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Invited review article

Food allergy: Past, present and future

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Abbreviations:
IgE, immunoglobulin E; DBPCFC, double-blind placebo-controlled food challenge; OIT, oral immunotherapy; RAST, radioallergosorbent test; Ara h 2, Arachis hypogaea component protein #2; Cor a 9 and 14, Corylus avellana component proteins #9 and #14; TLR, toll-like receptor; OFC, oral food challenge

ABSTRACT

Hippocrates is often credited with first recognizing that food could be responsible for adverse symptoms and even death in some individuals, but it was not until the seminal observations by Prausnitz that the investigation of food allergy was viewed on a more scientific basis. In the first half of the 20th century, there were periodic reports in the medical literature describing various food allergic reactions. In the mid- to late- 1970's, the studies of Charles May and colleagues began to penetrate the medical world's skepticism about the relevance of food allergy and how to diagnose it, since standard skin testing was known to correlate poorly with clinical symptoms. With May's introduction of the double-blind placebo-controlled oral food challenge, the study of food allergy became evidence-based and exponential strides have been made over the past four decades in the study of basic immunopathogenic mechanisms and natural history, and the diagnosis and management of food allergies. Today IgE- and non-IgE-mediated food allergic disorders are well characterized and efforts to treat these allergies by various immunotherapeutic strategies are well under way.

Historical background

Although the first account of food allergy is generally attributed to Hippocrates, the Chinese emperors Shen Nong (~2735 BC) and Huang Di (2698-2598 BC) provided advice in “Shi Jin-Jing” (“Interdictions concerning food”) for pregnant women to avoid certain foods, e.g. shrimp, chicken and meats, and for individuals with certain skin lesions (possibly atopic dermatitis lesions) to avoid certain foods.[1] In Hippocrates' writings (460–377 BC), he referred to the presence of “hostile humors” (now known as IgE antibodies) in some men that made them “suffer badly” following ingestion of cheese.[1] An often quoted line from a poem of Titus Lucretius Cato (98–55 BC), “*What is food to one, to another is rank poison*,”[1] strongly suggests an understanding of adverse reactions to foods over 2000 years ago. In the 17th century case reports of food hypersensitivity reactions began to appear in the medical literature[1]; Jean Baptiste van Helmont reported asthmatic attacks following the ingestion of fish in *Oriatrike* published in 1662. Later Robert Willan described urticaria following the ingestion of almonds, mushrooms, fish, crab, lobsters and mussels, and “*urticaria febralis*” (fatal anaphylaxis) following ingestion of mussels and lobsters in his *Treatise on Dermatology*, (a multi-volume publication; 1798–1808).

While various reports of reactions to foods appeared periodically in the medical literature, the classic experiment of Prausnitz in 1921 initiated the scientific investigation of food allergy and established the immunologic basis of allergic reactions.[2] In his experiment, Prausnitz injected serum from a fish-allergic patient, Kustner, and a non-allergic control subject into his own skin, and on the following day he injected fish extract into the same areas. A positive local reaction (Prausnitz–Kustner test) proved sensitivity could be transferred by a factor in serum (now known to be IgE antibodies) from an allergic to a non-allergic individual. In a similar experiment four years later, Freeman passively sensitized his middle nasal turbinate with serum from an egg allergic patient and demonstrated the induction of rhinitis (rhinorrhea and sneezing) shortly after the ingestion of an egg the following day.[3]

Other early studies of food allergy focused on radiologic changes associated with immediate hypersensitivity reactions in the gastrointestinal tract. In one of the first of these reports, hypertonicity of the transverse and pelvic colon and hypotonicity of the

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cecum and ascending colon were noted in a patient with wheat allergy following the ingestion of wheat.[4] In a later fluoroscopic study, Rowe and colleagues[5] compared the effect of barium contrast material containing food allergens with standard barium contrast material in 12 food-allergic children. They noted prolonged gastric hypotonia and retention of the allergen test meal, prominent pylorospasm, and subsequently increased or decreased peristaltic activity of the intestines.

