

Position paper

*Adverse reactions to food

Bruijnzeel-Koomen C, Ortolani C, Aas K, Bindslev-Jensen C, Björkstén B, Moneret-Vautrin D, Wüthrich B. Adverse reactions to food. Allergy 1995; 50: 623-635. © Munksgaard 1995.

C. Bruijnzeel-Koomen¹, C. Ortolani²,
K. Aas³, C. Bindslev-Jensen⁴,
B. Björkstén⁵, D. Moneret-Vautrin⁶,
B. Wüthrich⁷

¹ The Netherlands, ² Italy, ³ Norway,
⁴ Denmark, ⁵ Sweden, ⁶ France, ⁷ Switzerland

Dr C. Ortolani
Department of Allergology
Ospedale Niguarda
Piazza Ospedale
Maggiore 3
20162 Milan
Italy

Accepted for publication 10 January 1995

CONTENTS

Preface

1. Terminology of adverse reactions to food
 - 1.1. Introduction
 - 1.2. Classification
 - 1.3. Characterization of food allergens
 - 1.4. References
2. Symptoms of adverse reactions to food
 - 2.1. Introduction
 - 2.2. Systemic anaphylaxis
 - 2.3. Reactions of the gastrointestinal tract
 - 2.4. Skin reactions
 - 2.5. Reactions of the respiratory system
 - 2.6. Allergic reactions following skin contact with food
 - 2.7. Miscellaneous symptoms
 - 2.8. References
3. Diagnostic procedures
 - 3.1. Introduction
 - 3.2. Case history and clinical examination
 - 3.3. Skin tests
 - 3.4. *In vitro* assays for determination of food-specific IgE antibodies
 - 3.5. Other tests
 - 3.6. Elimination-reintroduction diets

- 3.7. Oral challenge procedures
- 3.8. Conclusions
- 3.9. Recommendations
- 3.10. References
4. Treatment and prevention
 - 4.1. Treatment
 - 4.1.1. Dietary management of established food allergy
 - 4.1.2. Training and psychological support
 - 4.1.3. Rescue medication
 - 4.1.4. Special considerations in infants and young children
 - 4.1.5. Food intolerance
 - 4.2. Prevention of food allergy
 - 4.3. Conclusions
 - 4.4. References
5. Conclusions
6. Future directions

Preface

Adverse reactions to food are frequently suspected and are therefore routine work in daily practice. However, in spite of this, our knowledge of the structure of food allergens and the involved pathomechanisms is poor. This is reflected by a lack of standardized diagnostic procedures and specific therapy, and controversial studies in the literature. The European Academy of Allergology and Clinical Immu-

* This paper was initiated during the Arbatax-Allergy Meeting, June 1990, in Italy (C. Bruijnzeel-Koomen, C. Ortolani, W. Canonica, P. Cortina, O. Frick, G. Loggi, R. Paganelli, G. Patriarca, D. Schiavino, L. Sensi, G. Stefanini).

nology (EAACI) subcommittee (see Appendix) on adverse reactions to food decided to write a position paper on adverse reactions to food with the aim of reaching consensus on terminology, symptoms which have been proved to be due to an adverse reaction to food, diagnostic procedures with special emphasis on the double-blind, placebo-controlled oral provocation (DBPCOP), and therapeutic measures. Since the field of adverse reactions to food is too large to be covered by one position paper, the EAACI subcommittee decided to start with a first position paper dealing with adverse reactions to food which are induced by immunologic mechanisms. A second position paper will deal with controversial aspects of adverse reactions to food with special emphasis on pharmacologically mediated symptoms. The EAACI subcommittee has planned to finish this within the next year.

A hallmark of the terminology used in the first position paper is that it is based on mechanisms rather than clinical symptoms. The EAACI subcommittee on adverse reactions to food is aware of the fact that this new classification differs from the one used by the National Institutes of Health (NIH) and the American Academy of Allergy and Clinical Immunology (AAACI). Therefore, the subcommittee asked colleagues from the AAACI and NIH for comments, which have been included in the position paper.

The outline of the position paper on adverse reactions to food has been discussed by the EAACI subcommittee on many occasions and was presented to the EAACI members during the EAACI meeting in Stockholm in 1994.

1. Terminology of adverse reactions to food

- 1.1. Introduction
- 1.2. Classification
- 1.3. Characterization of food allergens
- 1.4. References

1.1. Introduction

Over the years, many hypotheses have been advanced in the controversial field of adverse reactions to food. However, only a few of them have been tested with the appropriate methodology. This position paper includes only data that are supported by scientific studies, and that have been almost generally accepted.

In 1984 the AAACI committee on adverse reactions to food and the National Institute of Allergy and Infectious Diseases (NIAID) published the NIH manual *Adverse reactions to food* (3). The terminology suggested by the NIH manual improved the

classification of adverse reactions to food. However, we believe that a classification based only on mechanisms would be simpler and more clear.

1.2. Classification

Adverse reactions to food are divided into toxic reactions and nontoxic reactions. Toxic reactions will occur in any exposed individual provided that the dose is high enough.

