

Crossreactions In Food Allergy

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Introduction

Food allergy is still widely debated, especially with regard to its pathogenic mechanisms and predisposing factors. It is generally accepted that immaturity of local immunity in the gastrointestinal system or breakdown of so-called oral tolerance is involved in sensitization to foods in infancy (1); but little is known about its development in adults, in whom impaired gastrointestinal immunity is unlikely.

One of the possible mechanisms underlying the appearance of adverse reactions to foods in adults is sensitization by alternative routes, such as the respiratory route, by which aeroallergens sharing homologous epitopes with some food allergens can induce the synthesis of specific IgE antibodies able to crossreact with the different allergen sources, thus evoking clinical symptoms. This kind of crossreaction seems particularly important in the development of sensitization to fruits and vegetables, which causes one of the most common forms of food allergy in adults, the oral allergy syndrome (OAS), in addition to other clinical situations such as the latex-fruit and the bird-egg syndromes. Crossreactions may also account for the clusters of hypersensitivity described for taxonomically related or unrelated foods, including reactions to foods and pollens (Table 1). The culprit in crossreactivity between inhalant and food allergen sources and between different foods is often found to be one of the few major food-allergens so far identified and characterized (Table 2). This shows how much work is still needed to improve our knowledge in this field.

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Table 1
Clusters of Hypersensitivity Between Foods, and Foods and Pollens

Study	Year	Foods	
Eriksson (61)	(1984)	Nut, hazelnut, peanut, apple, pear, potato, carrot	
Ortolani (62)	(1988)	Melon, watermelon, tomato, fennel, celery	
Pastorello (27)	(1994)	Peach, apricot, plum, cherry	
Study	Year	Foods	Pollens
Andersen (63)	(1978)	Hazelnut	Birch
Lahti (64)	(1980)	Apple	Birch
Halmepuro (65)	(1984)	Apple, carrot, celery	Birch
Pauli (66)	(1985)	Celery	Birch, mugwort
Calkhoven (67)	(1987)	Apple, cherry, peach, potato	Birch, grass
Enberg (68)	(1987)	Watermelon	Ragweed
de Martino (44)	(1988)	Tomato, peanut	Grass
Vallier (69)	(1988)	Celery	Mugwort, birch
Wüthrich (70)	(1990)	Celery	Mugwort
Ebner (34)	(1991)	Apple	Birch
Hirschwehr (36)	(1992)	Hazelnut	Hazel tree
Ortolani (26)	(1993)	Fennel, celery	Birch
Gall (71)	(1994)	Kiwi	Grass
		Kiwi	Birch

Table 2
Crossreacting Major Food Allergens

Food	Allergen	Mol wt, kDa	Crossreactivity
Codfish <i>Gadus callarias</i>	Gad c 1: parvalbumin	12	Other fish species
Shrimp <i>Penaeus aztecus</i> , <i>Penaeus indicus</i> , <i>Metapenaeus ensis</i>	Pen a 1: tropomyosin Pen i 1: tropomyosin Met e 1: tropomyosin	36 34 34	Mites, insects, mollusca, snails (?)
Barley <i>Hordeum vulgare</i>	Hor v 1	15	Other cereals
Apple <i>Malus domestica</i>	Mal d 1: pathogenesis related protein	18	Birch pollen
Celery <i>Apium graveolens</i>	Mal d 2: profilin	15	Bet v 1
	Api g 1: pathogenesis related protein	17	Bet v 2
	Mal d 2: profilin	15	Bet v 1
Hazelnut <i>Corylus avellana</i>	Cor a 1: pathogenesis related protein	17	Bet v 2
Carrot <i>Daucus carota</i>	Yet unnamed: profilin	15	Bet v 1

Crossreactivity Among Crustacea

Adverse reactions to crustacea are relatively common in subjects with food allergy. The clinical picture covers the symptoms generally observed that are outlined in an important study by Lehrer et al. (2). They performed a double-blind placebo-controlled food challenge (DBPCFC) with a fresh shrimp extract in 30 patients with reactions to crustacea. The symptoms were both systemic (including urticaria, angioedema, and anaphylactic shock) and local (presenting with OAS). Shrimp is commonly involved in allergic reactions, but other crustacea frequently elicit positive skin tests and radioallergosorbent test (RAST) (3).

