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Food allergy. Part 1: Immunopathogenesis and clinical disorders

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Up to 8% of children less than 3 years of age and approximately 2% of the adult population experience food-induced allergic disorders. A limited number of foods are responsible for the vast majority of food-induced allergic reactions: milk, egg, peanuts, fish, and tree nuts in children and peanuts, tree nuts, fish, and shellfish in adults. Food-induced allergic reactions are responsible for a variety of symptoms involving the skin, gastrointestinal tract, and respiratory tract and may be caused by IgE-mediated and non-IgE-mediated mechanisms. In part 1 of this series, immunopathogenic mechanisms and clinical disorders of food allergy are described. (*J Allergy Clin Immunol* 1999;103:717-28.)

Key words: Food allergy, hypersensitivity, food intolerance, urticaria, food-associated exercise-induced anaphylaxis, asthma, allergenic epitope, allergic eosinophilic gastroenteritis, enteropathy, dietary protein-induced enterocolitis, dietary protein-induced colitis, oral tolerance, atopic dermatitis, anaphylaxis, allergic rhinitis, pulmonary hemosiderosis, celiac disease, dermatitis herpetiformis

Food is essential for life, a major source of pleasure, and often intrinsic to our cultural identity. Most individuals ingest 3 meals a day plus snacks and typically consume some food at most social gatherings. The average person in westernized societies is likely to ingest 2 to 3 tons of food in a lifetime. Consequently, it is not surpris-

Abbreviations used

APC:	Antigen-presenting cell
DBPCFC:	Double-blind, placebo-controlled, oral food challenge
IEC:	Intestinal epithelial cell
OAS:	Oral allergy syndrome
tTGase:	Tissue transglutaminase

ing that food is so frequently implicated in a variety of maladies and that it causes so much distress in individuals who believe they are afflicted with food allergy. The plethora of articles in newspapers and magazines, news stories on radio and television, and books and websites on the subject bespeak the importance and concern our society places on the topic of food allergy.

Hippocrates, often hailed as the "Father of Medicine," first described adverse reactions to food over 2000 years ago, but the medical community has been very reticent to acknowledge or investigate these disorders until recently. Other Greek scholars recorded adverse reactions to cow's milk in the first and second centuries.¹ The first anaphylactic reaction to egg was recorded by Marcello Donati in the sixteenth century and to fish by Philipp Sachs in the seventeenth century.² In the early part of the twentieth century, physicians began reporting series of children with eczematous rashes exacerbated by food allergies.³ However, it was not until 1950 that Loveless⁴ first used blinded, placebo-controlled food challenges to establish the diagnosis of food allergy and demonstrate the unreliability of patient history. Subsequently, Goldman et al^{5,6} proposed a diagnostic protocol that required reproduction of presenting symptoms during 3 successive milk challenges after milk withdrawal when he reported on the evaluation of 89 infants with suspected cow's milk allergy. In 1976, May⁷ introduced the use of double-blind,

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TABLE I. Components of the gut barrier

Physiologic barriers
Block penetration of ingested antigens:
Epithelial cells—one cell layer of columnar epithelium
Glycocalyx—coating of complex glycoprotein and mucins that trap particles
Intestinal microvillus membrane structure—prevents penetration
Tight junctions joining adjacent enterocytes—prevents penetration, even of small peptides
Intestinal peristalsis—flushes “trapped” particles out in the stool
Break down ingested antigens:
Salivary amylases and mastication
Gastric acid and pepsins
Pancreatic enzymes
Intestinal enzymes
Intestinal epithelial cell lysozyme activity
Immunologic barriers
Block penetration of ingested antigens:
Antigen-specific s-IgA in gut lumen
Clear antigens penetrating gastrointestinal barrier:
Serum antigen-specific IgA and IgG
Reticuloendothelial system

placebo-controlled, oral food challenges (DBPCFCs) for the diagnosis of food allergy, a protocol now considered the gold standard for the diagnosis of food-induced allergic disorders.

Some of the controversy surrounding food allergy has stemmed from disparate use of terms. In an attempt to bring uniformity to the nomenclature related to food allergies, the European Academy of Allergy and Clinical Immunology proposed a mechanistic classification of these disorders.⁸ *Adverse food reactions* are defined as any aberrant reaction after the ingestion of a food or food additive. Adverse food reactions may be the result of *toxic* or *nontoxic* food reactions. Toxic reactions can occur in anyone, provided a sufficient dose is ingested (eg, histamine in scombroid fish poisoning). Nontoxic reactions depend on individual susceptibilities and may be the result of immune mechanisms (*allergy* or *hypersensitivity*) or nonimmune mechanisms (*intolerance*). IgE-mediated food allergies have been most clearly delineated, but non-IgE-mediated immune reactions, especially of the gastrointestinal tract, are being increasingly recognized. Food intolerances probably account for the majority of adverse food reactions and may be caused by pharmacologic properties of the food (eg, headaches from tyramine in aged cheeses and jitteriness from caffeine in coffee or soft drinks), or unique susceptibilities of the host, such as metabolic disorders [eg, lactase deficiency) or idiosyncratic responses.