Toxic compounds may be naturally occurring or induced during food processing or by contaminants. They are not discussed in this position paper. Allergists should, however, be aware of the possibility of a toxic food reaction, as the symptoms may be indistinguishable from those caused by allergy.

The occurrence of nontoxic food reactions depends on individual susceptibility to a certain food. The nontoxic adverse reactions to food are either immune mediated or non-immune mediated. For immune-mediated reactions, the term "food allergy" is recommended, while non-immune-mediated reactions are referred to as "food intolerance" (4).

Food allergy can be further divided into IgE-mediated and non-IgE-mediated reactions. Food allergens are defined as the antigenic molecules giving rise to the immunologic response.

The role of type I, IgE-mediated reactions in food allergy is well established. Symptoms include anaphylaxis and symptoms from the skin and respiratory and gastrointestinal tracts, usually in combination (10). None of these symptoms are specific.

Immunoglobulins of isotypes other than IgE, immune complexes, and cell-mediated immune reactions have been incriminated in food allergic reactions. None of them have, however, been proven to be causative by double-blind, placebo-controlled food challenge (DBPCFC).

The precise role of food in immune mechanisms involved in disorders such as celiac disease, eosinophilic gastroenteritis, cutaneous vasculitis, and protein-induced gastroenteropathy is not known. The only conclusively proven immunologic mechanism in food allergy is IgE-mediated. Other immune mechanisms probably play a role, although this is not understood.

Food intolerance is divided into enzymatic, pharmacologic, and undefined food intolerance.

Secondary lactase deficiency affects most of the adult world population, whereas most of the other enzyme deficiencies are rare inborn errors of metabolism.

Pharmacologic food intolerance is present in individuals who are abnormally reactive to substances such as vasoactive amines normally present in some foods.

The role of histamine release by food and its importance in symptom provocation in man are not well defined.

Confirmed adverse reactions to food for which the offending mechanisms are unknown are included in food intolerance.

The field of additive intolerance has not been as well studied as food allergy. Intolerance to some food additives may be based on an IgE-mediated allergy or an enzymatic inhibition such as bisulfite and azoic dye intolerance. Other studies show a nonspecific mediator release *in vivo* induced by challenge with additives, as in intolerance to acetylsalicylic acid. The mechanisms involved in additive intolerance remain largely unknown (12).

Some patients are convinced that they are allergic to foods, although this cannot be objectively verified. These psychological reactions are reduced by the appropriate food-allergy and food-intolerance diagnostic procedures.

1.3. Characterization of food allergens

Allergens are the antigenic molecules which provoke the allergic reaction. Food allergens reacting with IgE antibodies are proteins. Each food may contain several distinct allergens together with nonallergen antigens and other material. Some food allergens have been identified, purified, and characterized. In a few of them, IgE-binding epitopes have also been identified (1).

The allergenic activity of some food allergens is easily destroyed by heating or other denaturing (e.g., apples), whereas others are resistant to denaturing as in cooking and digestion (e.g., egg and fish). Although rare, trace amounts of allergenic proteins may be found as contaminants in oils such as those made from pea, soybean, sesame seed, and cod liver (5).

Different proteins may share epitope structures, allowing antigenic and allergenic cross-reactivity. The demonstration of cross-reactivities by means of skin testing or specific IgE does not necessarily indicate clinical relevance. Frequently, however, patients sensitized to pollen also suffer from adverse reactions to fruits and vegetables which cross-react with the pollen in question (7). Most patients allergic to birch pollen react also to raw apples, hazelnut, peach, apricot, cherry, raw carrot, and numerous other fruits and vegetables (6).

Many mugwort-sensitive persons react to vegetables of the family Umbelliferae: celery root, fennel, carrot, parsley, and spices (8, 11). Ragweed-sensitive individuals may get symptoms when eating banana or melon (2). Patients allergic to latex proteins from *Hevea brasiliensis* (rubber tree) may have food allergy to avocado, kiwi, banana, and chestnut (9). Grass pollens and wheat flour share allergenic

epitopes but do not commonly provoke food allergy.

Most of these allergens are heat labile and are destroyed by cooking.

1.4. References

1. AAS K. Chemistry of food allergens. In: HAMBURGER RN, ed. Food intolerance in infancy. New York: Raven Press, 1989: 9-21.
2. ANDERSON BL, DREYFUSS EM, LOGAN J, JOHNSTONE DE, GLASER J. Melon and banana sensitivity coincident with ragweed pollinosis. *J Allergy* 1970; 45: 310-19.
3. ANDERSON SA, SOGU DD, eds. Adverse reaction to food. AAAI and NIAID. NIH publication no. 84-2442, 1984.
4. BROSTOFF J, CHALLACOMBE SJ, eds. Food allergy and intolerance. London: Baillière Tindall, 1986.
5. CHIU JT, HAYDIK IB. Sesame seed oil anaphylaxis. *J Allergy Clin Immunol* 1991; 88: 414-15.
6. ERIKSSON NE, FORMGREN H, SVENOUS E. Food hypersensitivity in patients with pollen allergy. *Allergy* 1982; 37: 437-43.
7. ORTOLANI C, PASTORELLO EA, FARIOLI L, et al. IgE mediated allergy from vegetable allergens. *Ann Allergy* 1993; 71: 470-6.
8. PAULI G, BESSOT JC, DIETEMANN MOLARD A, BRAUN PA, THIERRY R. Celery sensitivity: clinical and immunological correlations with pollen allergy. *Clin Allergy* 1985; 15: 273-9.
9. RODRIGUEZ M, VEGA F, GARCIA NT, PANIGO CEA. Hypersensitivity to latex, chestnut, and banana. *Ann Allergy* 1993; 70: 31-4.
10. SAMPSON HA. IgE mediated food intolerance. *Allergy Clin Immunol* 1988; 81: 495-504.
11. WÜTHRICH B, STAGER J, JOHANSSON SGO. Celery allergy associated with birch and mugwort pollinosis. *Allergy* 1990; 45: 566-71.
12. WÜTHRICH B. Adverse reactions to food additives. *Ann Allergy* 1993; 71: 379-84.

