor responses to the diet. Specific IgG concentrations to β-lactoglobulin were fourfold higher in the cow milk–allergic group but were not significantly different from those in the nonallergic, control group. The author's use of more

conventional diagnostic measures (i.e. oral food challenge and specific IgE antibodies to cow milk proteins) confirmed the clinical history and helped predict the response to an elimination diet. The milk-specific IgG concentrations did not provide any further diagnostic advantages.

The double-blind placebo-controlled food challenge (DBPCFC) has been labeled the gold standard for the diagnosis of food allergies (61). Over the last several years, many investigators have successfully utilized this test to examine a wide variety of food-related complaints from both children and adults. The foods to be tested in the oral challenge are based on a significant history and/or PSTs (RASTs). The food challenge should be administered with the patient in a fasting state, starting the challenge with a dose of food (generally 125–500 mg lyophilized) unlikely to provoke symptoms. This dose is then doubled every 15–60 min, depending on the type of reaction suspected to have occurred. Clinical reactivity is generally ruled out when the patient has tolerated 10 g of lyophilized food blinded in capsules or liquid. If the blinded portion of the challenge is negative, however, it must be confirmed by an open feeding under observation to rule out the uncommon false-negative challenge. A DBPCFC is the best means of controlling for the variability of chronic disorders (i.e. chronic urticaria, atopic dermatitis), for any potential temporal effects, and for acute exacerbations secondary to reducing or discontinuing medications. Particularly psychogenic factors and observer bias are eliminated. Overall, the DBPCFC has proven the most accurate means of diagnosing food allergy.

The diagnosis of food-induced colitis is established by eliminating the suspected food allergen(s) and by oral challenge. Hematochezia generally resolves within 72 h of appropriate food allergen elimination, but the resolution of mucosal lesions may take up to one month (26). Refeeding the food allergen elicits symptoms within several hours to days. Sigmoidoscopy findings are variable but range from areas of patchy mucosal injection to severe friability with small aphthoid ulcerations and bleeding. Colonic biopsy reveals a prominent eosinophilic infiltrate in the surface and crypt epithelia and in the lamina propria (56). Cow milk– and soy protein–induced colitis generally resolve by two to three years of age with allergen avoidance (57), and it is generally recommended that small amounts of milk or soy be cautiously reintroduced after the first year of life (42).

The diagnosis of the malabsorption syndromes is established by excluding the responsible food allergen from the diet and rechallenging the patient once symptoms have resolved. On endoscopy, a patchy villous atrophy is evident, and biopsy reveals a prominent mononuclear round cell infiltrate of the epithelium and lamina propria with a small number of eosinophils, not unlike celiac disease but generally much less severe (52). When the responsible allergen is excluded from the diet, symptoms resolve in several days to weeks, but villous atrophy and increased numbers of eosinophils, activated CD4+ cells

(HLA-DR+) in the lamina propria, and CD8+ cells in the intraepithelium (52) may take several weeks to months to revert to normal. Unlike celiac disease, this disorder appears to be transient, but a well-controlled series on the natural history of this disorder has not been carried out.

The European Society for Pediatric Gastroenterology and Nutrition proposed revised diagnostic criteria for celiac disease, which require greater dependency on serologic tests (81). Studies indicate that infants under 2 years of age should be screened for IgA anti-gliadin antibodies (25), whereas older individuals should first be screened for IgA anti-gliadin antibodies and then confirmed with IgA anti-endomysium antibodies (20), and possibly IgA anti-jejunal antibodies (80). However, the intestinal biopsy remains the gold standard (50), and the diagnosis is dependent on demonstrating biopsy evidence of villous atrophy and inflammatory infiltrate, resolution of biopsy findings after 6–12 weeks of gluten elimination, and recurrence of biopsy changes following gluten challenge. Once the diagnosis of celiac disease is established, gluten-containing foods should be avoided for life to control symptoms and avoid the increased risk of malignancy (33).

The diagnosis of allergic eosinophilic gastroenteritis is based on supportive history and biopsy findings of an eosinophilic infiltration of the gastrointestinal wall. Since the eosinophilic infiltrate may be sporadic, multiple biopsies are often required. A six- to eight-week trial on an elemental diet may be warranted in severe cases. A marked reduction in symptoms should occur within three to six weeks, although normalization of gut histology may require months. If symptoms resolve on the elemental diet, foods must be systematically reintroduced in order to determine which foods are provoking symptoms. Unlike classic IgE-mediated disorders, multiple food sensitivities appear more common in this disorder.