PREVALENCE OF FOOD HYPERSENSITIVITY

About one fourth of American households alter their dietary habits because at least one member of the family is perceived to have food allergies.⁹ True food allergy is much less frequent and more prevalent in young children

and individuals with atopic disease. In a prospective study of 480 consecutive newborns followed through their third birthday, 28% were reported to have experienced adverse food reactions, most during the first year of life.¹⁰ About one fourth of the reactions reported (or 8% of the cohort) could be confirmed by oral food challenge. Prospective studies from several countries indicate that about 2.5% of newborn infants experience hypersensitivity reactions to cow's milk in the first year of life.¹⁰⁻¹³ IgE-mediated reactions account for about 60% of milk-induced allergic disorders. Although most infants with non-IgE-mediated cow's milk allergy “outgrow” their sensitivity by the third year of life,¹¹ 15% of infants with IgE-mediated cow's milk allergy retain their sensitivity into the second decade, and 35% have allergic reactions to other foods.¹⁴ Hypersensitivity reactions to egg occur in about 1.3% of young children (based on data from Nickel et al¹⁵) and to peanut in 0.5% of children in the UK¹⁶ and US.¹⁷ Children with atopic disorders tend to have a higher prevalence of food allergy. About 35% of children with moderate-to-severe atopic dermatitis have skin symptoms provoked by food hypersensitivity,¹⁸ and about 6% of asthmatic children attending a general pulmonary clinic will have food-induced wheezing.¹⁹ Adverse reactions to food additives have been demonstrated in children and affect less than 1% of children.²⁰

The prevalence of food hypersensitivity in adults is reportedly less common. However, a recent national survey in the US suggested that peanut and tree nut allergy together affect 1.3% of adults.¹⁷ Surveys from the United Kingdom indicated that 1.4% to 1.8% of adults experience adverse food reactions,²¹ and 0.01% to 0.23% of adults are affected by adverse reactions to food additives.²² Similarly, a study in the Netherlands concluded that about 2% of the adult Dutch population are affected by adverse food reactions.²³ Given the estimated frequency of shellfish allergy (approximately 0.5%²⁴) and sensitivities to a variety of other foods, it is likely that about 2% of the adult population in the US is affected by food allergies.

PATHOGENESIS OF FOOD HYPERSENSITIVITY REACTIONS

Gut barrier

Within hours of birth, a newborn's gastrointestinal tract and gut-associated lymphoid tissue (gut barrier) are confronted with foreign proteins in the form of bacteria and food antigens. This immature system must process ingested food into a form that can be absorbed and used for energy and cell growth, mount rapid and potent responses against various pathogens (ie, develop immunity), and remain unresponsive to enormous quantities of foreign nutrient antigens (ie, develop tolerance). A number of nonimmunologic and immunologic mechanisms (Table I) operate to prevent foreign antigens (eg, bacteria, viruses, parasites, and food proteins) from penetrating the gut barrier.²⁵ However, immaturity of these mechanisms in infants reduces the efficiency of the infant

mucosal barrier. For example, basal acid output is relatively low during the first month of life,²⁶ intestinal proteolytic activity does not reach mature levels until approximately 2 years of age,²⁷ and intestinal microvillus membranes are immature, resulting in altered antigen binding and transport through mucosal epithelial cells.²⁸ In addition, the newborn lacks IgA and IgM in exocrine secretions and salivary s-IgA concentrations, which are absent at birth and remain low during the early months of life.²⁹ The relatively low concentrations of s-IgA in the young infant's intestine and the relatively large quantities of ingested proteins place a tremendous burden on the immature gut-associated lymphoid tissue. Not surprisingly, the early introduction of numerous food antigens has been shown to stimulate excessive production of IgE antibodies^{30,31} or other adverse immune responses in genetically predisposed infants. A prospective study of over 1200 unselected infants demonstrated a direct linear relationship between the number of solid foods introduced into the diet by 4 months of age and the subsequent development of atopic dermatitis, with a 3-fold increase in recurrent eczema at 10 years of age in infants who had received 4 or more solid foods before 4 months of age.³²

The development of an IgE-mediated response to an allergen (generally a glycoprotein) is the result of a series of molecular and cellular interactions involving antigen-presenting cells (APCs), T cells, and B cells.³³ APCs present small peptide fragments (T-cell epitopes) in conjunction with MHC class II molecules to T cells. T cells bearing the appropriate complementary T-cell receptor will bind to the peptide-MHC complex. This interactive "first signal" leads to T-cell proliferation and cytokine generation and the generation of a "second" signal, which promotes an IgE response (T_{H2}-like cell activation). These cells and their products, in turn, interact with B cells bearing appropriate antigen-specific receptors, leading to isotype switching and the generation of antigen-specific IgE. At all stages, a number of specific cytokines are secreted, which modulate the cell interactions. The antigen-specific IgE then binds to surface receptors of mast cells, basophils, macrophages, and other APCs, arming the immune system for an allergic reaction with the next encounter of the specific antigen.

Even in the mature gut, about 2% of ingested food antigens are absorbed and transported throughout the body in an "immunologically" intact form.³⁴⁻³⁶ Increased stomach acidity and the presence of other food in the gut decrease antigen absorption, whereas decreased stomach acidity (eg, antacids) and ingestion of alcohol increase absorption.³⁷ The immunologically recognizable proteins that gain access to the circulation do not normally cause adverse reactions because tolerance develops in most individuals, but in the sensitized host they can provoke a variety of hypersensitivity responses. Although more common in the developing gut-associated lymphoid tissue of young children, it is clear that both cellular and IgE-mediated hypersensitivity responses to foods can develop at any age.

Recent studies suggest that intestinal epithelial cells play a central regulatory role in determining the rate and pattern of uptake of ingested antigens. Studies in sensitized rats indicate that intestinal antigen transport proceeds in 2 phases.³⁸ In the first phase of antigen uptake, transepithelial transport occurs through endosomes, is antigen specific and mast cell independent, and occurs 10 times faster in sensitized rats compared with nonsensitized controls.³⁹ In the second phase paracellular transport predominates, is mast cell dependent, is not antigen specific, and is markedly increased by antigen challenge in sensitized rats compared with mast cell-deficient sensitized rats or nonsensitized controls. These studies clearly demonstrate that the rate and amount of antigen absorbed during IgE-mediated reactions in the gastrointestinal tract is markedly increased. They also suggest that both antigen-specific and nonspecific factors may accelerate antigen transport across the epithelium. Although the specific pathway may involve antibody, the nonspecific pathway most likely involves cytokines. Consistent with this concept, intestinal epithelial cells (IECs) express receptors for a number of different cytokines (IL-1, IL-2, IL-6, IL-10, IL-12, IL-15, GM-CSF, and IFN- γ), and IECs have been shown to be functionally altered by exposure to these cytokines.