2. Symptoms of adverse reactions to food

- 2.1. Introduction
- 2.2. Systemic anaphylaxis
- 2.3. Reactions of the gastrointestinal tract
- 2.4. Skin reactions
- 2.5. Reactions of the respiratory system
- 2.6. Allergic reactions following skin contact with food
- 2.7. Miscellaneous symptoms
- 2.8. References

2.1. Introduction

The true prevalence of food allergy is unknown because properly performed epidemiologic studies have not been done. North American reports claim the overall prevalence of food allergy to be 10% of the general population (13% of children and 7% of adults). European reports suggest 0.3-7.5% of children and 2% of adults (12). The prevalence among atopic individuals is higher; 10% has been reported (11, 12).

2.2. Systemic anaphylaxis

Acute, often severe, and sometimes fatal episodes of systemic anaphylaxis usually involve the gastrointestinal and respiratory tracts and the skin (4, 21, 28). Foods inducing anaphylaxis include peanuts, nuts, seeds, egg, milk, seafood, spices, celery, and some fruits (8, 10, 23, 24, 27).

In exercise-induced food anaphylaxis, the intake of a food, e.g., mollusks, shrimp or celery, elicits severe anaphylactic reactions in combination with exercise (14, 22).

Other allergic reactions of the gastrointestinal tract include vomiting, nausea, diarrhea, and abdominal pain (cramps or colic) (3, 4, 13, 24).

2.3. Reactions of the gastrointestinal tract

Oral allergy syndrome (OAS). Oral and/or pharyngeal pruritus appearing within minutes after the intake of certain foods may be the first symptom of generalized anaphylactic reactions or the only manifestation of OAS. There is a frequent association with pollen allergy, particularly birch and mugwort pollen allergy (1, 18).

Gluten-sensitive enteropathy (celiac disease) (CD). Clinical manifestations of CD reflect the consequences of malabsorption. In children, it is often an acute disease with diarrhea and failure to thrive. The diagnostic procedure for CD is defined by the ESPGAN (European Society for Pediatric Gastroenterology and Nutrition) (25) and is based on the histology of the small intestine. Indicators include villous atrophy, crypt hyperplasia, and infiltration of lymphocytes. These characteristic features resolve after a gluten-free diet.

Dermatitis herpetiformis (DH). Some DH patients may have villous atrophy similar to that seen in celiac disease, even without gastrointestinal symptoms. Furthermore, anti-gladin antibodies of both the IgG and the IgA isotypes are commonly found in DH (6). The cutaneous manifestations may or may not respond to a gluten-free diet (19).

Eosinophilic gastroenteritis (EG). Clinical manifestations of EG include vomiting, abdominal pain, diarrhea, malabsorption, bowel obstruction, and ascites. The cause of EG is unknown. There may be a relation to food intake, particularly in children (13). Food-induced enterocolitis syndrome and food-induced colitis may be separate clinical entities in young infants. The symptoms respond to elimination of cow's milk or soy protein. The immunopathogenesis is believed to be non-IgE-mediated (18a, 21a).

Ulcerative colitis (UC). UC is an inflammatory bowel disease of unknown origin. No food adverse reactions have been shown to cause UC (2).

2.4. Skin reactions

Urticaria and angioedema. Although most often seen in combination with symptoms of other organ systems, generalized urticaria and/or angioedema may be the only symptoms of an acute systemic reaction to food. Sometimes only intense pruritus, localized or generalized erythema, and a feeling of warmth may be present. Most cases of chronic urticaria, present for longer than 6 weeks, are not caused by food allergy (5). However, some cases of chronic urticaria/angioedema may be due to a type I reaction to a hidden food or to different foods (15, 26).

Atopic dermatitis. Many patients with atopic dermatitis, especially with associated respiratory allergies, pollinosis, and asthma, show high levels of IgE antibodies as well as positive prick or intracutaneous tests to various food allergens. The role of food allergens in the pathogenesis of atopic dermatitis is still controversial (20). However, there is no doubt that, particularly in young children, food allergens can induce atopic dermatitis lesions or at least a flare-up of preexisting lesions.