TREATMENT

After the diagnosis of food hypersensitivity is established, the only proven therapy is strict elimination of the offending allergen. It is important to remember that prescribing an elimination diet is like prescribing a medication: both can have positive effects and unwarranted side effects. Patients and parents should be taught and given educational material to help them detect potential sources of hidden food allergens by reading food labels appropriately. Symptomatic reactivity to food allergens is generally very specific. Patients, especially children, rarely react to more than one member of a botanical family or animal species (9).

The specific role of the diet in the ultimate resolution of food allergy is unknown. Shinoda et al (70) investigated the effect of elimination diets on T-cell responses to ovalbumin in hen egg–sensitive atopic dermatitis patients.

The proliferative responses of the patient's peripheral blood mononuclear cells and CD4+ T cells with monocytes decreased after a hen egg elimination diet. Similar proliferative responses to a recall antigen and phytohemagglutinin did not decrease after the same elimination diet. The authors concluded that elimination diets may help reduce the responsiveness of food-sensitive T cells. Certainly these results are intriguing, but they need confirmatory studies before further conclusions can be reached.

A multitude of articles address the influence of dietary manipulation on the incidence of atopic disease. One prospective study reported a reduced cumulative incidence of cow milk allergy during the first 18 months in high-risk infants who were fed breast milk, an extensively hydrolyzed casein formula, or an ultrafiltrated whey hydrolysate in combination with avoidance of solid foods during the first six months of life (27). No significant differences were observed between the breast milk–fed and formula-fed groups. A review by Hill & Hosking (30) summarized three studies examining the effect of dietary modifications during infancy on prevention of atopic disease in high-risk subjects. All three studies reported a reduced incidence of atopic dermatitis around the age of 12 months. The ultimate development of rhinitis or asthma was not changed. In another study, the influence of diet on the incidence of atopic disease in the first year of life was also compared in two groups of infants at high risk for atopy with and without breast-feeding for six months (maternal diet restricted to minimal egg and milk protein), soy formula as a supplement if necessary, and delayed introduction of solids after six months (7). Similar to previous studies, the treatment group experienced significantly fewer atopic symptoms. In summary, practical recommendations for the prophylaxis of allergic infants are currently available but will need continual evaluation as additional controlled studies are completed.

Continued studies evaluating a rush immunotherapy protocol to treat patients with food-induced anaphylaxis have been reported from the National Jewish Center for Immunology and Respiratory Medicine (53). Initial double-blind studies demonstrated that a reduction in titrated PSTs and DBPCFCs could be induced by a rush immunotherapy protocol over a five-day period with peanut extract and subsequent weekly maintenance extract injections (58). Follow-up studies confirm that weekly or biweekly maintenance immunotherapy with peanut extract for 8–11 months effectively reduces the sensitivity to peanut in terms of both reduction in PSTs and increase in threshold on DBPCFC, with peanut in the actively treated group but not the untreated peanut-allergic patients. The authors caution that the rush and maintenance immunotherapy protocols are associated with frequent, although usually not severe, systemic reactions, and that further controlled studies are needed to determine the practical use of this form of therapy for food-allergic patients.

NATURAL HISTORY

The natural history regarding the development of tolerance in food allergy was prospectively evaluated in 69 children with IgE-mediated cow milk allergy (29). Compared with 54 children remaining clinically reactive to cow milk, the 15 children who ultimately achieved clinical tolerance demonstrated a significant decrease in PST reactivity and had lower serum IgE antibodies to cow milk proteins both at the initial and at the final evaluation in the study (median two-year follow-up). No consistent change in the IgG antibody responses to cow milk proteins was observed in either group during the study. The authors concluded that children with more persistent severe cow milk allergy have a more severe dysregulation of IgE synthesis to proteins contained in this milk source. These findings confirm similar results from a previously published investigation on the development of tolerance in cow milk–allergic children (37).

SUMMARY

The research in food allergy has made significant progress, as evidenced by the multitude of studies related to various aspects of the immunopathogenesis of this disorder. Important work continues to examine the prevalence, mechanism, and diagnosis of food allergy. Future studies will no doubt have an impact on the treatment and modify the natural history.

