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Food Allergy: Problems, Fiction and Hard Facts

A.L. de Weck

Gerimmun Foundation, Allergy Research Laboratory, Fribourg, Switzerland

The distinction to open this interesting Symposium certainly does not stem from my own long experience and expertise in the field of food allergy. In fact, I have always found food allergy one of the most frustrating domains of allergology and something in which very little new is ever happening. Therefore, I rather avoided this topic, until a few years ago when I realized that (a) food allergy is possibly a key to effective allergy prevention and (b) we are beginning to have at hand new tools to tackle the problem.

Taking a fresh look at the whole problem from some distance may indeed be a justification for this lecture. Food allergy has been with us for a very long time, starting with the Hippocrates description of urticaria following ingestion of cheese. Indeed, in the early descriptions of allergic reactions in the Middle Ages and in the pre-industrial age, food allergies are more frequently to be found in the early history of allergy than hay fever [1]!

If we listen to what patients are telling us or if we read what journalists write, food allergy is a major medical problem affecting up to 20% of the population [2]. The reality, however, may be somewhat different. On the one hand, in a population believing to suffer from some food allergy or intolerance, a double-blind placebo-controlled challenge will confirm the subjective beliefs only in about 10-20% of the cases. On the other hand, food allergies may be responsible for atopic dermatitis or asthma but remain unsuspected by the patient.

What is therefore the true incidence of food allergy? Data in this respect are rather variable, because criteria for inclusion and diagnosis are variable and to some extent subjective [3]. Anaphylactic reactions due to food ingestion and needing emergency treatment are certainly an objective manifestation; some recent enquiries have shown that this event is not so rare [4, 5] and represents the most immediately dramatic outcome of sensitization to foods (fig. 1). Taking into account the results of food provocation in various allergic diseases and manifesta-

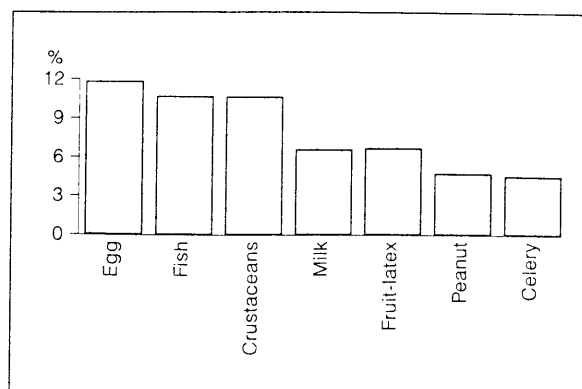


Fig. 1. Epidemiology of anaphylactics (food-induced) shock in France (multicentric study: 46 emergency departments; 29 departments of dermatology, and 19 departments internal medicine). Total anaphylactic shocks $n = 794$: Food induced, 10.2%; relapsing, > 30%; food allergy previously known, 23.4%; food allergen hidden, 30.8%; enhancing factors (alcohol, exercise, drugs), 25.9%; 'idiopathic' (hidden food allergen?), 10.2%; diagnostic efficiency in allergy department, 94% [from 4].

Table 1. Epidemiological evaluation on the incidence of food allergy [adapted from 3, 6]

	Cumulated prevalence in population, %	Manifestations caused by food allergy in % of cases
Allergic asthma	6–8	10–40
Atopic dermatitis	13–18	40–50
Hay fever	10–15	50 ¹
Gastrointestinal	2–3	100

¹ Oral allergy syndrome.

tions, such as asthma, atopic dermatitis, urticaria and rhinitis, one must come to the conclusion that food allergy affects about 13–18% of the population (table 1) [6].

The particular incidence of food and egg allergy in early infancy and its possible role as a gate opener towards the 'allergic march' in genetically predisposed newborns [7] are increasingly recognized. After the initial phase in which allergy to milk and/or egg predominates and causes atopic dermatitis, the atopic syndrome evolves into sensitization to various inhalation allergens causing primarily rhinitis and asthma. From studies on allergen-specific IgE in cord blood [8] and of cord blood lymphocyte reactivity [9–11], it increasingly appears that sensitizing contacts with allergens already occur in utero and that IgE produc-

tion indeed starts in early life. Whether this phenomenon is restricted to or particularly intense in genetically predisposed infants (at high risk of atopy) still requires more extensive confirmation [11].