This sharing of allergens among crustacea has been demonstrated by RAST-inhibition experiments with lobster and crawfish, both potent inhibitors of RAST with shrimp, and crab, which was also a good inhibitor though to a lesser extent (4). These observations were confirmed by crossed-line and crossed-radioimmuno-electrophoresis, showing that crustacea share some allergens (5). The molecular background of this crossreactivity emerged when the major allergen of shrimp, Pen a 1, was identified as tropomyosin, a 34- to 36-kDa protein involved in actin activation during muscle contraction (6). Findings by immunoblotting confirmed the presence of this protein in all crustacea investigated, and the use of monoclonal antibodies (MAbs) to Pen a 1 demonstrated a similar pattern of reactivity in three crustacea extracts (7), providing a solid scientific basis for this crossreactivity. Tropomyosin also seems involved in crossreactivity between crustacea, insects, and house dust mites, giving rise to a clinical syndrome with respiratory and food allergy that we shall deal with later. Crossreactivity was also reported between crustacea and shellfish, as showed by the inhibition of RAST with oyster by crustacea extracts (8), but considering the poor clinical value of skin tests and RAST for oyster, the significance of this finding is questionable. However, in at least one case—a fish worker allergic to shrimp and shellfish—IgE-reactivity to a 35-kDa antigen present in both extracts was demonstrated in vitro (9).

On the other hand, patients with positive RAST for crustacea and shellfish often have symptoms limited to crustacea. This crossreactivity might be explained by findings reported by Aalberse's group, who detected IgE to crossreactive carbohydrate determinants (CCD). These structures are known to crossreact widely but with no clinical significance in subjects with multiple positive RAST to crustacea and molluscs that are often unrelated to clinical symptoms (10). Thorough investigations are needed on the allergenic pattern of shellfish, as the two phyla *Crustacea* and *Mollusca* are distant and theoretically unrelated with regard to immunological aspects; only the demonstration of molecular homology in the apparently crossreactive structures will clarify this issue.

Crossreactivity Among Fish

The fish that has been investigated most frequently for allergenicity is cod, whose major allergen Gad c 1 (formerly allergen M) was identified in pioneering studies by Aas in 1967 (11). Gad c 1 is a 12-kDa allergen with an IgE-reactive epitope formed by a repetitive group of a few amino acids constituting a sequential antigen that resists cooking, digestion, and denaturation. For many years, cod-allergic patients were placed on a diet avoiding all fish, but it has now been shown that crossreactivity is quite limited. In RAST-inhibition experiments with sera from children allergic to fish, de Martino et al. found that, out of 18 fish species, crossreacting allergens were likely to be present only in 6; namely, cod, bass, dentex, eel, sole, and tuna (12). Clinical crossreactions to different fish were reported in a minority of patients, as demonstrated by a positive DBPCFC to more than one fish in only 3 of 10 patients with positive skin tests to a number of fish species (13). The authors of this study suggested, on the basis of IgE-reactivity in immunoblotting to components of molecular weight in the range of Gad c 1, that sensitization to Gad c 1 might account for reactions to different fish.

Crossreactivity Among Legumes

Foods belonging to the family of legumes are of particular importance to the study of allergy because some of them—especially peanut—may give rise to fatal anaphylaxis (14). Taylor et al. found no crossreactions between peanut and its oil in ten peanut-allergic patients undergoing DBPCFC (15). This suggests that the culprit allergen is lost in the preparation of the oil. However, in one study, peanut oil was responsible for dermatitis in two babies, although the antigen involved was not known (16).

Considering crossreactivity between peanut and other legumes, we must clearly distinguish the *in vitro* and *in vivo* observations. Wide crossreactivity between members of the *Leguminosae* family was observed by RAST-inhibition (17); but, on verifying the clinical reactivity to each member by DBPCFC, it was found that, in most patients, only a leguminous food caused allergic reactions, and only 5% of patients reacted to more than one legume, despite a positive RAST for almost all legumes (18). The same investigators demonstrated multiple IgE-binding bands in each of six legumes (peanut, pea, soybean, lima bean, garbanzo bean, and green bean) by SDS-PAGE/immunoblotting, with a band at 20 kDa in all legumes except the green bean (19). The structures crossreacting in leguminous foods have not yet been identified; but major allergens from peanut, namely Ara h 1 (20), and Ara h 2 (21), and from soybean (22), as well as minor allergens from these two

legumes (23), showed distinct characteristics. These immunochemical findings highlight the need in each patient with clinical reactions to legumes to assess the reactivity to each of these foods before prescribing an elimination diet free of all legumes.