Oral tolerance induction

The dominant response in the gut-associated lymphoid tissue is suppression or tolerance. The means by which the immune system is "educated" to avoid sensitization to ingested food antigens is not well understood. Early studies suggested that M cells (specialized epithelial cells overlying the Peyer's patches) were the major sites of immune antigen sampling in the intestine.⁴⁰ More recent studies, however, indicate that IECs may be the central APCs used for generating immunosuppression in the gut.⁴¹ These "nonprofessional" APCs have been shown to express MHC class II molecules, take up soluble protein from the apical end and transport it basolaterally, and selectively activate CD8⁺ suppressor cells. The latter appears to be regulated by nonclassical class I molecules (CD1d) and other novel membrane molecules that interact with CD8.⁴² It has been hypothesized that soluble antigens in the gut lumen are sampled and presented primarily by IECs, leading to suppression of the immune response, whereas particulate antigens and intact bacteria, viruses, and parasites are sampled by M cells, leading to active immunity and generation of IgA. A study of reovirus supports this notion.⁴³ Reovirus type I infects IECs, whereas receptors for reovirus type III are expressed on M cells. Administration of reovirus type I results in "tolerance," whereas administration of reovirus type III results in an active IgA response, suggesting that the route of entry (ie, M cell vs IEC) determines the type of immune response generated (ie, active immunity vs tolerance).

Although the mechanisms of tolerance induction in mice have been partially elucidated in recent years, the existence of tolerance and its regulation in humans is less

TABLE II. Major food allergens that have been isolated and characterized

Cows' milk		
Caseins	α_s -Caseins	
	β -Casein	
	κ -Casein	
Whey	β -Lactoglobulin	
	α -Lactalbumin	
Chicken egg white	Ovomucoid	(Gal d 1)
	Ovalbumin	(Gal d 2)
	Ovotransferrin	(Gal d 3)
Peanut	Vicilin	(Ara h 1)
	Conglutin	(Ara h 2)
	Glycinin	(Ara h 3)
Soybean	Vicilin	
	Conglycinin	(Gly m 1)
Fish	Parvalbumin	(Gad c 1 [cod]; Sal s 1 [salmon])
	Tropomyosin	(Pen a 1; Pen i 1; Met e 1)
Brazil nut	2S albumin	(Ber m 1)
Walnut	2S albumin	(Jug r 1)
Rice	α -Amylase inhibitor	(Ory s 1)
Wheat	α -Amylase inhibitor	
Barley	α -Amylase inhibitor	(Hor v 1)
Buckwheat	11S globulin	(Fag e 1)
Mustard	2S albumin	(Sin a 1 [yellow]; Bra j 1 [oriental])
		(Api g 1)
Celery	Pathogenesis-related protein	
	Profilin	(Api g 2)
Potato	Patatin	(Sol t 1)
Carrot	Pathogenesis-related protein	(Dau c 1)
Apple	Pathogenesis-related protein	(Mal d 1)
	Profilin	(Mal d 2)

well characterized. Studies in mice suggest that B cells require larger amounts of oral antigen than T cells to become tolerized⁴⁴ and that there is a hierarchy in tolerance induction, with T_{H1}-like cells being more easily tolerized than T_{H2}-like cells.⁴⁵ Very few studies have addressed oral tolerance development in humans. Lowney⁴⁶ demonstrated decreased cutaneous response to an injected hapten after feeding subjects the hapten.

Husby⁴⁵ demonstrated that feeding keyhole limpet hemocyanin to normal human volunteers resulted in systemic T-cell tolerance but led to B-cell priming with detection of keyhole limpet hemocyanin antibodies in serum and saliva. This study indicated that the development of tolerance to food has little effect on B-cell function because antibody production against food proteins is a universal phenomenon in both infants and adults, which is not generally associated with hypersensitivity to the antigen in question.⁴⁷ Most low-level antibodies to foods in clinically tolerant individuals are of the IgG class, with high levels of IgE antibodies more likely to be an indicator of a pathologic process (eg, milk allergy).

Ingestion of dietary proteins normally activate CD8⁺ T suppressor cells, which reside in the gut-associated lymphoid tissue⁴⁸⁻⁵⁰ and, after prolonged ingestion of antigens, in the spleen.⁴⁸ Initial activation of these cells depends on the nature, dose, and frequency of antigen exposure; the host's age; and possibly LPS produced by the host's intestinal flora.⁵¹ Refeeding dietary antigens generally promotes systemic unresponsiveness of delayed-type hypersensitivity. Several studies in human subjects have demonstrated increased lymphocyte proliferation or IL-2 production after food antigen stimulation in vitro in patients with food allergy, celiac disease, and inflammatory bowel disease.⁵² However, in vitro T-cell responses are commonly found in normal individuals as well.⁵³⁻⁵⁶

Food allergens

Although hundreds of different foods are included in the human diet, a relatively small number account for the vast majority of food-induced allergic reactions. In young children milk, eggs, peanuts, soy, and wheat account for approximately 90% of hypersensitivity reactions, whereas in adolescents and adults peanuts, fish, shellfish, and tree nuts account for approximately 85% of reactions. However, the increased accessibility of fresh fruits and vegetables from all over the world and our insatiable appetite for a more diversified and natural diet have resulted in an increase in allergic reactions to fruits, such as kiwi and papaya, and seeds, such as sesame, poppy, and rape (canola). The allergenic fraction of food is generally comprised of heat-stable, water-soluble glycoproteins ranging in size from 10 to 70 kd. As depicted in Table II, the allergenic proteins in many foods have been identified, isolated, sequenced, and cloned. In addition, IgE- and IgG-binding epitopes and T-cell epitopes have been mapped on many of these protein fractions.⁵⁷⁻⁶¹ With the definition of many of these food proteins and pollen proteins at the molecular level, it is now apparent why certain patients allergic to pollen experience oral symptoms when ingesting various fresh fruits and vegetables, as discussed below.