In a novel series of experiments over 70 years ago, Walzer and his colleagues in New York utilized sera from food-allergic patients to passively sensitize volunteers and demonstrate that "immunologically" intact antigens can cross the gastrointestinal mucosal barrier and disseminate rapidly throughout the body. The investigators passively sensitized skin on the arms of a large cohort of normal adults with serum from a fish allergic patient and similarly a large cohort of normal children with serum from an egg allergic patient, as well as with control non-allergic serum.[6,7] Twenty-four hours later the adults and children were fed fish and eggs, respectively, and within about 90 min, nearly 90% of the study subjects developed a large wheal and flare response at the site on their arm sensitized with "allergic sera," but not at the site with "non-allergic, control sera." Using similar passive sensitization, colonic mucosa of patients who had previously undergone an ileocolostomy was injected with sera from food allergic patients and normal controls.[8] Serum from the allergic patient was injected at the distal (non-contiguous) site of the ileocolostomy opening and 24 h later the study subjects ingested the food allergen. Within 10–15 min, they developed hyperemia at the sensitized distal colonic site followed shortly thereafter by pallor and edema, and prolonged, copious mucus secretion and petechia at the injection site. Walzer and his colleagues also studied the effects of stomach acidity on food allergen uptake. They demonstrated that increased stomach acidity and the presence of other food in the gut decreased antigen absorption, while decreased stomach acidity, such as from today's H2-blockers and proton pump inhibitors, and ingestion of alcohol increased antigen absorption.[9]

In the late 1930's, six patients with gastrointestinal food allergy or wheezing exacerbated by the ingestion of a food allergen and control subjects were evaluated by gastroscopy.[10] Thirty minutes after a food allergen was placed on the gastric mucosa, patients with gastrointestinal food allergy developed markedly hyperemic and edematous patches with overlying thick gray mucus and scattered petechiae at the site of allergen placement, similar to the findings reported earlier by Walzer and colleagues in passively sensitized intestinal mucosal sites.[9] Only mild hyperemia of the gastric mucosa was noted in patients with wheezing provoked by food ingestion. Fifty years later a study confirmed these earlier observations in a cohort of 30 patients with gastrointestinal food allergy, and established an IgE-mediated mechanism for these reactions.[11] These investigators demonstrated that food-allergic patients had significant food-specific IgE antibodies and increased numbers of intestinal mast cells in the gastric mucosa compared to normal controls, and significant decreases in stainable mast cells and tissue histamine following a positive food allergen response.

In 1912, Schloss introduced the concept of using extracted protein from foods for scratch testing in the diagnosis of food allergy,[1] but by then there were already calls for curbing the growing practice of "*scratching the skin with a few food tests and putting the patient on a weird and impracticable diet which usually accomplishes no result…*"[1] In 1950, Loveless demonstrated that the patient's history and presence of positive skin tests were often insufficient to diagnose food allergy in her report of the first blinded, placebo-controlled food trials in patients with milk allergy.[12] In a later report of 89 children being evaluated for milk allergy, Goldman and colleagues recommended that the diagnosis of food allergy could only be established when withdrawal of the food (milk) from the diet led to complete resolution of symptoms and three successive challenges with the food (milk) duplicated the presenting symptoms.[13] Due to the potential severity of reactions developing during food challenges, this approach was not widely accepted. In the mid-1970's, Charles May and his colleagues reported on the use of the double-blind, placebo-controlled oral food challenge (DBPCFC),[14] which has emerged as the accepted "gold standard" for the diagnosis of food allergy. A consensus document (Practall) attempting to standardize the DBPCFC was published in 2012 by the American Academy of Allergy & Immunology and the European Academy of Allergy and Clinical Immunology.[15]

Even before Prausnitz's classic experiment demonstrating that a transferable factor, i.e. IgE, was likely involved in the pathogenesis of food allergy, physicians began experimenting with immunotherapeutic approaches to treat food allergy. The first report of successful oral immunotherapy (OIT) was published in the *Lancet* in 1908 and described the successful treatment of a child with egg-induced anaphylaxis.[16] A few scattered case reports followed including a report by Keston, which provided very limited details on a "*…method as outlined above has been effective in desensitizing about fifty patients with allergic symptoms,*"[17] and reports by Edwards[18] and Unger[19] that were equally vague on outcomes, e.g. "*Twelve of thirteen patients attempted have been successfully desensitized by the oral method.*"[18]