Allergic vasculitis. Most case reports of allergic purpura have been verified only by single challenges with foods and food additives (26). Since most of these reports are anecdotal, more studies are needed to prove a relation between allergic vasculitis and food intake.

2.5. Reactions of the respiratory system

Perennial allergic rhinitis (pruritus of the nose, sneezing, nasal stuffiness, and acute nasal obstruction) is usually not caused by allergy to food and is rarely the only clinical manifestation of a food allergy (4). However, food allergy may result in life-threatening laryngeal edema (21).

Allergic asthma. Food allergy occasionally contributes to allergic asthma (17). Asthma may also occur after inhalation of certain food, e.g., flour, alpha amylase, green coffee, castor bean, soybean, spices, egg white, and crustaceans (16). This may cause occupational allergy among workers exposed to those items. Inhalation of the steam from cooking legumes, fish, and lobster may provoke respiratory symptoms in sensitized patients (16).

Food-induced pulmonary hemosiderosis has been described as a distinct entity associated with IgG antibodies to cow's milk in young children (8a, 15a).

However, the role of these antibodies and the identity of this syndrome are not generally accepted.

2.6. Allergic reactions following skin contact with food

Urticarial lesions can be provoked by contact with certain foods, such as fish, shrimp, and flour (8). Chronic contact with food may induce protein-contact dermatitis in food handlers (7, 9).

2.7. Miscellaneous symptoms

There is no convincing evidence of an IgE-mediated relationship between the intake of food and hyper-reactivity, depression, migraine, rheumatoid arthritis, otitis media, chronic fatigue syndrome, cystitis, and enuresis.

2.8. References

1. AMLOT PL, KEMENY DM, ZACHARY C, et al. Oral allergy syndrome (OAS): symptoms of IgE-mediated hypersensitivity to foods. *Clin Allergy* 1987; 17: 33.
2. BAENKLER HW, LUX G, GUNTHER R, et al. Biopsy histamine in ulcerative colitis and Crohn's disease. *Hepato-gastroenterology* 1987; 34: 289-90.
3. BENGSSON U, ROGNUM TP, BRANDTZAEG P, et al. IgE-positive duodenal mast cells in patients with food-related diarrhea. *Int Arch Allergy Appl Immunol* 1991; 95: 86-91.
4. BOCK SA, ATKINS EM. Pattern of food hypersensitivity during sixteen years of double-blind, placebo controlled food challenges. *J Pediatr* 1990; 117: 561-7.
5. CHAMPION RH, ROBERTS SOB, CARPENTER RG, ROGER JH. Urticaria and angio-oedema. A review of 554 patients. *Br J Dermatol* 1969; 81: 588-97.
6. Chorzelski TP, Beutner EJ, Sulej J, et al. IgA anti-endomysium antibody: a new immunological marker of dermatitis herpetiformis and coeliac disease. *Br J Dermatol* 1984; 111: 395.
7. HAFNER J, RIESS CE, WÜTHRICH B. Protein contact dermatitis from paprika and curry in a cook. *Contact Dermatitis* 1992; 26: 51-2.
8. HANNUKSELA M, LAHTI A. Immediate reactions to fruits and vegetables. *Contact Dermatitis* 1977; 3: 79-84.
- 8a. HEINER DC, SEARS JW. Chronic respiratory disease associated with multiple circulating precipitins to cow's milk. *Am J Dis Child* 1969; 100: 500-2.
9. HJORTH N, ROED-PETERSEN J. Occupational protein contact dermatitis in food handlers. *Contact Dermatitis* 1976; 2: 28-42.
10. KÄGI MK, WÜTHRICH B. Falafel burger anaphylaxis due to sesame seed allergy. *Ann Allergy* 1993; 71: 127-9.
11. KAJOSAARI M. Food allergy in Finnish children aged 1 to 6 years. *Acta Paediatr Scand* 1982; 71: 815-19.
12. KARDINAAL AFM. Epidemiology of food allergy and food intolerance. In: SOMOGYI JC, MÜLLER HR, ÖCKHUIZEN TH, eds. Food allergy and food intolerance. Nutritional aspects and developments. Basel: Karger, 1991: 105-15.
13. KATZ AJ, TWAROG FJ, ZEIGER RS, et al. Milk-sensitive and eosinophilic gastroenteropathy: similar clinical features with contrasting mechanisms and clinical course. *J Allergy Clin Immunol* 1984; 74: 72.
14. KIDD JM, COHEN SH, SOSMAN AJ, FIND JN. Food-dependent exercise-induced anaphylaxis. *J Allergy Clin Immunol* 1983; 71: 407-11.