Literature Cited

1. Agata H, Kondo N, Fukutomi O, Shinji S, Orii T. 1993. Effect of elimination diets on food-specific antibodies and lymphocyte proliferative responses to food antigens in atopic dermatitis patients exhibiting sensitivity to food allergens. *J. Allergy Clin. Immunol.* 91: 668–79
2. Amelot PL, Kemeny DM, Zachary C, Parkes P, Lessof MH. 1987. Oral allergy syndrome: symptoms of IgE-mediated hypersensitivity to foods. *Clin. Allergy* 17:33–42
3. Anderson JA. 1994. Milestones marking the knowledge of adverse reactions to foods in the decade of the 1980's. *Ann. Allergy* 72:143–54
4. Anderson JA, Sogn DD, eds. 1984. *Adverse Reactions to Foods*, NIH Publ. 84–2442,Am, pp. 1–6. Washington, DC: NIAID
5. Anet J, Back JF, Baker RS, Barnett D, Burley RW, Howden ME. 1985. Allergens in the white and yolk of hen's egg. *Int. Arch. Allergy Appl. Immunol.* 77: 364–71
6. Armentia A, Sanchez-Monge R, Gomez L, Barber D, Salcedo G. 1993. In vitro allergenic activities of eleven purified members of a major allergen family from wheat and barley flour. *Clin. Exp. Allergy* 23:410–15
7. Bardare M, Vaccari A, Allievi E, Brunelli I, Coco F, et al. 1993. Influence

of dietary manipulation on incidence of atopic disease in infants at risk. *Ann. Allergy* 71:366–71

8. Bernhisel-Broadbent J, Dintzis HM, Dintzis RZ, Sampson HA. 1994. Allergenicity and antigenicity of chicken egg ovomucoid (*Gal d* III) compared with ovalbumin (*Gal d* I) in children with egg allergy and in mice. *J. Allergy Clin. Immunol.* 93:1047–59
9. Bernhisel-Broadbent J, Sampson HA. 1989. Cross-allergenicity in the legume botanical family in children with food hypersensitivity. *J. Allergy Clin. Immunol.* 83:435–40
10. Bernhisel-Broadbent J, Yolken RH, Sampson HA. 1990. Allergenicity of orally administered immunoglobulin preparations in food-allergic children. *Pediatrics* 87:208–14
11. Bock SA. 1987. Prospective appraisal of complaints of adverse reaction to foods in children during the first 3 years of life. *Pediatrics* 79:683–88
12. Bock SA, Buckley J, Houst A, May CD. 1978. Proper use of skin tests with food extracts in diagnosis of food hypersensitivity. *Clin. Allergy* 8:559–64
13. Burks AW, Casteel HB, Fiedorek SC, Williams LW, Pumphrey CL. 1994. Prospective oral food challenge study of two soybean protein isolates in patients with possible milk or soy protein enterocolitis. *Pediatr. Allergy Immunol.* 5:40–45
14. Burks AW, Cockrell G, Stanley JS, Helm RM, Bannon GA. 1995. Recombinant peanut allergen *Ara h* I expression and IgE binding in patients with peanut hypersensitivity. *J. Clin. Invest.* 96:1715–21
15. Burks AW, Williams LW, Connaughton C, Cockrell G, O'Brien TJ, Helm RM. 1992. Identification and characterization of a second major peanut allergen, *Ara h* II, utilizing the sera of patients with atopic dermatitis and positive peanut challenge. *J. Allergy Clin. Immunol.* 90: 889–97