Recent past and present history

In the early 1980's, the landscape of food allergy was very different from today: food allergy was less prevalent, there was little public awareness of the problem, most clinicians were highly skeptical of the diagnosis, and there was little active research going on, primarily because many investigators did not consider the field to be "*a real science*." Skin testing and food-specific serum IgE values (radioallergosorbent tests [RASTs]) were seen as unreliable diagnostic tools, given their poor correlation with oral food challenge (OFC) outcomes.[20] Thirty-five years ago the perceived prevalence of food allergy in the United States was similar to what is reported today, i.e. about 20%, but the actual prevalence then was thought to be less than 1%[21] compared to more recent estimates today of 3.5%–5% of the general population[22] and 8% of the pediatric population.[23] Some have referred to the increase in food allergy and atopic dermatitis as the "*second wave of the allergy epidemic*,"[24] as suggested by the National Health Interview Survey in the US (Fig. 1). Severe food-allergic reactions were rare 35 years ago, but now represent the single leading cause of anaphylaxis treated in American emergency departments, and data from the USA and Australia indicate that there has been a marked increase in hospitalizations due to food allergy in the past two decades, as depicted in Figure 2.[25] The reason for this rapid rise in food allergy among industrialized countries around the world remains an open question.[26]

Many of the same diagnostic tools used today to diagnose food allergy were utilized 30 years ago, but these tools have been refined. Patient history and skin testing remain the cornerstone for diagnosing food allergy. However, the characteristics of food allergic disorders (Table 1) and food allergic symptoms (Table 2) have been more precisely defined, which has improved the diagnostic accuracy of the medical history and its utility in guiding appropriate laboratory studies.[27] Until the mid-1990's, most allergists rarely utilized *in vitro* food-specific IgE measurements (RASTs) in their food allergy work-up because of poor sensitivity and specificity in identifying symptomatic food allergy.[20] However, with the advent of a quantitative *in vitro* assay, it was shown that there was a direct correlation between the quantity of food-specific

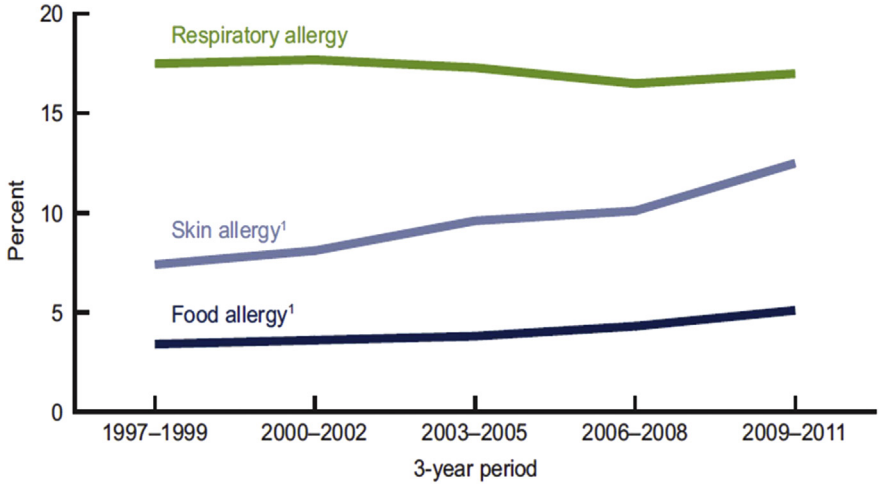

Fig. 1. The percentage of children 0–17 years of age in the United States with a reported allergic condition in the past 12 months; 1997–2011. From Jackson KD *et al.* National Child Health Services Data Brief #121; May 2013.