CLINICAL DISORDERS

Gastrointestinal food hypersensitivity reactions

Given the complexity of the gastrointestinal immune system and the fact that the gastrointestinal tract is first to confront an enormous quantity of food allergens, it is not surprising that a variety of gastrointestinal hypersensitivity disorders may develop. As indicated in Fig 1 from a recent consensus workshop [*Workshop on the Classification of Gastrointestinal Diseases of Infants and Children*-November 1998, Washington, DC], gastrointestinal hypersensitivities may be exclusively IgE mediated, partially IgE mediated, or exclusively cell mediated. Regardless of the immunologic mechanism involved, symptoms of GI hypersensitivity are very similar in nature, but generally vary in time of onset, severity, and persistence.

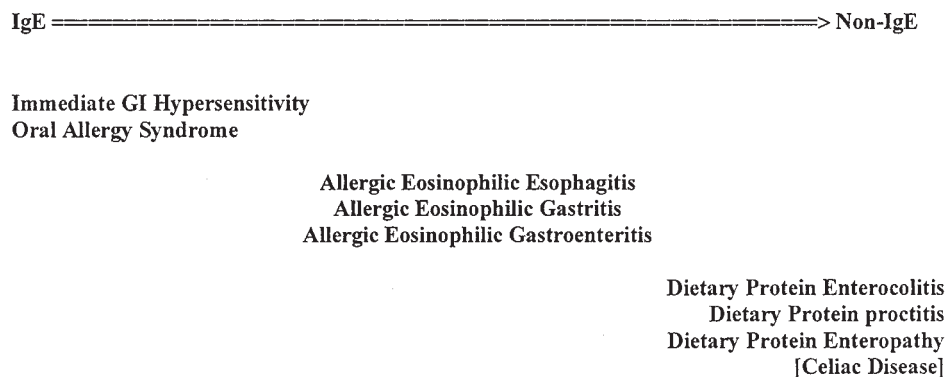


FIG 1. Gastrointestinal hypersensitivity disorders.

IgE-mediated disorders. Immediate gastrointestinal hypersensitivity is an IgE-mediated gastrointestinal reaction that often accompanies allergic manifestations in other target organs (eg, skin and lungs) and results in a variety of symptoms.⁶² Early studies of IgE-mediated food hypersensitivity evaluated radiologic changes associated with food-induced allergic reactions. In one report 4 patients allergic to food were given barium mixtures containing specific food allergens and studied radiographically.⁶³ Gastric retention, hypermotility of the intestine, and colonic spasm were observed. In fluoroscopic studies of 12 children allergic to food, the outcome of barium sulfate meals with and without food allergens were compared.⁶⁴ The most prominent findings included gastric hypotonia and retention of the allergen test meal, prominent pylorospasm, and subsequent increased or decreased peristaltic activity of the intestines. Pollard and Stuart⁶⁵ used a rigid gastroscope to observe “immediate” allergic reactions in the stomachs of 6 patients with food allergy. A small amount of the appropriate food allergen was placed on the gastric mucosa and then revisualized 30 minutes later. The mucosa appeared markedly hyperemic and edematous, with patches of thick gray mucous and scattered petechiae, findings similar to those described earlier by Walzer³⁷ using passively sensitized intestinal mucosa. More recently, similar studies have been conducted with flexible endoscopes, which confirmed these earlier observations.⁶⁶ In addition, biopsy specimens taken before and after challenges have demonstrated significant decreases in stainable mast cells and tissue histamine after positive food challenges. Positive skin test or RAST responses to responsible food allergens are present in virtually all cases (>95%).

Symptoms caused by immediate gastrointestinal hypersensitivity typically develop within minutes to 2 hours of consuming the responsible food allergen and consist of nausea, abdominal pain, colic, vomiting, and/or diarrhea. In young infants immediate vomiting is not always a consistent finding, and some of these infants are first seen with intermittent vomiting and failure to thrive. In children with atopic dermatitis and food allergy, the repeated ingestion of a food allergen induces partial desensitization of gastrointestinal mast cells, result-

ing in subclinical reactions. Generally these children are first seen with complaints of poor appetite, poor weight gain, and intermittent abdominal pain, but carbohydrate absorption studies, a measure of gut wall integrity, demonstrate malabsorption in such patients.^{67,68}

The oral allergy syndrome (OAS) appears to have become more prevalent in the past decade, but this may be due in large part to increased awareness. It is estimated that OAS affects up to 40% of adults with pollen allergy, especially to birch, ragweed, and mugwort pollens.⁶⁹ OAS is a form of contact allergy that is confined almost exclusively to the oropharynx and rarely affects other target organs. Local IgE-mediated mast cell activation provokes the rapid onset of pruritus; tingling and angioedema of the lips, tongue, palate, and throat; and occasionally a sensation of pruritus in the ears, tightness in the throat, or both. Symptoms are generally short-lived and are most commonly associated with the ingestion of various fresh fruits and vegetables.^{70,71} Patients allergic to ragweed may experience OAS after contact with various fresh melons (eg, watermelon, cantaloupe, and honeydew) and bananas.^{71,72} Symptoms may be more prominent after the ragweed season, corresponding to the seasonal rise in ragweed-specific IgE levels. Patients allergic to birch pollen may have symptoms after the ingestion of raw potatoes, carrots, celery, apples, hazelnuts, and kiwi.^{71,73,74} Cross-reactivity between birch pollen and various fruits and vegetables is due to homology among various pathogenesis-related proteins, which are important in the defense against plant diseases. For example, Mal d 1, the major apple allergen, is 63% homologous to the major birch pollen allergen, Bet v 1.⁷⁵ Other birch pollen-related, pathogenesis-related proteins have been identified in hazel nut and celery (Api g 1).⁷⁶ Similarly, the birch pollen profilin, Bet v 2, cross-reacts with profilins found in apple (Mal d 2), celery (Api g 2), and potato.⁷⁷ Oral symptoms also have been described among several fruits in the Prunoideae subfamily and appear to be caused by a homologous 9-kd protein found in these fruits (peach [Pru p 1], cherry, apricot, and plum) and Brazil nuts (Ber e 1).^{76,78} Patients with OAS generally can ingest these foods in the cooked form without difficulty.