16. Burks AW, Williams LW, Helm RM, Connaughton C, Cockrell G, O'Brien T. 1991. Identification of a major peanut allergen, *Ara h* I, in patients with atopic dermatitis and positive peanut challenge. *J. Allergy Clin. Immunol.* 88:172–79
17. Bush RK, Taylor SL, Nordlee JA. 1989. Peanut sensitivity. *Allergy Proc.* 10: 261–64
18. Casimir GLA, Duchateau J, Gossart B, Cuvelier PH, Vandeale F, Vis HL. 1993. Atopic dermatitis: role of food and house dust mite allergens. *Pediatrics* 92:252–56
19. Cavell B, Stenhammar L, Ascher H, Danielsson L, Dannaeus A, et al. 1992. Increasing incidence of coeliac disease in Sweden: results of a national study. *Acta Paediatr.* 81:589–92
20. Corrao G, Corazza G, Andreani M, Torchio P, Valentini R, et al. 1994. Serological screening of coeliac disease: choosing the optimal procedure according to various prevalence values. *Gut* 35:771–75
21. DuBuske LM. 1993. Introduction basophil histamine release and the diagnosis of food allergy. *Allergy Proc.* 14:243–49
22. Eigenmann PE, Belli DC, Ludi F, Kahn KM, Polla BS. 1995. In vitro lymphocyte proliferation with milk and a casein/whey protein hydrolyzed formula in cow's milk allergic children. *J. Allergy Clin. Immunol.* 96:544–57
23. Gjesing B, Osterballe O, Schwartz B, Wahn U, Lowenstein H. 1986. Allergen-specific IgE antibodies against antigenic components in cow milk and milk substitutes. *Allergy* 41:51–56
24. Goldman AS, Anderson DW, Sellers WA, et al.1963. Milk allergy. I. Oral challenge with milk and isolated milk proteins in allergic children. *Pediatrics* 32:425–43
25. Grodzinsky E, Jansson G, Shogh T, Stenhammar L, Falth-Magnusson K. 1995. Anti-endomysium and anti-gliadin antibodies serological markers for coeliac disease in childhood: a clinical study to develop a practical routine. *Acta Paediatr.* 84:294–98
26. Gryboski J. 1967. Gastrointestinal milk allergy in infancy. *Pediatrics* 40:354–62
27. Halken S, Host A, Hansen LG, Osterballe O. 1993. Safety of a new ultrainfiltrated whey hydrolysate formula in children with cow milk allergy: a clinical investigation. *Pediatr. Allergy Immunol.* 4:53–59
28. Hill DJ, Ball G, Hosking CS, Wood PR. 1993. Gamma-interferon production in cow milk allergy. *Allergy* 48:75–80
29. Hill DJ, Firer MA, Ball G, Hosking CS. 1993. Natural history of cow's milk allergy in children: immunological outcome over 2 years. *Clin. Exp. Allergy* 23:124–31
30. Hill DJ, Hosking CS. 1993. Preventing childhood allergy. *Med. J. Aust.* 158: 367–69
31. Ho AMH. 1993. Food anaphylaxis: an important cause of acute respiratory distress in infants. *Anesth. Analg. Cleveland* 77:1289–90
32. Hoffman KM, Sampson HA. 1995.