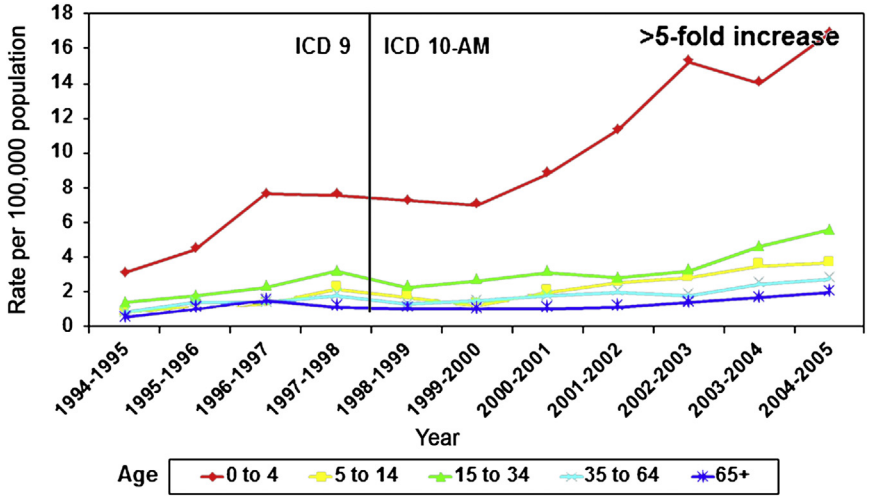

Fig. 2. Food-induced hospital anaphylaxis admissions in Australia by age group from 1994 to 2005. From WK Liew *et al.* J Allergy Clin Immunol 2009; 123:434–42.

IgE in the serum and the likelihood that a patient would react to a specific food.[28,29] Since then, numerous studies in different patient populations have been undertaken in an attempt to refine the diagnostic accuracy of quantitative serum food-specific IgE measurements.[30,31] More recently, the advent of quantitative IgE measurements to major allergenic proteins within certain foods, e.g. Ara h 2 in peanut[32,33] and Cor a 9 and 14 in hazelnut,[34,35] has further improved the diagnostic accuracy of *in vitro* testing. In the mid-1970's, May and Bock reported that prick skin test wheal diameters less than 3 mm greater than the negative control were unlikely to indicate symptomatic IgE-mediated food allergy and that OFCs were necessary in patients with larger wheal diameters in order to establish symptomatic food allergy.[14,36] However, in 2000, Sporik and colleagues reported that analogous to results with food-specific IgE values, the larger the prick skin test wheal diameter, the greater the likelihood that a patient would experience allergic symptoms to a food and suggested wheal diameter cut-off values that were highly predictive of positive OFCs.[37] However, given the variability in skin test extracts, methods and interpretation, and the selected high-risk populations used in Sporik's and subsequent studies, the generalizability of these values have to be interpreted with caution.[38] Three decades ago few allergists performed oral food challenges, whereas today oral food challenges are the accepted "gold standard"[27,39] and efforts have been made to standardize the procedure worldwide.[15]

For decades allergists and clinicians have been aware that many young infants "outgrow" their food allergies, especially to foods such as milk, egg, soy and wheat, whereas allergies to other foods, e.g. peanuts, tree nuts and seafood, are more likely to persist throughout life. However, it was not until the late 1990's when investigators began mapping allergenic (IgE-binding) epitopes on food proteins that an immunologic mechanism underlying this phenomenon became more apparent. These studies showed that children who outgrew their egg or milk allergy, i.e. about 80% of this population, produced IgE antibodies primarily to conformational (3-dimensional) epitopes whereas those with persistent (lifelong) allergy also generated significant quantities of IgE antibodies to sequential (linear) epitopes,[40,41] suggesting different phenotypes of IgE-mediated food allergy in children. In contrast, most children with peanut allergy, who typically do not outgrow their peanut allergy, i.e. 80%–85%, make large quantities of IgE antibodies to sequential epitopes. In addition it was shown more recently that the greater a patient's IgE-binding diversity to allergenic epitopes on peanut proteins, i.e. the more different allergenic epitopes

Table 1
Classification of food allergic reactions.