In any case, it is clear that the atopic syndrome starts early in life [12] and usually encompasses multiple successive IgE sensitivities. There is, however, another type of IgE-mediated allergy, which may occur as well in non-genetically predisposed individuals. Both clinically and experimentally [13], we encounter individuals who may become exquisitely sensitized and produce high levels of IgE to isolated allergens (fig. 2). In this way, isolated food allergies may be encountered also in nonatopic individuals. The probable mechanism of such an event has been somewhat forgotten in recent years but was appropriately termed 'allergic breakthrough' [13]. We must remind ourselves of these different pathways to high allergen-specific IgE production, because they will influence diagnosis, interpretation, prognosis and possibly treatment.

Among other allergic diseases, food allergies have some pathophysiological and immunological peculiarities. The first one is the very developed immunological system of the gut which, in comparison with other target organs, such as the skin, the nose or the lung, has not yet been investigated as extensively. Studies of IgE-mediated allergies in these other organs have pointed out to the importance of late phase reactions and to the interplay of cytokines and inflammatory cells which accompany them [14]. While dynamic immunological studies following allergen provocation on these various local targets (e.g. skin window, nasal and bronchial lavages) have considerably extended our knowledge in recent years, we still have little information on the pathophysiological events occurring in the gut after ingestion of allergenic food in a sensitive individual. In particular, we know little about the local events distinguishing IgE- from lymphocyte-mediated reactions in the gut.

A second peculiarity of allergy to food allergens is the fact that most allergenic proteins are profoundly modified by total or partial digestion upon travelling through the gut and that they are also subject to active and passive resorption mechanisms. In that sense, allergen contact profoundly differs from those occurring on the skin or on other mucosae. The important role played by disturbances in local mucosal contact with allergens is exemplified clinically by the recently reported high incidence of IgE-mediated allergies in patients afflicted by cystic fibrosis [15].

A major source of frustration for allergologists in dealing with food allergy is certainly the continuing difficulty in diagnosis, since our usual techniques such as serological IgE tests or skin tests to a large extent fail us in this field. In this context and also because a suspicion of food allergy often rests on highly subjective and emotional considerations, the procedure of double-blind placebo-controlled food challenge (DBPCFC) has evolved and is almost unanimously praised as the 'golden standard' of food allergy diagnosis [16]. DBPCFC may be the best