Evaluation of the usefulness of lymphocyte proliferation assays in the diagnosis of cow milk allergy. *J. Allergy Clin. Immunol.* Submitted for publication
33. Holmes G, Prior P, Lane M, Pope D, Allan RN. 1989. Malignancy in coeliac disease—effect of a gluten-free diet. *Gut* 30:333–38
34. Host A, Halken S. 1990. A prospective study of cow's milk allergy in Danish infants during the first 3 years of life. *Allergy* 45:587–96
35. Jaffe JS, James SP, Mullins GE, Braun-Elwert L, Lubensky I, Metcalfe DD. 1994. Evidence for an abnormal profile of interleukin-4 (IL-4), IL-5, and gamma-interferon (gamma-IFN) in peripheral blood T cells from patients with allergic eosinophilic gastroenteritis. *J. Clin. Immunol.* 14:299–309
36. Jaffe JS, Metcalfe DD. 1993. Cytokines and their role in the pathogenesis of severe food hypersensitivity reactions. *Ann. Allergy* 71:362–64
37. James JM, Sampson HA. 1992. Immunologic changes associated with the development of tolerance in children with cow's milk allergy. *J. Pediatr.* 121:371–77
38. Kaplan MS. 1993. Complications in children with a severe allergy to cow milk. *Ann. Allergy* 71:529–32
39. Kelly KJ, Lazenby AJ, Rowe PC, Yardley JH, Perman JA, Sampson HA. 1995. Eosinophilic esophagitis attributed to gastroesophageal reflux: improvement with an amino-acid based formula. *Gastroenterology.* 109:1503–12
40. Kondo N, Agata H, Fukutomi O, Nishida T, Kameyama T, et al. 1993. Reduced responses of antigens in food-sensitive atopic dermatitis. *Ann. Allergy* 70:467–69
41. Kondo N, Fukutomi O, Agata H, Motoyoshi F, Shinoda S, et al. 1993. The role of T lymphocytes in patients with food-sensitive atopic dermatitis. *J. Allergy Clin. Immunol.* 91:658–68
42. Kosnai I, Kuitunen P, Savilahti E, Sipponen P. 1984. Mast cells and eosinophils in the jejunal mucosa of patients with intestinal cow's milk allergy and celiac disease of childhood. *J. Pediatr. Gastroenterol. Nutr.* 3:368–74
43. Kuitunen P, Visakorpi J, Savilahti E, Pelkonen P. 1975. Malabsorption syndrome with cow's milk intolerance: clinical findings and course in 54 cases. *Arch. Dis. Child.* 50:351–56
44. Lake AM, Whitington PF, Hamilton SR. 1982. Dietary protein-induced colitis in breast-fed infants. *J. Pediatr.* 101:906–10
45. Langland T. 1982. A clinical and immunological study of allergy to hen's egg white. II. Allergens in hen's egg white studied by crossed radio-immunoelectrophoresis. *Allergy* 37:521–30
46. Langland T, Harbitz O. 1983. A clinical and immunological study of allergy to hen's egg white. V. Purification and identification of a major allergen (antigen 22) in hen's egg white. *Allergy* 38:131–39
47. Lemanske RF, Taylor SL. 1987. Standardized extracts, foods. *Clin. Rev. Allergy* 5:23–36
48. Lothe L, Lindberg T. 1989. Cow's milk whey protein elicits symptoms of infantile colic in colicky formula-fed infants: a double-blind crossover study. *Pediatrics* 83:262–66
49. Machida H, Smith A, Gail D, Trevenen C, Scott RB. 1994. Allergic colitis in infancy: clinical and pathologic aspects. *J. Pediatr. Gastroenterol. Nutr.* 19:22–26
50. McNeish AS, Harms HK, Rey T, Shmerling D, Visakorpi J, Walker-Smith J. 1979. Re-evaluation of diagnostic criteria for coeliac disease. *Arch. Dis. Child.* 54:783–86
51. Min K, Metcalfe D. 1991. Eosinophilic gastroenteritis. *Immunol. Allergy Clin. North Am.* 11:799–813
52. Nagata S, Yamashiro Y, Ohtsuka Y, Shioya T, Oguchi S, et al. 1995. Quantitative analysis and immunohistochemical studies on small intestinal mucosa of food-sensitive enteropathy. *J. Pediatr. Gastroenterol. Nutr.* 20:44–48
53. Nelson HS, Conkling RN, Areson J, Sampson HA, Bock A, Leung DYM. 1994. Treatment of patients anaphylactically sensitive to peanuts with injections of peanut extract. *J. Allergy Clin. Immunol.* 93:211 (Abstr.)
54. Niestiji Jansen JJ, Kardinaai AFM, Huijbers GH, Vlieg-Boerstra BJ, et al. 1994. Prevalence of food allergy and intolerance in the adult Dutch population. *J. Allergy Clin. Immunol.* 93:446–56
55. Novey HS. 1993. Exercise-induced asthma and anaphylaxis. *West. J. Med.* 158:613
56. Odze AM, Bines J, Leichtner A, Goldman H, Antonioli D. 1993. Allergic proctocolitis in infants: a prospective clinical-pathologic biopsy study. *Hum. Pathol.* 24:668–74
57. Odze R, Weshil B, Leichtner A. 1995. Allergic colitis in infants. *J. Pediatr.* 126:163–70
58. Oppenheimer JJ, Nelson HS, Bock SA,