IgE-mediated	Mixed IgE- & non-IgE-mediated	Non-IgE mediated (cellular)
Skin		
Urticaria	Atopic dermatitis	Dermatitis herpetiformis
Angioedema		Contact dermatitis
Erythematous morbilliform rash		
Flushing		
Respiratory		
Allergic rhinoconjunctivitis	Asthma	Food-induced pulmonary hemosiderosis (Heiner's Syndrome)
Acute bronchospasm		
Gastrointestinal		
Oral Allergy Syndrome	Eosinophilic esophagitis (EOE)	Food protein-induced entero-colitis syndrome (FPIES)
Acute gastrointestinal spasm	Eosinophilic gastritis	Food protein-induced procto-colitis syndrome (FPIPS)
	Eosinophilic gastroenteritis	Food protein-induced enteropathy syndrome
		Celiac disease
Cardiovascular		
Dizziness & fainting		
Anaphylaxis		
Food-associated, exercise-induced anaphylaxis		
Miscellaneous		
Uterine cramping & contractions		
Feeling of “pending doom”		

bound by a patient's IgE, the more likely the patient was to experience a severe allergic reaction following an accidental ingestion.[42,43]

Until relatively recently, it was believed that the best strategy to promote “outgrowing” food allergies was strict allergen avoidance, which would prevent “boosting” and sustaining the IgE response, and the concept of patients with different allergic phenotypes, i.e. those with different ratios of IgE directed at conformational and sequential epitopes, was not known.[27] The theory at that time behind adherence to strict elimination diets was based primarily on retrospective observational studies of children with atopic dermatitis in which it appeared that children who maintained a strict elimination diet were more likely to outgrow their milk or egg allergy compared to those who had frequent accidental ingestions.[44] However, this observation was likely confounded by “reverse causation” since children with persistent food allergy, i.e. those who had IgE to sequential epitopes, would experience allergic reactions to any form of milk or egg, whereas those likely to outgrow their allergy, i.e. those who had IgE predominately to conformational epitopes, would only react to unbaked egg or milk. In fact, the realization that children who outgrew their milk and egg allergy made IgE antibodies primarily to conformational epitopes[40] led to the hypothesis that these children could safely ingest baked-milk and egg products in which conformational epitopes were heat-denatured by high oven temperatures, and subsequent studies confirmed this hypothesis to be true.[45,46] In addition, it was shown that the addition of baked-milk or egg to the diet of these children actually accelerated the development of tolerance to all forms of milk and egg products,[47,48] and today baked-milk and egg OFCs and early introduction of baked-milk and egg products into the diet of infants with milk or egg allergy has become standard practice.[27]

Table 2
Symptoms associated with food allergic reactions.

Cutaneous	Pruritus
	Erythema/Flushing
	Urticaria
	Angioedema
Ocular	Pruritus
	Tearing
	Conjunctival injection
	Periorbital edema
Respiratory	
Upper	Pruritus
	Nasal congestion
	Rhinorrhea
	Sneezing
	Hoarseness
	Laryngeal edema
Lower	Cough
	Wheezing
	Dyspnea
	Chest tightness/pain
Gastrointestinal	Oral pruritus
	Oral angioedema (lips, tongue, or palate)
	Pharyngeal pruritus/tightness
	Colicky abdominal pain
	Nausea
	Vomiting
	Diarrhea
Cardiovascular	Tachycardia
	Dizziness
	Loss of consciousness/fainting
	Hypotension
Miscellaneous	Metallic taste in mouth
	Uterine cramping/contractions
	Sense of impending doom

Over 80 years ago Grulee and Sanford reported that exclusive breast feeding in newborn infants reduced the development of atopic dermatitis 7-fold compared to infants receiving cow's milk.[49] This led to a series of studies in the late 1980's and 1990's demonstrating the benefit of exclusive breast feeding, use of extensively hydrolyzed infant formulas and/or avoidance of major allergenic foods from the mothers' and infants' diets in the prevention of atopic dermatitis and milk allergy.[50–53] These studies supported the hypothesis that delaying the exposure to major food allergens (milk, egg, peanut and fish) would allow the infant's immune system to mature, respond appropriately to food antigens, and decrease the likelihood of the child developing food allergies. Murine studies had shown that very early introduction of antigen to immature mouse pups could lead to sensitization and that by delaying allergen exposure, their immune system would not generate antibodies against foreign substances.[54] At the time, however, it was not appreciated how much food allergen was present in house dust,[55–57] and how it is likely that many food-allergic children are sensitized to food proteins by environmental exposure to food allergens on irritated/inflamed skin, e.g. atopic dermatitis.[58] Consequently, by delaying oral exposure that would normally induce tolerance to allergenic foods, these atopic infants are left vulnerable to cutaneous sensitization for a more prolonged

period of time.[59] In fact, Lack and his colleagues have shown conclusively that early oral introduction of peanut into the diet of high risk infants can dramatically reduce the prevalence of peanut allergy compared to the standard practice of later introduction.[60,61] Whether this finding is similar for other major food allergens remains to be established.[62,63]