15. KUSHIMOTO H, AOKI T. Masked type I wheat allergy. *Arch Dermatol* 1985; 121: 355-60.
- 15a. LEE SK, KNIKER WT, COOK CD. Cow's milk-induced pulmonary disease in children. *Adv Pediatr* 1978; 25: 39-57.
16. MARTIN JA, COMPAIRE JA, DE LA HOZ B, et al. Bronchial asthma induced by chickpea and lentil. *Allergy* 1992; 47: 185-7.
17. ONORATO J, MERLAND M, TERRAL C, et al. Placebo-controlled double-blind food challenge in asthma. *J Allergy Clin Immunol* 1986; 78: 1139-46.
18. ORTOLANI C, ISPANO M, PASTORELLO E, et al. Comparison of results of skin prick tests (with fresh foods and commercial food extracts) and RAST in 100 patients with oral allergy syndrome. *J Allergy Clin Immunol* 1989; 83: 683-90.
- 18a. PEARSON JR, KINGSTON D, SHINER M. Antibody production to milk protein in the jejunal mucosa of children with cow's milk protein intolerance. *Pediatr Res* 1983; 17: 406-12.
19. REUNALA T, SALO OP. Effects of long term gluten free diet in dermatitis herpetiformis. In: KUKITA A, SEIMI M, eds. Proceedings of the XVth International Congress of Dermatology. Tokyo: University of Tokyo Press, 1983: 411-13.
20. SAMPSON HA. The role of food allergy and mediator release in atopic dermatitis. *J Allergy Clin Immunol* 1988; 81: 635-45.
21. SAMPSON HA. Fatal and near-fatal anaphylactic reactions to food in children and adolescents. *N Engl J Med* 1992; 327: 380-4.
- 21a. SELBEKK BH. A comparison between *in vitro* jejunal mast cell degranulation and intragastric challenge in patients with suspected food intolerance. *Scand J Gastroenterol* 1985; 20: 299-303.
22. SHEFFER AL, AUSTEN KF. Exercise-induced anaphylaxis. *J Allergy Clin Immunol* 1984; 73: 699-703.
23. STÄGER J, WÜTHRICH B, JOHANSSON SGO. Spice allergy in celery-sensitive patients. *Allergy* 1991; 46: 475-8.
24. STÖGER P, WÜTHRICH B. Type I allergy to cow milk proteins in adults. A retrospective study of 34 adult milk- and cheese-allergic patients. *Int Arch Allergy Immunol* 1993; 102: 399-407.
25. WALKER-SMITH JA, GUANDALINI S, SCHMITZ J, SHMERLING DH, VISAKORPI JK. Revised criteria for diagnosis of coeliac disease. *Arch Dis Child* 1990; 65: 909-11.
26. WINKELMANN RK. Food sensitivity and urticaria or vasculitis. In: BROSTOFF J, CHALLACOMBE SJ, eds. Food allergy and intolerance. London: Baillière Tindall, 1986: 602-17.
27. WÜTHRICH B, STÄGER J, JOHANSSON SGO. Celery allergy associated with birch and mugwort pollinosis. *Allergy* 1990; 45: 566-71.
28. YUNGINGER JW, SWEENEY KS, STURNER WQ, et al. Fatal food-induced anaphylaxis. *J Am Med Assoc* 1988; 260: 1450-2.

3. Diagnostic procedures

- 3.1. Introduction
- 3.2. Case history and clinical examination
- 3.3. Skin tests
- 3.4. *In vitro* assays for determination of food-specific IgE antibodies
- 3.5. Other tests
- 3.6. Elimination-reintroduction diets
- 3.7. Oral challenge procedures
- 3.8. Conclusions
- 3.9. Recommendations
- 3.10. References

3.1. Introduction

Several diagnostic procedures are available for the diagnosis of adverse reactions to foods. The only accepted test for the confirmation of the diagnosis of adverse reactions to food is a properly performed DBPCFC (1, 2, 5-8, 10, 13, 15). However, there are several practical problems connected with the DBPCFC, and its interpretation is not always straightforward (9, 12).

The diagnosis of IgE-mediated food allergy is based on combinations of several diagnostic procedures (18). It is important to realize that allergenic foods behaved differently in the various assays (4). Experience with one food in a certain test is not necessarily valid for another item in the same or another test procedure. Therefore, each allergen has to be assayed individually (4).

3.2. Case history and clinical examination

Food allergy is usually associated with atopic manifestations from several tissues, and there is often a history of atopy in siblings and parents (7, 11). A careful recording of food intake and its relation to clinical symptoms may provide useful information. However, history is less reliable when symptoms are continuous. There are no pathognomonic manifestations of food allergy, although a history of a systemic reaction immediately after food intake is convincing.

3.3. Skin tests

For practical reasons, the skin prick test (SPT) remains the test of choice to demonstrate sensitization to defined food antigens in a patient. The allergenic activity of extracts now commercially available varies, and results obtained with extracts from different manufacturers or even with various batches from the same producer differ (6, 14, 16, 19).

Fresh food items may be used instead of extracts (14, 16). This can be done by punctating the food with a skin prick test needle and then the skin. This "prick-prick" method is usually more sensitive and reproducible than using extracts from most manufacturers.

In most allergy centers, SPT is the initial screening procedure for suspected food allergy. The test should be interpreted according to EAACI guidelines.

The scratch patch test offers no advantage over SPT and is technically more difficult to perform.

Intracutaneous tests (ICT) are sometimes used as they are more sensitive than SPT. However, they are not recommended because of their low specificity and the potential danger of systemic reactions in

highly sensitive individuals. If the method is used at all, it should be preceded by a negative SPT.