Mixed IgE- and non-IgE-mediated disorders. Allergic eosinophilic esophagitis, gastritis, or gastroenteritis are characterized by infiltration of the esophagus, stomach, and/or intestinal walls with eosinophils, basal zone hyperplasia, papillary elongation, absence of vasculitis, and peripheral eosinophilia in about 50% of patients. The eosinophilic infiltrate may involve the mucosal, muscular, and/or serosal layers of the stomach or small intestine, and clinical symptoms correlate with the extent of eosinophil infiltration of the bowel wall.⁷⁹⁻⁸² Eosinophilic infiltration of the muscular layer leads to thickening and rigidity, provoking symptoms of obstruction, whereas infiltration of the serosal area results in ascites containing eosinophils. Although peripheral blood T cells from these patients have been shown to secrete excessive amounts of IL-4 and IL-5 compared with that found in normal control subjects,⁸³ the underlying immunopathogenesis of these disorders is poorly understood.

Allergic eosinophilic esophagitis is seen most frequently during infancy through adolescence and presents with chronic reflux (gastroesophageal reflux), intermittent emesis, food refusal, abdominal pain, dysphagia, irritability, sleep disturbance, and failure to respond to conventional reflux medication. One study of children less than 1 year of age with gastroesophageal reflux found that 40% had cow's milk-induced reflux.⁸⁴ Allergic eosinophilic gastritis also is more common between infancy and adolescence, and such patients are first seen with postprandial vomiting, abdominal pain, anorexia, early satiety, hematemesis, failure to thrive, and gastric outlet obstruction (rarely pyloric stenosis).⁸⁵ Allergic eosinophilic gastroenteritis may occur at any age and may appear with symptoms similar to esophagitis, gastritis, or both. Weight loss or failure to thrive is a hallmark of this disorder. Up to 50% of patients with these allergic eosinophilic disorders are atopic, and food-induced IgE-mediated reactions have been implicated in a minority of patients. Generalized edema secondary to hypoalbuminemia may occur in some infants with marked protein-losing enteropathy, often in the presence of minimal gastrointestinal symptoms, such as occasional vomiting and diarrhea.⁸⁶ Resolution of symptoms may require 3 to 8 weeks after the elimination of the responsible food allergens (frequently multiple foods).⁸⁷

Non-IgE-mediated disorders. Dietary protein enterocolitis syndrome is a disorder most frequently seen in the first several months of life in which infants are first seen with irritability, protracted vomiting, and diarrhea, not infrequently resulting in dehydration.^{88,89} Vomiting generally occurs 1 to 3 hours after feeding, and continued exposure may result in bloody diarrhea, anemia, abdominal distention, and failure to thrive. Symptoms are most commonly provoked by cow's milk or soy protein-based formulas but occasionally result from food proteins passed in maternal breast milk. A similar enterocolitis syndrome has been reported in older infants and children, which is caused by egg, wheat, rice, oat, peanut, nut, chicken, turkey, and fish sensitivity.⁹⁰ Hypotension occurs in about 15% of cases after allergen ingestion.^{5,90}

In adults shellfish (eg, shrimp, crab, and lobster) sensitivity may provoke a similar syndrome with severe nausea, abdominal cramps, and protracted vomiting. Stools often contain occult blood, polymorphonuclear neutrophils and eosinophils, and Charcot-Leyden crystals. Skin prick test responses to the suspected foods are negative. Jejunal biopsy specimens classically reveal flattened villi, edema, and increased numbers of lymphocytes, eosinophils, and mast cells. Increased numbers of IgM- and IgA-containing plasma cells are seen in the jejunal mucosa.⁹¹ Although the immunopathogenic mechanism of this syndrome remains to be elucidated, recent studies suggest that food antigen-induced secretion of TNF- α from local mononuclear cells may be responsible for the secretory diarrhea and hypotension.⁹²

Dietary protein proctitis is first seen typically in the first few months of life as blood-streaked stools in otherwise healthy looking infants. About 60% of cases are seen in breast-fed babies,⁹³⁻⁹⁵ with the remainder largely in infants fed cow's milk or soy protein-based formula. Blood loss is typically modest but occasionally can produce anemia. Mild hypoalbuminemia and peripheral eosinophilia occur rarely. Bowel lesions generally are confined to the distal large bowel, and endoscopy reveals linear erosions and mucosal edema with infiltration of eosinophils in the epithelium and lamina propria. In severe lesions with crypt destruction, PMNs are also prominent.⁹⁶

Dietary protein enteropathy is first seen often in the first several months of life with diarrhea (not infrequently steatorrhea) and poor weight gain.⁹⁷ Symptoms include protracted diarrhea, vomiting in up to two thirds of patients, failure to thrive, abdominal distention, early satiety, and malabsorption. Anemia, edema, and hypoproteinemia are occasionally seen. Cow's milk sensitivity is the most frequent cause of this syndrome in young infants, but it also has been associated with sensitivity to soy, egg, wheat, rice, chicken, and fish in older children. Patchy villous atrophy with cellular infiltrate on biopsy is characteristic of this disorder. In cow's milk-induced enteropathy, serum IgA and IgG antibodies to cow's milk proteins are elevated.