In the past 35 years, we have witnessed remarkable changes in our basic understanding of food allergic disorders, which have elevated food allergy from a collection of case reports largely discounted by investigators and clinicians to a "serious science" with hundreds of articles published annually in high-impact scientific journals. Certain potential pathogenic factors, such as the gut microbiota,[64] were barely discussed three decades ago, whereas today new technologies have enabled investigators to focus on this new frontier.[65–68] Although the first case of oral immunotherapy was published in 1908, no immunotherapeutic approaches to treat food allergy were being pursued 35 years ago. In 1998, Patriarca and colleagues described a protocol used in desensitizing a small cohort of children with food allergy,[69] and noted that "…*although further studies (such as a randomized trial) are needed to reinforce the conclusions of this paper, oral desensitization may represent an alternative and safe approach in children with food allergy*…,"[70] In the past decade, over twenty studies evaluating the effects of OIT,[71–77] as well as other forms of immunotherapy have been published,[78–80] but due the prevalence of significant adverse allergic reactions and the risk of inducing eosinophilic esophagitis, most authorities have agreed that OIT is not yet ready for general use in the clinic.[27,81–83]

Future

While tremendous progress has been made in the diagnosis and management of food allergy, especially in the past decade, the next decade will undoubtedly witness further advances in our understanding of basic underlying immunologic mechanisms associated with food allergy and the development of tolerance. Recent murine studies indicate that not only the gastrointestinal tract, but normal skin is a powerful tolerogenic organ that may be exploited for the prevention and treatment of food allergy.[84–87] A recent double-blind placebo-controlled study demonstrated that the use of omalizumab in combination with oral immunotherapy (OIT) to milk could markedly reduce adverse reactions due to OIT compared to placebo, significantly improving the risk:benefit ratio of this approach.[88] A number of other novel therapies are in pre-clinical or early clinical trials for treating food allergies: epicutaneous immunotherapy has shown promise in pre-clinical murine models and in a phase I and II clinical trial[89,90]; an herbal formulation based on traditional Chinese medicine has proved effective in pre-clinical murine studies and shown some positive responses in early human trials[91–93]; and CpG-coated nanoparticles containing food protein,[94] modified allergenic proteins[95,96] and toll-like receptor (TLR)-conjugated proteins similar to those used for grass pollen immunotherapy,[97,98] have all shown promise in murine models of food allergy. A number of trials are now underway to determine the most effective strategies for preventing food allergies and a number of diagnostic approaches, e.g. allergenic epitope analysis[99] and basophil activation assays[100–102] are being evaluated for their ability to provide better tools for accurately identifying patients with symptomatic food allergy.

While the past three decades have witnessed a major expansion in funding and the number of investigators pursuing food allergy research, an exponential growth in our knowledge about food allergies and some promising therapeutic approaches that could become available in the clinic in the next few years, many questions remain. To move the field forward it is essential that we critically reassess published studies and retain strict adherence to the scientific method in future investigation, seek a better understanding of the basic immunology of "tolerance" and immunopathogenic mechanisms of food allergy in man, evaluate the structural properties of food allergens and effects of food processing and additives, explore the gut and skin microbiome and their effects on immune tolerance and hypersensitivity, and explore the human genome to uncover clues as to other mechanisms and pathways not yet appreciated that may contribute to the development of symptomatic food allergies. Despite the great advances in the field of food allergy, the remaining questions will likely keep investigators occupied for at least the next three decades.

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Conflict of interest

The author is a part-time employee of DBV Technologies as their chief scientific officer directing the research program. He has 4% ownership and stock options of Allertein Therapeutics, LLC, a start-up company developing nanoparticle therapeutics, and 42% ownership of Herbs Spring, LLC, a start-up company developing herbal therapeutics for food allergy and asthma. He also is a member of the Scientific Advisory Board of Dannone.

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