The sensitivity and specificity of SPT in comparison with DBPCFC are controversial. The allergen source is of major importance. The diagnostic accuracy is high for well-defined allergenic proteins such as those of fish, egg, and milk and poorer for less defined antigens.

3.4. In vitro assays for determination of food-specific IgE antibodies

The search for IgE antibodies in serum is an alternative to SPT (4, 16, 17, 20). The problem with quality of antigen material is similar to that for the commercial extracts used for SPT. It is acceptable for certain proteins such as egg, cow's milk, fish, and peanut, but unclear for most other foods. The advantage of the test is that many determinations can be done on a single blood sample. The disadvantages are mainly high cost and results that are not immediately available when the patient is still in the office; relevant allergens may be missing.

Histamine release from basophils has not been approved for routine use in patients with suspected food allergy. It is time-consuming and relatively complicated to perform, and fresh blood with viable cells must be used. Recently, a new simplified technique based on glass microfibers has been described which reduces many of the technical problems connected with histamine release (14). Great variability in sensitivity and specificity has been reported, as for SPT and IgE determinations *in vitro* (4). With the use of fresh foods as antigens, the correlation with DBPCFC is similar to that of SPT with the same antigen (14). The results should be cautiously interpreted, as proper provocations have been done in only small numbers of patients.

3.5. Other tests

Recently, immunoassays for determination of the eosinophil-derived proteins, eosinophil cationic protein (ECP) and eosinophil peroxidase (EPX), as well as the mast-cell-derived enzyme, tryptase, have been introduced. The clinical usefulness of these tests has not been documented; therefore, they should be regarded as research tools.

Some new methods to diagnose food allergy have been reported recently, including histamine release from duodenal mast cells, intragastric challenge, and lavage with measurement of histamine in the lavage fluid. All these tests should be regarded as experimental procedures.

The clinical relevance of serum antibodies of IgG, IgA, and IgM isotypes to food antigens and tests for cell-mediated immunity, including lymphocyte trans-

formation tests with foods as antigens, has not been documented by carefully controlled studies. This is also true of various other diagnostic procedures, including determination of circulating immune complexes, sublingual neutralization tests, and suggested changes of muscular strength after sublingual food challenge.

3.6. Elimination-reintroduction diets

Elimination diets can be used in patients with chronic symptoms when the food SPT and IgE assays to food are positive or when some foods are strongly suspected. Patients are first asked to keep a daily record of their symptoms for 2 weeks (the basic registration of symptoms). The elimination diet is given for another 2 weeks. If there is doubt with respect to the outcome of the diet period, if there are no clinically suspected foods, if skin and laboratory tests are negative, and if the patient has pronounced symptoms, then a trial with a standard oligoallergenic diet may be considered. The patient should keep a symptom score diary during the test period. If there is no clear improvement within 2 weeks, then it is unlikely that food allergy is the cause of the patient's complaints. If there is consistent improvement of symptoms, the diet period is followed by an open challenge. A negative open challenge excludes food allergy, whereas a positive challenge should be confirmed by DBPCFC, except in obvious cases.

The following procedures have been suggested.

Baseline registration of symptoms. During this initial phase, the nature and severity of symptoms are determined while patients eat their regular diet. Patients at risk of severe systemic reactions should be properly supervised.

Diet period. This period serves to obtain freedom from symptoms, or at least a significant reduction in

their severity. There are several elimination diets, all based on the exclusion of foods that most frequently cause hypersensitivity.

3.7. Oral challenge procedures

A positive DBPCFC is the only conclusive evidence of a food allergy, provided it is performed properly. There are several procedures for performing oral provocation (Table 1).

The DBPCFC should be performed in a hospital where emergency care is immediately available. If patients present only subjective symptoms which cannot be objectively verified (e.g., abdominal pain, itching, or headache), the number of provocations must be increased to obtain statistical significance. Negative results in DBPCFC should be followed by an open-meal provocation with normally processed food. Before initiation of the controlled program, other reasons for the patient's complaints should be excluded.

3.8. Conclusions

The diagnosis of food allergy is based on the clinical history, supported by the demonstration of IgE antibodies to the food, and confirmed by positive oral provocation. The diagnostic procedures are summarized in a flowchart in Fig. 1 (adapted from reference 3).

3.9. Recommendations

When tests for IgE antibodies in the skin or blood are negative in spite of a suspect history, oligoallergic diets can be considered for a limited time period, i.e., 2 weeks. This diet should result in unequivocal improvement in the patients; otherwise, the possible presence of food allergy should be reconsidered.