Celiac disease is a dietary protein enteropathy characterized by a more extensive loss of absorptive villi and hyperplasia of the crypts, leading to malabsorption, chronic diarrhea, steatorrhea, abdominal distention, flatulence, and weight loss or failure to thrive. Oral ulcers and other extraintestinal symptoms secondary to malabsorption are not uncommon. Patients with celiac disease are sensitive to gliadin, the alcohol-soluble portion of gluten found in wheat, oat, rye, and barley. Celiac disease is associated with the HLA-DQ2 (and DQ8) haplotype, and about 90% of patients with celiac disease ingesting gliadin possess IgA anti-gliadin and antiendomysium antibodies.⁹⁸ Endoscopy typically reveals total villous atrophy and extensive cellular infiltrate. The prevalence of celiac disease has been reported to be between 1:3700 and 1:300,⁹⁹ and a recent study among normal blood donors in the US revealed antiendomysium antibodies in

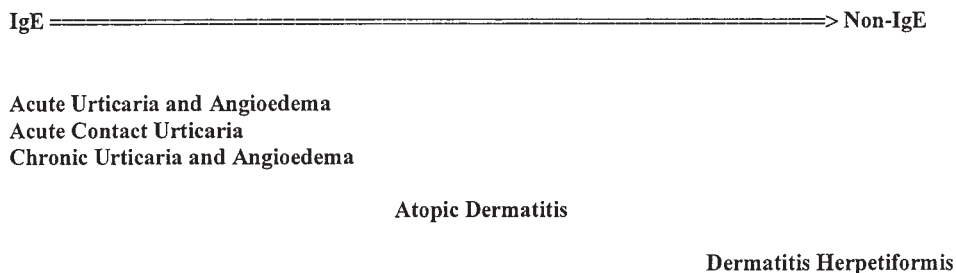


FIG 2. Cutaneous hypersensitivity disorders.

1:250 subjects.¹⁰⁰ Recent studies suggest that the severity of celiac disease varies from a debilitating malabsorption syndrome to a “silent,” subclinical disorder. Chronic ingestion of gluten-containing grains in patients with celiac disease is associated with increased risk of malignancy, especially T-cell lymphoma.¹⁰¹

Histopathologic studies reveal that lymphocytes, predominantly of the CD8⁺ cytotoxic/suppressor phenotype, are prominent in the intraepithelial space, and γ/δ T cells are increased in the jejunal mucosa and the peripheral blood.¹⁰² Recent evidence suggests that celiac disease is associated with increased mucosal activity of tissue transglutaminase (tTGase) on specific protein-bound glutamine.¹⁰³ Gliadin is one of the few substrates for tTGase, which deamidates specific glutamines within gliadin-creating epitopes that bind efficiently to DQ2 gut-derived T cells.¹⁰⁴ tTGase has been shown to be the target of the antiendomysium antibodies. It is now believed that generation of unique gliadin epitopes by tTGase enzymatic modification leads to activation of DQ2- and DQ8-restricted T cells, a breakdown in tolerance, and initiation of an autoimmune process that generates inflammation in the gut. Elimination of gliadin from the diet results in a downregulation of the T cell-induced inflammatory process.

Other gastrointestinal disorders have been described that are believed to be the result of food-induced inflammatory processes, although the pathogenesis is unclear. Ingestion of pasteurized, whole cow’s milk by infants, especially those less than 6 months of age, frequently leads to occult gastrointestinal blood loss and occasionally leads to iron deficiency anemia.¹⁰⁵ Substitution of infant formula (including cow’s milk-derived formulas that have been subjected to more extensive heating) for whole cow’s milk will generally normalize fecal blood loss within 3 days. In a recent study chronic constipation was found to be associated with cow’s milk hypersensitivity in 68% of the children studied.¹⁰⁶ The role of food hypersensitivity in inflammatory bowel disease (Crohn’s disease and ulcerative colitis) remains speculative, although elemental diets have been shown to promote resolution of symptoms.

Cutaneous food hypersensitivity reactions

The skin probably represents the second most frequent target organ in food hypersensitivity reactions (Fig 2).

Ingestion of food allergens may provoke the rapid onset of cutaneous symptoms or aggravate more chronic conditions.

IgE-mediated disorders. Acute urticaria and angioedema are believed to be among the most common symptoms of food-induced allergic reactions. The prevalence of these reactions, however, is unknown because they are often easily self-diagnosed and patients do not seek medical assistance or necessarily inform their physicians of their reactions. Onset of symptoms may be very rapid, following within minutes of ingesting the responsible allergen. Symptoms are caused by activation of IgE-bearing mast cells by circulating food allergens, which are absorbed and circulated rapidly throughout the body.¹⁰⁷ Foods most commonly incriminated in adults include fish, shellfish, nuts, and peanuts, and those in children include eggs, milk, peanuts, and nuts, although reactions to various seeds (eg, sesame, and poppy) and fruits (eg, kiwi) are becoming more common. Acute contact urticaria secondary to food ingestion also is believed to be quite common, but again the true prevalence is unknown. Foods most often incriminated in these reactions include raw meats, fish, vegetables, and fruits.^{108,109}

Chronic urticaria and angioedema (symptoms lasting >6 weeks) are rarely caused by food allergy. In one series of 554 adults, food allergy was implicated in only 1.4% of patients with chronic urticaria.¹¹⁰ In a study of 226 children with chronic urticaria, 31% had positive skin test responses to food, but only 4% had symptoms confirmed by blinded food challenge.¹¹¹ Food additives (dyes and preservatives) have been implicated in chronic urticaria but are rarely confirmed by appropriate challenges.