Crossreactivity Among Nuts

Allergy to peanuts is frequently associated with allergic reactions to nuts, as recently reported in the United Kingdom (24) and in Italy (25). Both studies found a significant association between allergy to peanuts and to hazelnuts and walnuts, but no association with soybean and other legumes, thus confirming the data reported in the previous section. In the Italian study, which involved an evaluation of clinical history, skin test, and RAST results in 79 patients with OAS for at least one vegetable food, about 40% of patients had reactions to item(s) of the nut group, with a highly significant ($p = 0.008$) cluster of association between walnuts, hazelnuts, and peanuts (25). The search for a molecular support to these clinical findings has not yet produced any definite evidence, as the known major allergens of these foods are different and cannot account for the crossreactivity.

Crossreactivity Among *Prunoideae*

Hypersensitivity to fruits belonging to the botanical subfamily of *Prunoideae*, such as peach, apricot, plum, and cherry, is a well-defined cluster (26). The clinical picture most often presents with the symptoms of OAS. We designed a study to identify the allergens in *Prunoideae*, and to assess the *in vivo* crossreactivity by challenge tests with fresh fruits and the *in vitro* crossreactivity by SDS-PAGE/immunoblotting and blotting inhibition (27). The study population comprised 23 patients with OAS from peach, and positive skin test and RAST results for all the *Prunoideae*. Crossreactivity was quite wide, since 63% of patients reacted to challenge with more than one fruit, and 26% reacted to all fruits (Table 3). Laboratory techniques enabled us to identify the major allergen of *Prunoideae* as a 13-kDa protein, recognized by specific IgE of 90% of patients clinically sensitive to these fruits (as shown by Fig. 1). Other allergenic components were detected as proteins of 14 kDa (probably a profilin) and 20 kDa. Blotting inhibition showed they crossreacted with grass and birch pollen, whereas no crossreaction was observed between the 13-kDa allergen and pollen allergens (Fig. 2). These observations provided a solid immunochemical basis for the cluster of association regarding *Prunoideae*, owing to an important major allergen present in all these fruits not crossreacting with pollens.

Table 3
Open Food Challenge (OFC) Findings, History (Pollens),
and RAST Results in the 21 Patients Admitted to the In Vitro Part of the Study^a

Patient No.	Symptoms										RAST ^b			
	OFC					History					Plum	Grass	Birch	
	Peach	Cherry	Apricot	Plum	OP	Grass	Birch	Peach	Cherry	Apricot				
1	OP	-	-	OP	-	-	-	2	1	2	2	0	0	
2	OP	-	-	-	+	+	-	3	2	3	3	3	0	
3	OP	-	-	-	-	-	-	3	2	3	2	0	0	
4	OP	-	-	-	-	-	-	3	2	2	2	0	0	
5	OP	OP	-	-	-	-	-	3	2	3	3	0	0	
6	OP	OP	OP	OP	+	+	-	3	1	3	3	3	0	
7	OP	OP	OP	OP	-	-	-	4	3	4	4	0	0	
8	GI	OP	-	-	+	+	+	3	2	3	3	4	4	
9	OP	-	OP	-	-	+	-	3	2	3	3	4	3	
10	OP	-	-	-	+	+	-	2	3	3	2	2	3	
11	OP	OP	OP	OP	+	+	+	2	2	2	2	3	2	
12	OP	OP	-	OP	+	+	+	3	2	3	3	4	4	
13	OP	GI	-	OP	-	-	-	2	2	2	2	3	3	
14	OP	-	-	-	+	+	+	4	3	4	4	4	2	
15	GI	GI	-	-	+	+	-	2	1	2	2	4	2	
16	OP	OP	OP	OP	+	+	+	3	2	3	3	3	4	
17	OP	-	-	-	+	+	-	3	2	3	3	4	4	
18	OP	OP	OP	OP	+	+	+	4	3	3	3	3	3	
19	OP	-	-	-	+	+	+	3	3	3	3	4	2	
20	-	-	-	-	+	+	+	2	3	3	3	3	4	
21	-	-	-	-	-	-	+	2	2	2	2	2	4	

^aOP, oropharyngeal; GI, gastrointestinal.

^bRAST results are expressed as classes of positivity: 0, <0.35 PRU; 1, 0.35-0.7 PRU; 2, 0.7-3.5 PRU; 3, 3.5-17.5; 4, >17.5 PRU. -, negative; +, positive.