Table 1. Provocation models

Method	Characteristics	Advantages	Disadvantages
DBPCFC with capsules or tablets	Dehydrated food Can be titrated Commercially available	Known quantity Convenient for additives	Many capsules Reactions in mouth and throat not diagnosed Food quality unknown
DBPCFC with foods	Fresh food in relevant amount Can be titrated, and given via tube and masked vehicle	Quantity of allergen Reactions in mouth diagnosed Normal route of administration	Resource-demanding Not standardized
Open challenge with a food (OFC)	Fresh food in relevant amount Can be titrated	Easily performed Negative test makes DBPCFC superfluous	Risk of false positive results
Open provocation	Relevant amounts	Easily performed Negative test makes DBPCFC superfluous	Risk of false positive results

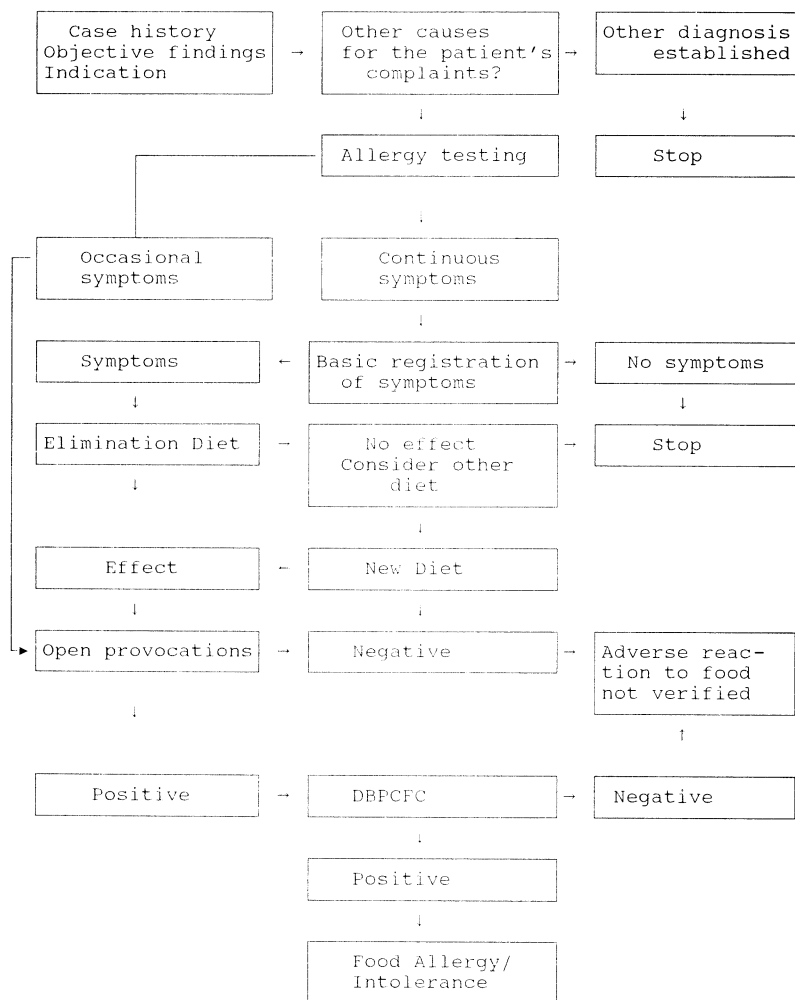


Fig. 1. Flowchart for diagnosis of nontoxic adverse reactions to food.

3.10. References

1. ATKINS FM. A critical evaluation of clinical trials in adverse reactions to foods in adults. *J Allergy Clin Immunol* 1986; 78: 174-82.
2. BERNSTEIN M, DAY JH, WELSH A. Double-blind food challenge in the diagnosis of food sensitivity in the adult. *J Allergy Clin Immunol* 1982; 70: 205-13.
3. BINDSLEV-JENSEN C. Rhinitis and food allergy. In: NACLERIO R, MYGIND N, eds. *Allergic rhinitis - clinical aspects*. Copenhagen: Munksgaard, 1992: 46-51.
4. BINDSLEV-JENSEN C, SKOV PS, MADSEN F, POULSEN LK.