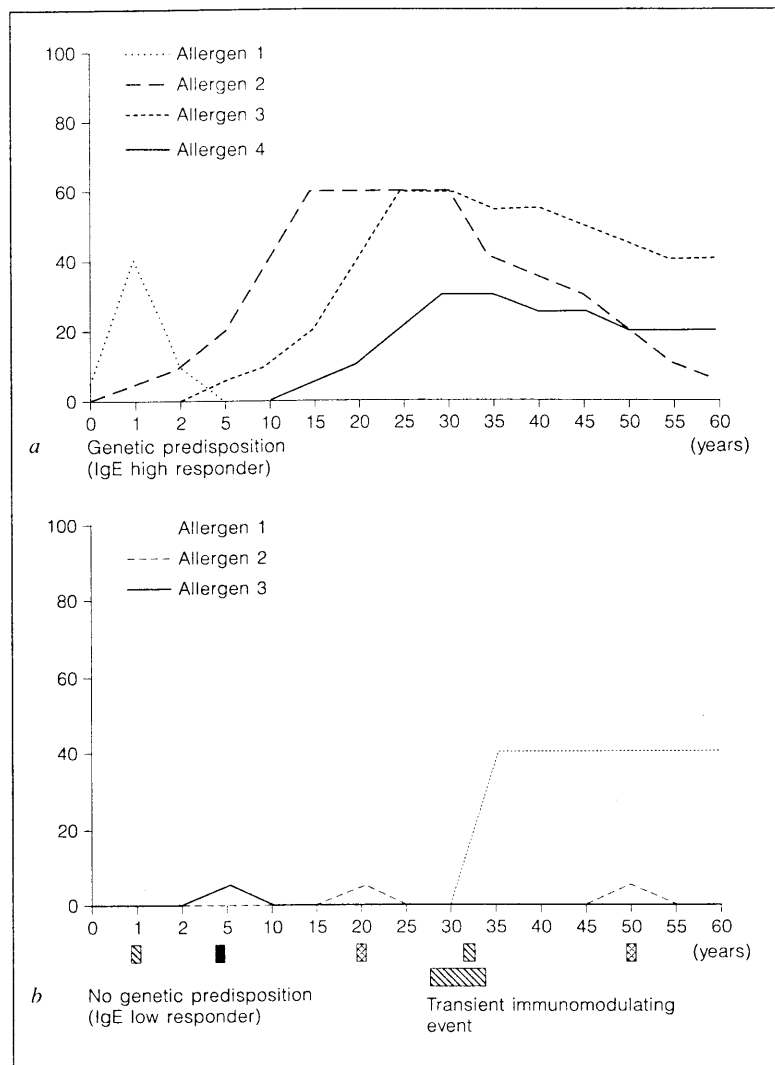


Fig. 2. Two types of IgE-mediated allergy: (a) the atopic march and (b) allergic breakthrough.

we have at the present time, but it remains a procedure with many drawbacks. Besides the difficulties to perform DBPCFC in daily practice, this procedure certainly also fails to take in account the fact that several factors beyond IgE sensitization often contribute or are required for elicitation of a clinical reaction to food challenge (e.g. exercise, stress, etc.). DBPCFC is also not strictly objective, since a number of readout criteria (e.g., itching, colics) are of subjective nature.

For progress to occur in food allergy, it is therefore, in my opinion, essential that we begin to look actively beyond and after DBPCFC procedures. Research in food allergy should now concentrate in investigating events following allergen challenge at the local level, such as the observation of local reactions after allergen challenge by colonoscopy, analysis of cellular reactions and mediator release in the gut mucosa and in intestinal fluid, or also 'copro-immunology', e.g. analyzing from stools the intraluminal events [17]. It is encouraging that several reports in this Symposium indeed show progress in these directions. Such techniques may soon become of great help in diagnosis of food allergy. With all due respect for DBPCFC, it should not happen that any study in the field, particularly pathophysiological studies following allergen challenge, become unpublishable if the patients have not been concomitantly subjected to the DBPCFC procedure.

My own interest in food allergy has taken some more concrete turn recently with the development of an excellent animal model, which appears to closely mimic food allergy in man. It has long been known that some dogs develop a genetically controlled atopy-like syndrome, in which atopic dermatitis, more rarely airway allergies, are the main symptoms [18]. IgE-like antibodies have also been described in the dog and are responsible for the clinical symptoms. However, progress in dog allergy research has been impaired for a long time by the lack of pure reference IgE myelomas. Thanks to a large collection of monoclonal anti-IgE antibodies, among which some recognize common epitopes on dog and human IgE [19, 20], it has become possible to establish dog allergy research on solid footing.

In a series of experiments which are reported in detail elsewhere [9, 19, 21, 22], we have been able to recognize the following interesting rules and observations:

(1) Beagle dogs may be segregated into and bred as high or low IgE responders [9, 21].

(2) Two levels of genetic control operate in the dog, as in man. The first level concerns a general propensity to produce high IgE levels when confronted with any or most allergens (atopy). The other concerns the individual capacity of becoming sensitized to individual allergens (or rather epitopes) and is probably linked, like in man and other species, to histocompatibility antigens.

(3) In high IgE responders, very early contact with some IgE-inducing allergen in the first days or weeks of life is essential to achieve an 'atopic state' in which the animals maintain a high IgE level and become also steadily able to develop additional specific IgE following new allergen contacts [22].

(4) High IgE responders, when entering in contact with allergen only 3–4 months after birth, as well as low IgE responders when confronted with allergen at any time (also at birth), produce only a short-lived specific IgE response, which can never be boosted. However, the allergen-specific IgG response is constant in these animals and not basically different from that of the high IgE responders.

(5) In high IgE responders, the allergen-specific IgE response is maintained only as long as allergen in very small doses continues to be administered. If no allergen contact persists, IgE antibodies decline by about 90% in 6 months, while immediate skin reactivity persists much longer (about 30% decline in 6 months). The response remains boostable at any later time, following renewed contact with allergen [22].

(6) While these rules were established with a pure recombinant allergen (Bet v 1 from birch pollen), they also appear to apply to food allergens, such as pure milk allergens or to food allergen mixtures (e.g. peanut, soya, shrimp). Indeed, it was interesting to observe that immunization with equal amounts of food proteins in high IgE responder dogs yields a similar food sensitization hierarchy as that observed in man (fig. 3).