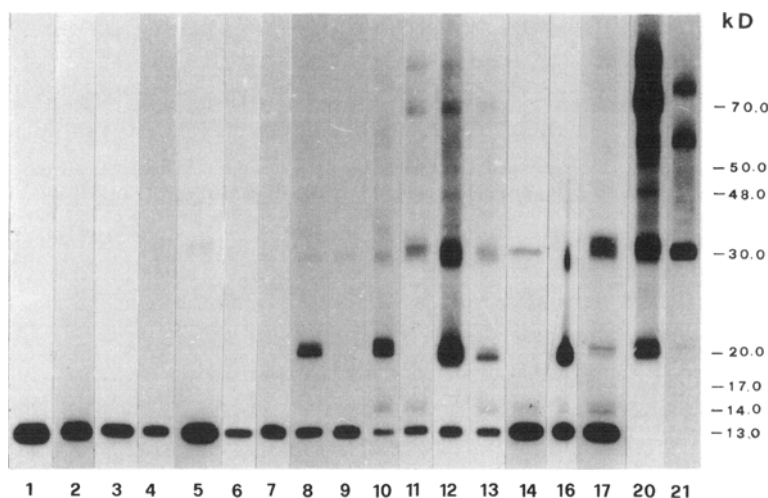


Fig. 1. Autoradiography of IgE-immunoblot analysis of peach extract with sera from 21 patients presenting specific IgE to peach. The molecular weight of some of the main allergens are given. Patients' identification numbers are reported in the lower part of the figure. Patients 1 to 19 presented OAS to peach.

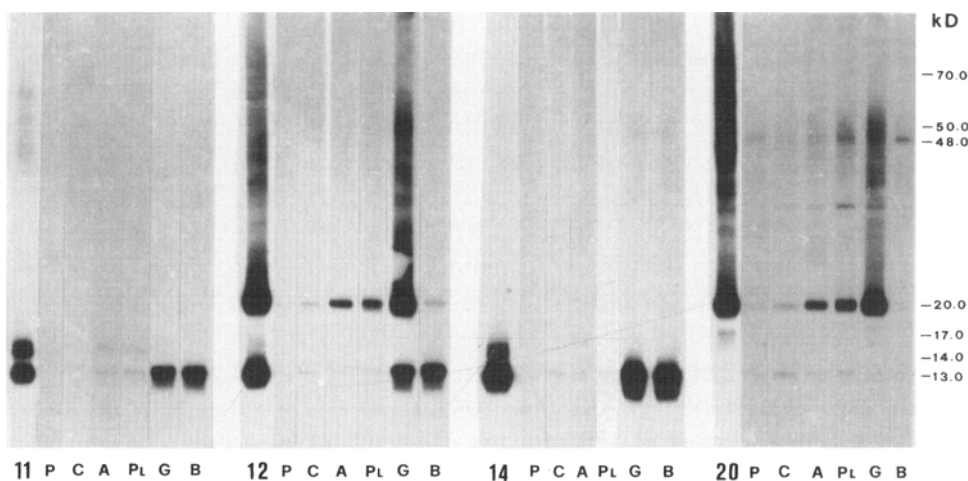


Fig. 2. Immunoblotting inhibition in the sera of four patients. P, peach; C, cherry; A, apple; PL, plum; G, grass; B, birch.

Crossreactivity Among Cereals

Most studies on allergy to cereals have used sera from patients with respiratory symptoms from inhalation of flour (baker's asthma) and found IgE-binding to proteins of 12–66 kDa (28,29). A recent study with sera from 35 patients with atopic dermatitis and positive skin tests

and RAST for one or more cereals (i.e., wheat, rye, barley, oats) found a similar IgE-binding profile with wheat, rye, and barley to proteins of 26, 28–30, 40–50, 69, and 79 kDa. This suggests crossallergenicity, whereas oats seemed to crossreact only weakly with the other cereals (30).

Clinical Syndromes Caused by Crossreactions Between Foods and Aeroallergens

OAS from Vegetables and Pollinosis

Recent epidemiological studies report prevalences of OAS ranging from 23 to 47% in populations of patients suffering from pollinosis (31,32), thus defining this syndrome as one of the most common forms of food allergy in adults. Sensitization to the causative allergens is likely to occur as a consequence of sensitization to pollen allergens. The prevalence of hypersensitivity to the various vegetables depends on their sharing allergens crossreactive with pollens. Consequently, fruit and vegetables belonging to the families of *Rosaceae* and *Umbelliferae*, in which such allergens have been demonstrated, are mainly involved. Additionally, in most cases, sensitization to pollens precedes the development of allergic reactions to foods. In a population of 335 patients with pollinosis, we found that the age of onset of pollinosis was significantly lower ($p = 0.041$) than the age of onset of OAS, and most pollinotic subjects showed a latent period before developing OAS (33). These findings confirmed our previous observations of a significant association between the onset of pollinosis and OAS (26).