Christensen F, Leung DY. 1992. Treatment of peanut allergy with rush immunotherapy. *J. Allergy Clin. Immunol.* 90:256–62
59. Powell GK. 1978. Milk and soy induced enterocolitis of infancy: clinical features and standardization of challenge. *J. Pediatr.* 93:553–60
60. Rihs HP, Rozynek R, May-Taube K, Welticke B, Baur X. 1994. Polymerase chain reaction based cDNA cloning of wheat profilin: a potential plant allergen. *Int. Arch. Allergy Immunol.* 105:190–94
61. Sampson HA. 1988. Immunologically mediated food allergy: the importance of food challenge procedures. *Ann. Allergy* 60:262–69
62. Sampson HA. 1992. Immunopathogenic role of food hypersensitivity in atopic dermatitis. *Acta Derm. Venereol.* 176: 34–37
63. Sampson HA, Albergo R. 1984. Comparison of results of skin tests, RAST, and double-blind placebo-controlled food challenges in children with atopic dermatitis. *J. Allergy Clin. Immunol.* 74:26–33
64. Sampson HA, Broadbent-Bernhisel J. 1989. "Spontaneous" basophil histamine release and histamine releasing factor in patients with atopic dermatitis and food hypersensitivity. *N. Engl. J. Med.* 321:228–32
65. Sampson HA, Jolie PL. 1984. Increased plasma histamine concentration after food challenges in children with atopic dermatitis. *N. Engl. J. Med.* 311:372–76
66. Sampson HA, MacDonald SM. 1993. IgE-dependent histamine-releasing factors. *Springer Semin. Immunopathol.* 15: 89–98
67. Sampson HA, Mendelson I, Rosen JP. 1992. Fatal and near-fatal anaphylactic reactions to food in children and adolescents. *N. Engl. J. Med.* 327:380–84
68. Schrander J, Dellevoet J, Arends JW, Forget PP, Kuijten R. 1993. Small intestinal mucosa IgE plasma cells and specific anti-cow milk IgE in children with cow milk protein intolerance. *Ann. Allergy* 70:406–9
69. Selby WS, Janossy G, Bofill M, Jewell DP. 1983. Lymphocyte subpopulations in the human small intestine. The findings in normal mucosa and in the mucosa of patients with adult coeliac disease. *Clin. Exp. Immunol.* 52:219–28
70. Shinoda S, Kondo N, Fukutomi O, Agata H, Suzuki Y, et al. 1993. Suppressive effects of elimination diets on T cell responses to ovalbumin in hen's egg-sensitive atopic dermatitis patients. *Clin. Exp. Allergy* 23:689–95
71. Sloan AE, Powers ME. 1986. A perspective on popular perceptions of adverse reactions to foods. *J. Allergy Clin. Immunol.* 78:127–33
72. Suomalainen H, Soppi E, Isolauri E. 1993. Immunologic disturbances in cow's milk allergy. I. Delayed maturation of suppressor activity. *Pediatr. Allergy Immunol.* 4:196–202
73. Suomalainen H, Soppi E, Laine S, Isolauri E. 1993. Immunologic disturbances in cow's milk allergy. II. Evidence for defective interferon-gamma generation. *Pediatr. Allergy Immunol.* 4:203–7
74. Taudorf E, Malling HJ, Laursen LC, Lanner A, Weeke B. 1985. Reproducibility of histamine skin prick test. *Allergy* 40:344–49
75. Taylor SL, Busse WW, Sachs MI, Parker JL, Yunginger JW. 1981. Peanut oil is not allergenic to peanut-sensitive individuals. *J. Allergy Clin. Immunol.* 68:372–75
76. Trier J, Sleisenger M, Fordtran J, Scharschmidt B, Feldman M, eds. 1993. *Gastrointestinal Disease: Pathophysiology/Diagnosis/Management,* 51:1078–96. Philadelphia: Saunders. 5th ed.
77. Trier JS. 1991. Celiac sprue. *N. Engl. J. Med.* 325:1709–10
78. US Department of Agriculture. 1983. *Federal Register: Rules and Regulations,* 48:32749. Washington, DC: USDA
79. Valenta R, Duchene M, Ebner C, Valent P, Sillaber C, et al. 1992. Profilins constitute a novel family of functional plant Pan-allergens. *J. Exp. Med.* 175:377–85
80. Volta U, Molinar N, Fratangelo D, Bianchi F. 1994. IgA antibodies to jejunum: specific immunity directed against target organ of gluten-sensitive enteropathy. *Dig. Dis. Sci.* 39:1924–29
81. Walker-Smith J, Guandalini S, Schmitz J, Schmerling D, Viskorpi J. 1990. Revised criteria for diagnosis of coeliac disease. *Arch. Dis. Child.* 65:909–11
82. Young E, Patel S, Stoneham MD, Rona R, Wilkinson JD. 1987. The prevalence of reactions to food additives in a survey population. *J. R. Coll. Physicians London* 21:241–47
83. Yunginer JW, Sweeney KG, Sturner WQ, Giannandrea LA, Teigland JD, et al. 1988. Fatal food-induced anaphylaxis. *JAMA* 260:1450–52