(7) High responder dogs immunized at birth with milk or milk proteins develop IgE against these allergens. These IgE, however, disappear within a few weeks following feeding of the puppies with cow's milk and can then no longer be boosted (fig. 4). The IgG response to milk, on the other hand, is not affected. This appears to be a similar instance of secondary tolerance induction as occurring in most infants with milk or egg allergy during years 2–3 of life.

(8) High responder dogs fed with high cow's milk doses during the first week of life develop a lifelong tolerance to milk allergens.

The model of experimental dog allergy appears to be clinically relevant since these animals produce immediate skin reactions when skin tested with allergens or anti-IgE antibodies, bronchial asthma when allergen-challenged by inhalation and even atopic dermatitis-like lesions when injected (or possibly fed) by allergen.

The availability of such an experimental model, as well as parallel studies on spontaneous food allergies in the dog, together with the further development of investigational techniques in man, should enable us to make great progress in the further understanding of food allergies in the next decade.

Conclusion

The field of food allergy has remained very frustrating in terms of understanding, diagnosis and therapy. Recent epidemiological data confirm the growing importance of the field. The double-blind placebo-controlled allergen challenge currently praised as the 'golden standard' of food allergy diagnosis has severe limitations. In the future, increasing research and attention should be devoted to objective techniques establishing the systemic and local (intestinal) consequences of food allergen provocation. The new availability of an experimental dog allergy model, including food allergy, should enable us to determine the rules of the game, particularly the factors responsible for induction of allergy or tolerance to foods, as well as the role of early food sensitization in the development of the atopic syndrome ('atopic march').

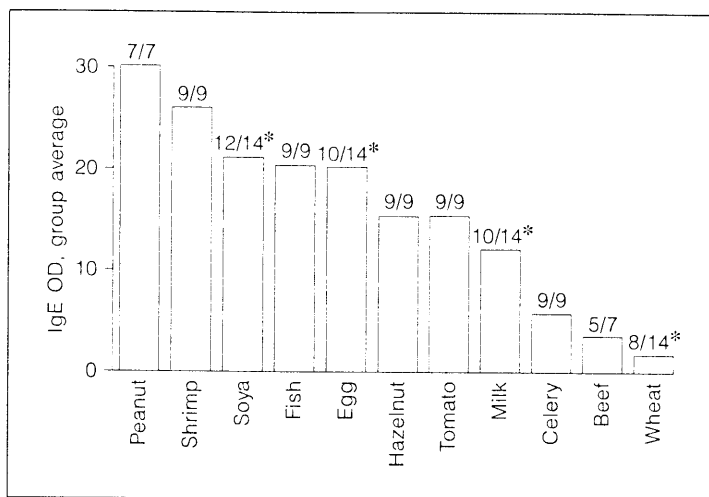


Fig. 3. Comparative allergenicity of food allergens in high IgE responder dogs (immunized with 10 µg protein in Al(OH)₃). *Four dogs immunized late (222 days) after oral induction of tolerance to milk.

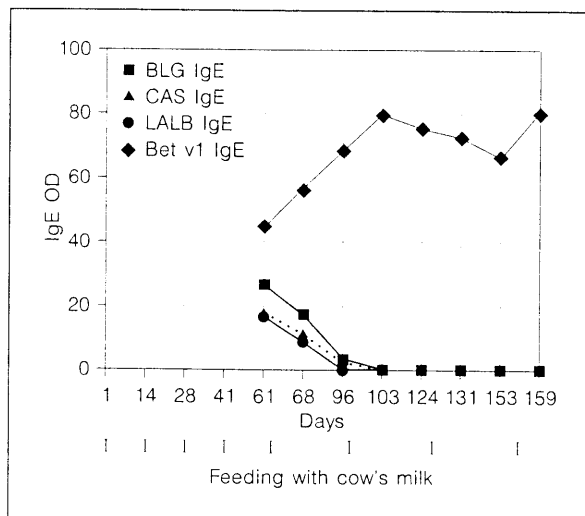


Fig. 4. Differential evolution of IgE to Bet v 1 and milk allergens. I = Immunization with 1 µg Bet v 1, 10 µg cow's milk in aluminum hydroxide.