The pollens most involved in crossreactivity with foods are birch and mugwort. In birch pollen, the two major allergens, Bet v 1 and Bet v 2 (respectively 16–18 and 14–15 kDa), have been identified as responsible for crossreactivity with apple, hazelnut, and celery (34–36). These proteins are so widespread in the vegetable kingdom as to be considered panallergens. Bet v 1 seems responsible for crossreactivity with apple, in which an 18-kDa allergen showing about 75% homology with Bet v 1 at DNA levels was identified (34). Recently, the same research group reported a homology of about 60% between Bet v 1 and the major allergen from celery, Api g 1, a 16.2-kDa protein (37). These proteins seem to belong to a group of so-called pathogenesis-related proteins, which are expressed under stress conditions, particularly if the plant is attacked by microorganisms. Bet v 2 is a profilin, belonging to a group of molecules of about 15 kDa involved in fertilization of plants, which are present in a large series of vegetable sources (38).

To confirm these crossreactivities, Kraft's group from Vienna studied sera from 20 patients with birch pollinosis and allergic reactions to various vegetables (39). Using MAbs to Bet v 1 and Bet v 2, they demonstrated the presence of proteins highly homologous with Bet v 1 in

apple, pear, and celery and with Bet v 2 in all these plus carrot and potato, thus confirming the ubiquity of Bet v 2.

Recently, the use of recombinant Bet v 1 and Bet v 2 for skin testing in a group of 51 patients sensitized to birch brought to light a positive response to Bet v 1 in 47 cases and to Bet v 2 in 10 (40). The subjects sensitized only to birch had a negative skin test to Bet v 2, which however gave a positive result in patients also sensitized to grass and *Compositae* pollens, probably because of crossreactivity between profilins from these sources. Among patients with reactions to vegetables, sensitization to Bet v 1 was specific for allergy to birch and *Rosaceae* fruits (apple, hazelnut, and so on), while sensitization to Bet v 2, detected in plurisensitized subjects, was related to allergy to *Umbelliferae* such as celery and carrot, though to a lesser degree.

Very recently, a third group of crossreacting proteins with mol wt 46–60 kDa, in the range of the major allergen of mugwort Art v 1 (41), was identified as responsible for crossreactions between celery and pollens from mugwort and birch (42). Further crossreactions include: birch and grass pollens with *Prunoideae* fruits (27) and with kiwi fruit (43), both regarding allergens besides the major ones, grass pollen with tomato and peanut (44), and ragweed pollen with banana and the gourd family (45). However, the crossreacting allergens have not yet been identified.

Allergy to Latex and Fruits

Allergy to latex mainly arises in persons frequently exposed to this substance extracted from the tree *Hevea brasiliensis*, because of either repeated surgical procedures (in children with spina bifida the prevalence of latex allergy is more than 50%) or professional exposure. Natural latex extract contains a large series of allergenic components, with molecular weights ranging from 17 to 128 kDa (46). Among these, a protein of about 20 kDa, identified as prohevein, seems to be the major allergen of latex and was, in fact, referred to as Hev b 1 (47), while other important allergens should be proteins of 30 kDa (hevamin) and 36 kDa. An immunoblotting study recently identified five major groups of allergens with respective molecular weights of 14, 25, 29, 37–45, and 50 kDa, and sera from patients with spina bifida specifically reacted with the 25-kDa allergen (48).

In recent years, associations between latex allergy and reactions to fruits such as banana, avocado, pear, chestnut, kiwi, and papaya have been reported (49–51). These concern about half of patients with latex allergy (49), and the immunochemical basis seems to be sensitization to the 30-kDa allergen, which was detected in latex, avocado, and banana by immunoblotting techniques (50). Two different patterns of blotting were reported: one found in patients allergic only to latex, showing an

IgE response to various allergens and especially to the major allergen Hev b 1; and the other found in those who are allergic to latex and fruits, who constantly presented IgE-binding with the 30-kDa allergen. A recent study using sera from patients allergic to latex and banana detected two crossreactive allergens of 33 and 37 kDa (51). These are likely to correspond to the above-mentioned 30- and 36-kDa allergens, slightly different in vitro conditions accounting for the small difference in molecular weight. Further crossreactivity among latex, tomato, and potato was ascribed to a 46-kDa allergen sharing epitopes with a homologous protein identified in raw, but not in cooked, potato (52).