Mixed IgE- and non-IgE-mediated disorders. Atopic dermatitis is a form of eczema that generally begins in early infancy and is characterized by typical distribution, extreme pruritus, chronically relapsing course, and association with asthma and allergic rhinitis.¹¹² The role of allergen-specific IgE antibodies in the pathogenesis of atopic dermatitis involves a number of cell types. Langerhans cells, “professional” APCs in the skin, are increased in lesions of atopic dermatitis and possess allergen-specific IgE antibodies on their surface.¹¹³ The high-affinity receptors for IgE on Langerhans cells, through bound antigen-specific IgE antibodies, play a unique role as “nontraditional” receptors.¹¹⁴ These IgE-bearing Langerhans cells are up to 1000 times more efficient at present-

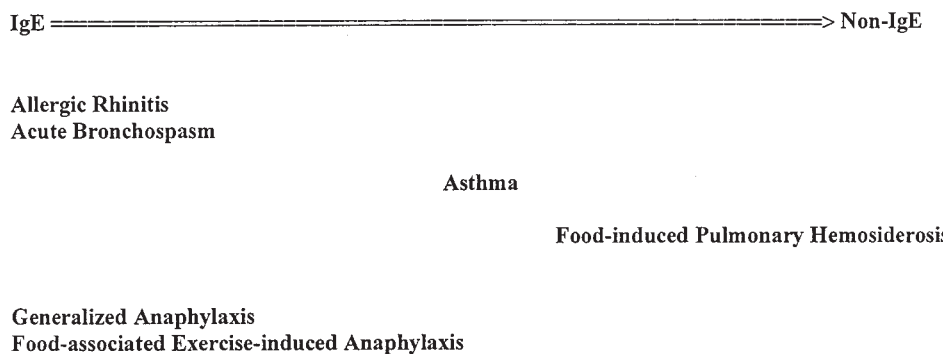


FIG 3. Respiratory hypersensitivity disorders.

ing allergen to T cells (primarily T_{H2} cells) and activating T-cell proliferation.¹¹⁵ Infiltrating T lymphocytes in acute eczematous lesions express predominantly T_{H2} cytokines, IL-4, IL-5, and IL-13, whereas T cells in chronic lesions express predominantly IL-5 and IL-13.^{116,117} This is in contrast to classic “delayed” cell-mediated responses, such as the tuberculin response, during which cells express primarily mRNA for IFN- γ and IL-2 but not IL-4 and IL-5.¹¹⁸ Oral food challenges in children with atopic dermatitis and food allergy have been shown to induce sharp increases in plasma histamine concentrations,¹¹⁹ activation of plasma eosinophils,¹²⁰ and elaboration of eosinophil products.¹²¹ Milk-specific, cutaneous lymphocyte antigen-bearing T cells have been identified in the circulation of children with IgE-mediated milk-induced skin symptoms, cells not present in patients with milk-induced gastrointestinal disease.¹²² In addition, food antigen-specific T cells have been cloned from active skin lesions and normal skin of patients with atopic dermatitis.¹²³ PBMCs from children allergic to food with atopic dermatitis elaborate an IgE-dependent histamine-releasing factor that primes basophils and possibly other IgE-bearing cells and has been correlated with disease activity.¹²⁴

In a recent study 35% to 40% of children with moderate-to-severe atopic dermatitis first seen by a university-based dermatologist were found to be allergic to food.¹⁸ An earlier study demonstrated a direct correlation between disease severity and the likelihood of food allergy.¹²⁵ In a follow-up study of 34 children with atopic dermatitis, 17 children with food allergy placed on an appropriate allergen elimination diet experienced marked significant improvement in their eczematous rash over the 4-year follow-up period compared with children without food allergy and children with food allergy not adhering to an allergen elimination diet.¹²⁶ In a prospective, blinded, randomized, controlled trial of egg elimination in young children with atopic dermatitis and positive RAST results for egg, Lever et al¹²⁷ demonstrated a significant decrease in both the area of affected skin and symptom scores in children avoiding egg compared with control subjects. In our studies of over 300 children with atopic dermatitis and food allergy, approximately one third of symptomatic food hypersensitivities are outgrown in 2 to

3 years (unpublished data). The probability of developing tolerance appeared dependent on the food antigen responsible, (ie, development of tolerance to soy was common, whereas development of tolerance to peanut was rare) and the stringency of allergen elimination. Results of skin prick tests often remained unchanged, but concentrations of allergen-specific IgE dropped significantly. The pathogenic role of food allergy in adults with atopic dermatitis remains to be elucidated.

Non-IgE-mediated disorders. Dermatitis herpetiformis is a highly pruritic skin rash that is associated with gluten-sensitive enteropathy and sometimes mistaken for atopic dermatitis. It is characterized by a chronic, intensely pruritic papulovesicular rash symmetrically distributed over the extensor surfaces and buttocks.¹²⁸ Like celiac disease, 80% to 90% of patients with dermatitis herpetiformis have the HLA-DQ2 (or DQ8) haplotype. Granular (85% to 90%) or linear (10% to 15%) deposits of IgA (almost exclusively IgA₁), PMNs, and C3 accumulate in the dermoepidermal junction of both involved and uninvolved skin. IgA deposits contain J chains, implying that the IgA is dimeric and had its origin in the gut. Some experimental observations suggest that the IgA deposits activate complement through the alternate pathway triggering the inflammation. The histology of the intestinal lesion is virtually identical to that seen in celiac disease, although villous atrophy and inflammatory infiltrates are generally milder and often clinically insignificant.¹²⁹

Respiratory food hypersensitivity reactions (Fig 3)