References

- 1 Footnotes on Allergy. Uppsala, Pharmacia, 1980.
- 2 Young E, Stoneham MD, Petrukevitch A, Barton J, Rona R: A population study of intolerance. *Lancet* 1994;343:1127–1130.
- 3 Host A: Adverse reactions to foods: Epidemiology and risk factors. *Pediatr Allergy Immunol* 1995;6(suppl 8):20–28.
- 4 Moneret-Vautrin DA, Kanny G: Food-induced anaphylaxis. A new French multicentric study. *Bull Acad Natl Med Paris* 1995;179:161–172, 178–184.
- 5 André F, André C, Collin L, Cacaraci F, Cavagna S: Role of new allergens and of allergen consumption in the increased incidence of food sensitization in France. *Toxicology* 1994;93:77–83.
- 6 Sampson HA: Clinical manifestations of adverse food reactions. *Pediatr Allergy Immunol* 1995;6(suppl 8):29–37.
- 7 Baba M, Yamaguchi K: 'The allergy march': Can it be prevented? *ACI News* 1989;1:71–73.
- 8 Host A, Husvby S, Gjesing B, Larsen JN, Loewenstein H: Prospective estimation of IgG, IgG subclass and IgE antibodies to dietary proteins in infants with cow milk allergy. *Allergy* 1992;47:218–219.
- 9 De Weck AL, Derer M, Mayer P, Stumper B: Allergy starts in early life; in *Prediction and Prevention of Childhood Allergy*. Sasaki S, Miyamoto T, Hopkin JM (eds): Osaka, Churchill-Livingstone, 1995, pp 181–197.
- 10 Warner JA, Miles EA, Jones AC: Is deficiency of interferon-gamma production by allergen-triggered cord blood cells a predictor of atopic eczema? *Clin Exp Allergy* 1994;24:425–430.
- 11 Van Duren-Schmidt K, Pichler J, Ebner C, Bartmann P, Förster E, Urbanek R, Szepefalusi Z: Prenatal contact with inhalant allergens. 1996, in press.
- 12 Kondo N, Fukutomi O, Agata H, Motoyoshi F, Shinoda S, Kobayashi Y, Kubawara N, Kameyama T, Orii T: The role of T lymphocytes in patients with food-sensitive atopic dermatitis. *J Allergy Clin Immunol* 1993;91:658–668.
- 13 Katz DH: Regulation of the IgE system: Experimental and clinical aspects. *Allergy* 1984;39:81–106.
- 14 De Weck AL, Stadler BM, Dahinden CA: New perspectives in the modulation of allergic inflammation. *Int Arch Allergy Appl Immunol* 1989;90:17–21.
- 15 Lucarelli S, Quatrucchi S, Zingoni AM, Frediani T, Diamanti S, Quintieri F: Food allergy and cystic fibrosis. *Minerva Pediatr* 1994;46:543–548.
- 16 Bock SA, Atkins FM: Patterns of food hypersensitivity during sixteen years of double-blind, placebo-controlled food challenges. *J Pediatr* 1990;117:561–567.
- 17 Sasai K, Furukawa S, Furukawa T: IgE levels in faecal extracts of patients with food allergy. *Allergy* 1992;49:791–794.
- 18 Haliwell REW, Schwartzmann RM: Atopic disease in the dog. *Vet Rec* 1971;89:209–214.
- 19 De Weck AL, Derer M, Morrison-Smith G, Stadler BM, Frick OL, De Boer RL, Bigler B: Detection of allergen-specific IgE and total IgE in dogs by polyclonal and monoclonal anti-IgE antibodies: A critical evaluation. *Vet Immunol Immunopathol* 1996 (in press).
- 20 De Boer DJ, Ewing KM, Schultz KT: Production and characterization of mouse monoclonal antibodies directed against canine IgE and IgG. *Vet Immunol Immunopathol* 1993;37:183–189.
- 21 De Weck AL: What can we learn from the allergic zoo? *Int Arch Allergy Immunol* 1995;107:13–18.
- 22 De Weck AL, Derer M, Mayer P, Stumper B, Schöni B: Experimental IgE sensitization in beagle dogs. *Vet Immunol Immunopathol* 1996 (in press).

Prof. A.L. de Weck, Gerimmun Foundation, Allergy Research Laboratory, 16 Grands Places, CH–1700 Fribourg (Switzerland)