The Bird-Egg Syndrome

The association of allergic reaction to egg and respiratory symptoms from inhalation of bird-derived antigens was reported in the late 1980s (53,54). A study investigating the characteristics of 31 subjects with allergy only to egg or to egg and avian proteins found that the bird-egg syndrome mainly affected adults (55). This suggests that, as in the association of OAS and pollinosis, sensitization to the causative allergen may occur through the inhalant route, thus predisposing the patient to subsequent reactions when eating egg. In that study, in vitro experiments showed a complete reciprocal inhibition between egg yolk and bird feathers. The main allergen was a 70-kDa protein, identified as α -livetin, corresponding to bird seroalbumin.

Respiratory Symptoms from Mites and Food Allergy from Crustacea and Mollusca

As reported above, extensive in vitro crossreactivity that is caused by CCD arises between mollusca, crustacea, and other arthropods, such as insects, although it is clinically insignificant (10). A more striking crossreaction regards tropomyosin, the major allergen of shrimp Pen a 1 (6), which has also been identified by means of MAbs in insects, snails, and mites (56). This might account for the reports of adverse reactions on eating seafood in subjects allergic to mites (57).

We verified the clinical significance of this crossreaction by performing DBPCFC with shrimp in patients with positive IgE tests for *Dermatophagoides pteronyssinus* (58). About half of the patients had a positive challenge to shrimp and a convincing history of mite asthma; and, on immunoblotting, their sera reacted to a 37-kDa allergen, probably tropomyosin.

D. pteronyssinus extract completely inhibited the shrimp blotting, demonstrating the importance of this crossreaction. However, it has yet to be ascertained whether clinical syndrome sensitization also occurs via the respiratory route. In fact, some patients with

crossreactive IgE to tropomyosin from shrimp and mite appeared primarily sensitized by the former (56). In other studies, allergic reactions to shrimp developed after sensitization to tropomyosin induced by specific immunotherapy (59), whereas allergy, presenting as asthma to snails in mite-allergic patients, seemed to involve crossreactive allergens other than tropomyosin (60).

Concluding Remarks

The observation of in vitro crossreactivity between allergens from different food items as well as between foods and other allergen sources does not necessarily indicate a clinically significant association. This can be confirmed only by complete clinical characterization of patients with apparent positivity to different allergen extracts. In recent years, important advances have been made in the understanding of some crossreactions in food allergy, in which hypersensitivity to food allergens is triggered by crossreactivity with homologous allergens, sensitizing the subject by the respiratory route. This provides a theoretical model that might help explain most cases of sensitization to foods in adults.

References

1. Mowat, A. M. (1987), *Immunol. Today* **8**, 93–98.
2. Daul, C. B., Morgan, J. E., Hughes, J., and Lehrer, S. B. (1988), *J. Allergy Clin. Immunol.* **81**, 1180–1186.
3. Musmand, J. J., Daul, C. B., and Lehrer, S. B. (1993), *Clin. Exp. Allergy* **23**, 722–732.
4. Halmeupuro, L., Salvaggio, J. E., and Lehrer, S. B. (1987), *Int. Arch. Allergy Appl. Immunol.* **84**, 165–172.
5. Lehrer, S. B., McCants, M. L., and Salvaggio, J. E. (1985), *Int. Arch. Allergy Appl. Immunol.* **77**, 192–194.
6. Shanti, K. N., Martin, B. M., Nagpal, S., Metcalfe, D. D., and Subba Rao, P. V. (1993), *J. Immunol.* **151**, 5354–5563.
7. Daul, C. B., Slattery, M., Morgan, J. E., and Lehrer, S. B. (1992), *J. Allergy Clin. Immunol.* **89**, 194–199.
8. Lehrer, S. B. and McCants, M. L. (1987), *J. Allergy Clin. Immunol.* **80**, 133–139.
9. Goetz, D. W. and Whisman, B. A. (1990), *J. Allergy Clin. Immunol.* **85**, 276–283.
10. Koshte, V. L., Kagen, S. L., and Aalberse, R. C. (1989), *J. Allergy Clin. Immunol.* **84**, 174–183.
11. Aas, K. and Jebsen, J. W. (1967), *Int. Arch. Allergy Appl. Immunol.* 1–20.
12. de Martino, M., Novembre, E., Galli, L., et al. (1990), *J. Allergy Clin. Immunol.* **86**, 909–914.
13. Bernhisel-Broadbent, J., Scanlon, S., Sampson, H. A. (1992), *J. Allergy Clin. Immunol.* **89**, 730–737.
14. Yunginger, J. W., Sweeney, K. G., Sturner, W. Q., et al. (1988), *JAMA* **260**, 1450–1452.
15. Taylor, S. L., Busse, W. W., Sachs, M. I., Parker, J. L., and Yunginger, J. W. (1981), *J. Allergy Clin. Immunol.* **68**, 372–375.
16. Moneret-Vautrin, D. A. (1991), *Lancet* **338**, 1149–1151.
17. Barnett, D., Bonham, B., and Howden, M. E. H. (1987), *J. Allergy Clin. Immunol.* **79**, 433–438.