IgE-mediated disorders. Both upper (allergic rhinoconjunctivitis) and lower (bronchospasm and asthma) respiratory reactions have been provoked in blinded food challenges, although respiratory symptoms in the absence of cutaneous or gastrointestinal symptoms appear to be rare. Symptoms provoked during oral food challenges suggest that both early- and late-phase IgE-mediated mechanisms are involved in the development of respiratory symptoms, and skin tests or RASTs usually demonstrate IgE sensitivity to the responsible food. In a survey of 323 patients with chronic rhinitis attending an allergy clinic, only 2 patients (0.6%) had nasal symptoms reproduced during

blinded food challenges.¹³⁰ Despite the notion that milk ingestion frequently leads to nasal congestion in young infants, only 0.08% to 0.2% of infants in 3 epidemiologic surveys were found to have nasal symptoms after a milk challenge.^{10,11,13} Children with atopic disorders and food allergy frequently experience nasal symptoms during oral food challenges. Of 480 children referred to Bock¹³¹ for evaluation of adverse food reactions, about 16% experienced respiratory symptoms (sneezing, rhinorrhea, nasal obstruction, wheezing, cough, or ocular signs) during DBPCFCs, but only 2% of symptoms were confined to the respiratory tract. Approximately 25% of 112 patients with histories of adverse food reactions developing after 10 years of age were found to develop respiratory symptoms after oral challenge, with the majority being nasal symptoms caused by fruit or vegetable sensitivities.¹³² In surveys of children with asthma attending pulmonary clinics, food-induced respiratory reactions were demonstrated in about 6% to 8% of children.^{19,133} Bock¹³⁴ found that about 25% of 279 children referred for evaluation with histories of food-induced wheezing/asthma actually experienced wheezing as one of their symptoms during DBPCFCs.

In our studies of children with atopic dermatitis, nasal symptoms typically develop within 15 to 90 minutes of initiating the DBPCFC and last about 0.5 to 2 hours. Nasal and periocular pruritus are commonly followed by prolonged bursts of sneezing and copious rhinorrhea. Nasal fluid histamine and eosinophil cationic protein were found to increase significantly in children experiencing nasal symptoms.¹³⁵ Similarly, a study of 88 children with atopic dermatitis and asthma revealed acute bronchospasm in 15% of patients (dyspnea, cough and wheezing) during DBPCFCs, with 8% demonstrating greater than a 20% fall in FEV₁.¹³⁶ In a study of 26 asthmatic patients with food allergies, 12 had mild, acute bronchospasm (cough and/or wheezing) during DBPCFCs, and 7 of the 12 (58%) had a significant increase in airway reactivity, as demonstrated by greater than a 2-fold decrease in their prechallenge and postchallenge methacholine inhalation challenge PD₂₀FEV₁.¹³⁷ Asthmatic reactions caused by airborne food allergens have been reported in cases where susceptible individuals are exposed to vapors or steam emitted from cooking food (eg, fish,¹³⁸ mollusks, crustacea, eggs, and garbanzo beans). Symptoms often include rhinoconjunctivitis, urticaria, laryngeal edema, bronchospasm, and rarely hypotensive shock.

Non-IgE-mediated disorders. Food-induced pulmonary hemosiderosis (Heiner's Syndrome) is a very rare syndrome characterized by recurrent episodes of pneumonia associated with pulmonary infiltrates, hemosiderosis, gastrointestinal blood loss, iron deficiency anemia, and failure to thrive in infants and young children.¹³⁹ It is most often associated with hypersensitivity to cow's milk, but reactivity to egg and pork have also been reported.¹⁴⁰ Although peripheral blood eosinophilia and multiple serum IgG-precipitating antibodies to cow's milk are a relatively constant feature, the immunologic mechanisms responsible for this disorder are not known.¹⁴¹

Generalized anaphylaxis

Food allergies are the single most common cause of generalized anaphylaxis seen in hospital emergency departments,^{142,143} accounting for about one third of cases seen (twice the number of cases seen for bee stings). It is estimated that about 100 fatal cases of food-induced anaphylaxis occur in the US each year.¹⁴⁴ In addition to the cutaneous, respiratory, and gastrointestinal symptoms noted above, patients may have cardiovascular symptoms, including hypotension, vascular collapse, and cardiac dysrhythmias, presumably caused by massive mast cell mediator release. However, most food-induced anaphylactic reactions are not associated with major increases in serum tryptase.¹⁴⁵ In a series of 12 fatal or near-fatal anaphylactic reactions, all patients experienced severe respiratory compromise, 10 of 12 experienced nausea and vomiting, and only 7 of 12 patients (or 1 of 6 fatal reactions) experienced cutaneous symptoms. About one third of patients had a biphasic reaction and one quarter experienced prolonged symptoms (eg, up to 3 weeks).¹⁴⁵ Factors associated with severe reactions include concomitant asthma, history of previous severe reactions, denial of symptoms, and failure to initiate therapy expeditiously.

Food-associated exercise-induced anaphylaxis

This unusual form of anaphylaxis occurs only when the patient exercises within 2 to 4 hours of ingesting a food, but in the absence of exercise the patient can ingest the food without any apparent reaction.¹⁴⁶⁻¹⁴⁸ The incidence of food-associated exercise-induced anaphylaxis appears to be increasing, possibly because of the increased popularity of exercising in the past decade. Patients generally have asthma and other atopic disorders, positive skin prick test responses to the food that provokes their symptoms, and occasionally a history of reacting to the food when they were younger. This disorder appears to be twice as common in females as males and most prevalent in the late teens to mid-thirties. The exact mechanism or mechanisms involved in this disorder are unknown, and several foods have been implicated, including wheat, shellfish, fruit, milk, celery, and fish.

It is apparent that a number of food hypersensitivity disorders have been well characterized and affect a significant portion of the population. Allergists are ideally suited to diagnose and manage these disorders, as will be reviewed in the second part of this review.

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