18. Bernhisel-Broadbent, J. and Sampson, H. A. (1989), *J. Allergy Clin. Immunol.* **83**, 435–445.
19. Bernhisel-Broadbent, J. and Sampson, H. A. (1989), *J. Allergy Clin. Immunol.* **84**, 701–709.
20. Burks, A. W., Williams, L. W., Helm, R. M., Connaughton, C., Cockrell, G., and O'Brien, T. (1991), *J. Allergy Clin. Immunol.* **88**, 172–179.
21. Burks, A. W., Williams, L. W., Connaughton, C., Cockrell, G., O'Brien, T., and Helm, R. M. (1992), *J. Allergy Clin. Immunol.* **90**, 962–969.
22. Burks, A. W., Brooks, J. A., and Sampson, H. A. (1988), *J. Allergy Clin. Immunol.* **81**, 1135–1142.
23. Burks, A. W., Cockrell, G., Connaughton, C., et al. (1994), *Int. Arch. Allergy Immunol.* **105**, 143–149.
24. Ewan, P. W. (1996), *BMJ* **312**, 7038–7041.
25. Pravettoni, V., Incorvaia, C., Vigano, G., Zara, C., Guidoboni, A., and Pastorello, E. A. (1996), *L'Internista* **4**, 39–42.
26. Ortolani, C., Pastorello, E. A., Farioli, L., et al. (1993), *Ann. Allergy* **71**, 470–476.
27. Pastorello, E. A., Ortolani, C., Farioli, L., et al. (1994), *J. Allergy Clin. Immunol.* **94**, 699–707.
28. Bjorksten, F., Backman, A., and Jarvinen, K. A. J. (1977), *Clin. Allergy* **7**, 473–483.
29. Pfeil, T., Schwabl, U., Ulmer, W. T., and König, W. (1990), *Int. Arch. Allergy Appl. Immunol.* **91**, 224–231.
30. Varjonen, E., Savolainen, J., Mattila, L., and Kalimos, K. (1994), *Clin. Exp. Allergy* **22**, 481–489.
31. Bircher, A. J., van Melle, G., Haller, E., Curty, B., and Frei, P. C. (1994), *Clin. Exp. Allergy* **24**, 367–373.
32. Pastorello, E. A., Spano, M., Pravettoni, V., Farioli, L., Mauro, M., and Incorvaia, C. Monduzzi, (1995), *Proc. XVI Congress of the European Academy of Allergology and Clinical Immunology*. Bologna, 883–888.
33. Incorvaia, C., Pravettoni, V., Viganò, G., Zara, C., Guidoboni, A., and Pastorello, E. A. (1996), *Allergy* **51**, 51.
34. Ebner, C., Birkner, T., Valenta, R., et al. (1991), *J. Allergy Clin. Immunol.* **88**, 588–594.
35. Vallier, P., Dechamp, C., Valenta, R., Vial, O., and Deviller, P. (1992), *Clin. Exp. Allergy* **22**, 744–752.
36. Hirschwehr, R., Valenta, R., Ebner, C., Rumpold, H., Scheiner, O., and Kraft, D. (1992), *J. Allergy Clin. Immunol.* **90**, 927–936.
37. Breiteneder, H., Hoffmann-Sommergruber, K., O'Riordain, G., et al. (1995), *Eur. J. Biochem.* **233**, 484–489.
38. Valenta, R., Duchene, M., Pettemburger, K., et al. (1991), *Science* **253**, 557–560.
39. Ebner, C., Hirschwehr, R., Bauer, L., et al. (1995), *J. Allergy Clin. Immunol.* **95**, 962–969.
40. Pauli, G., Oster, J. P., Deviller, P., et al. (1996), *J. Allergy Clin. Immunol.* **97**, 1100–1107.
41. De La Hoz, F., Polo, F., Del Prado, J. M., et al. (1990), *Mol. Immunol.* **27**, 651–657.
42. Bauer, L., Ebner, C., Hirschwehr, R., et al. (1996), *Clin. Exp. Allergy* **26**, 1161–1166.
43. Pastorello, E. A., Pravettoni, V., Spano, M., et al. (1996), *J. Allergy Clin. Immunol.* **98**, 601–610.
44. de Martino, M., Novembre, E., Cozza, G., et al. (1988), *Allergy* **43**, 206–213.
45. Anderson, B. L., Dreyfuss, E., Logan, S., Shonstane, E. D., and Glase, S. (1970), *J. Allergy* **45**, 310–319.
46. Levy, D. A., Charpin, D., Pecquet, C., Leynadier, F., and Vervloet, D. (1992), *Allergy* **47**, 579–587.
47. Alenius, H., Kalkkinen, N., Lukka, M., et al. (1995), *Clin. Exp. Allergy* **25**, 659–665.
48. Muguerza, J., Capo, C., Porri, F., et al. (1996), *Clin. Exp. Allergy* **26**, 1177.

49. Blanco, C., Carrillo, T., Castillo, R., Quiralte, J., and Cuevas, M. (1994), *Ann. Allergy* **73**, 309–314.
50. Lavaud, F., Prevost, A., and Cossart, C. (1995), *J. Allergy Clin. Immunol.* **95**, 557–562.
51. Delbourg, M. F., Guilloux, L., Moneret-Vautrin, D. A., and Ville, G. (1996), *Ann. Allergy. Asthma. Immunol.* **76**, 321–326.
52. Beezold, D. H., Sussman, G. L., Liss, G. M., and Chang, N. S. (1996), *Clin. Exp. Allergy* **26**, 1996.
53. Mandallaz, M., de Weck, A. L., and Dahinden, C. (1988), *Int. Arch. Allergy Appl. Immunol.* **87**, 143–148.
54. de Blay, F., Hoyet, C., Bessot, J. C., Thierry, R., and Pauli, G. (1990), *Rev. Fr. Allergol.* **30**, 97–102.
55. Szepefalusi, Z., Ebner, C., Pandjaitian, R., et al. (1994), *J. Allergy Clin. Immunol.* **93**, 932–942.
56. Witteman, A. M., Akkerdaas, J. H., van der Zee, J. S., and Aalberse, R. C. (1994), *Int. Arch. Allergy Immunol.* **105**, 56–61.
57. Baldo, B. A. and Panzani, R. C. (1988), *Int. Arch. Allergy Appl. Immunol.* **85**, 278–287.
58. Pastorello, E. A., Ispano, M., Pravettoni, V., et al. (1996), in *Highlights in Food Allergy. Monogr Allergy*, vol. 32, Wütrich, B. and Ortolani, C., eds., Karger, Basel, 57–62.
59. van Ree, R., Antonicelli, L., Akkerdaas, J. H., et al. (1996), *Allergy* **51**, 108–113.
60. van Ree, R., Antonicelli, L., Akkerdaas, J. H., et al. (1996), *Allergy* **51**, 387–393.
61. Eriksson, N. E. (1984), *Allergol. Immunopathol.* **12**, 28.
62. Ortolani, C., Ispano, M., Pastorello, E. A., et al. (1988), *Ann. Allergy* **61**, 47–52.
63. Andersen, K. E. and Löwenstein, H. (1978), *Contact Dermatitis.* **4**, 73–79.
64. Lahti, A., Bjorksen, F., and Hannauksela, M. (1980), *Allergy* **35**, 297–300.
65. Halmepuro, L., Wountela, K., Kalimo, K. K., and Bjorksen, F. (1984), *Int. Arch. Allergy Appl. Immunol.* **74**, 235–240.
66. Pauli, G., Bessot, J. C., Dieretmann-Molard, A., et al. (1985), *Clin. Allergy* **15**, 273–279.
67. Calkhoven, P. G., Aalbers, M., Koshte, V. L., et al. (1987), *Allergy* **42**, 382–390.
68. Enberg, R. N., Leickly, F. E., McCullough, S., et al. (1987), *J. Allergy Clin. Immunol.* **79**, 867–875.
69. Vallier, P., Descamps, C., Vial, O., and Deviller, P. (1988), *Clin. Allergy* **18**, 491–500.
70. Wüthrich, B., Staeger, J., and Johansson, S. G. O. (1990), *Allergy* **45**, 566–571.
71. Gall, H., Kalveram, K. J., Fork, G., and Sterry, W. (1994), *J. Allergy Clin. Immunol.* **94**, 70–76.