- Food allergy and food intolerance – what is the difference? *Ann Allergy* 1994; 72: 317–20.
5. BOCK SA, SAMPSON HA, ATKINS FM, et al. Double-blind, placebo-controlled food challenge (DBPCFC) as an office procedure: a manual. *J Allergy Clin Immunol* 1988; 82: 986–97.
 6. BOCK SA, LEE WY, REMIGIO L, HOLST A, MAY CD. Appraisal of skin tests with food extracts for diagnosis of food hypersensitivity. *Clin Allergy* 1978; 8: 559–66.
 7. BOCK SA. A critical evaluation of clinical trials in adverse reactions to foods in children. *J Allergy Clin Immunol* 1986; 78: 165–74.
 8. DAUL CB, MORGAN JE, HUGHES J, LEHRER SB. Provocation-challenge studies in shrimp-sensitive individuals. *J Allergy Clin Immunol* 1988; 81: 1180–6.
 9. DAVID TJ. Hazards of challenge tests in atopic dermatitis. *Allergy* 1989; 44 (Suppl. 9): 101–1.
 10. HANSEN TK, BINDSLEV-JENSEN C. Codfish allergy in adults. Identification and diagnosis. *Allergy* 1992; 47: 610–17.
 11. HOST A, HALKEN S. A prospective study of cow milk allergy in Danish infants during the first 3 years of life. *Allergy* 1990; 45: 587–96.
 12. LASAGNA L. The placebo effect. *J Allergy Clin Immunol* 1986; 78: 161–5.
 13. METCALFE DD, SAMPSON HA. Workshop on experimental methodology for clinical studies of adverse reactions to foods and food additives. *J Allergy Clin Immunol* 1990; 86: 421–31.
 14. NORGGAARD A, SKOV PS, BINDSLEV-JENSEN C. Egg and milk allergy in adults. Comparison between fresh foods and commercial allergen extracts in skin prick test and histamine release from basophils. *Clin Exp Allergy* 1992; 22: 940–7.
 15. NOVEMBRE E, DE MARTINO M, VIERUCCI A. Foods and respiratory allergy. *J Allergy Clin Immunol* 1988; 81: 1059–65.
 16. Ortolani C, Ispano M, Pastorello EA, Ansaloni R, Magri GC. Comparison of results of skin prick tests (with fresh foods and commercial food extracts) and RAST in 100 patients with oral allergy syndrome. *J Allergy Clin Immunol* 1989; 83: 683–90.
 17. PASTORELLO EA, STOCCHI L, BIGI A, et al. Value and limits of diagnostic tests in food hypersensitivity. *Allergy* 1989; 44 (Suppl. 9): 151–8.
 18. PASTORELLO EA, PRAVETTONI V, BIGI A, et al. IgE mediated food allergy. *Ann Allergy* 1987; 59: 82–9.
 19. SAMPSON HA. Comparative study of commercial food antigen extracts for the diagnosis of food hypersensitivity. *J Allergy Clin Immunol* 1988; 82: 718–26.
 20. VIERUCCI A, NOVEMBRE E, DE MARTINO M, LUCCI A, DINI L. Reliability of tests for specific IgE to food in atopic dermatitis. *Allergy* 1989; 44 (Suppl. 9): 90–4.

4. Treatment and prevention

4.1. Treatment

- 4.1.1. Dietary management of established food allergy
- 4.1.2. Training and psychological support
- 4.1.3. Rescue medication
- 4.1.4. Special considerations in infants and young children
- 4.1.5. Food intolerance
- 4.2. Prevention of food allergy
- 4.3. Conclusions
- 4.4. References

4.1. Treatment

The treatment of food allergy intolerance is avoidance of the offending food items and additives. In addition, psychological and social support is often needed. The diagnosis should be reconsidered at intervals in children, as very young children outgrow many food allergies. For milk and egg, this should be done yearly. Pharmacologic therapy should be considered only in highly selected cases. Immunotherapy is not of documented value.

4.1.1. Dietary management of established food allergy.

The following points should be addressed in dietary management:

- correct identification of the offending foods and additives
- knowledge of potential hidden sources of the food items
- awareness of possible cross-reactivities between foods and inhalants
- elimination of possible cross-reactivities between foods and inhalants
- proper supervision of elimination diets with regard to nutritional requirements, particularly in growing children.

Elimination of offending foods should lead to remission of clinical manifestations. If there is no clear improvement within 10 days or total remission within 1 month, the diagnosis should be reconsidered.

Elimination of cow's milk from the diet may cause problems, as it is a basic food for infants and young children and a major source of protein also for older children in many countries.

4.1.2. Training and psychological support. Many foods and food additives are present in processed foods in a hidden form. The food industry should list on labels all ingredients, including any additives. The present European Union policy requires listing only compounds comprising > 25% of the content of the food (1). This is unacceptable. Patients and their family should therefore be carefully instructed on how to read the labels of industrially processed foods, and advised not to buy products that are not properly labeled. They should also learn which foods are antigenically cross-reactive. Elimination diets, particularly extensive ones, may impose a heavy burden on patients and their family members. A diet may severely restrict social activities and may cause isolation. Psychological support for patients and/or families should therefore be considered in all cases where extensive elimination diets are suggested.

4.1.3. Rescue medication. Food allergy may cause severe reactions and even be fatal. Patients with a

history of severe anaphylactic reaction to foods should perhaps be provided with self-administered doses of epinephrine and an antihistamine. School and day-care center staff should be aware of patients' allergies and know how to deal with a reaction.

Oral sodium cromoglycate has been tried in several studies. Unfortunately, most of these studies have not been properly controlled. The treatment is expensive and should be considered only in carefully selected patients in whom multiple food allergy has been confirmed by challenges and avoidance is difficult or impossible.

Ketotifen has also been tried in recent years in some European countries. Studies claiming efficacy have not been properly controlled and controlled studies have not conclusively shown efficacy.

Parenteral immunotherapy with a food extract is not recommended in clinical practice because experimental evidence and safety are lacking. It is important that appropriate controlled studies be performed in the future.

Oral hyposensitization, starting with very small amounts of a food or additive to which the patient is intolerant, has also been tried. The efficacy of the therapy has not been documented in double-blind studies.

4.1.4. Special considerations in infants and young children. In breast-fed infants, the elimination of allergenic foods may pose special problems, since proteins of allergenic foods eaten by the mother can be transferred into the breast milk. Therefore, a reduced intake of an offending food such as cow's milk or egg may be considered by the mother of a breast-fed infant with a confirmed allergy. However, the mother should not stop breast-feeding, as there are many nutritional, immunologic, and psychological advantages of this practice.

There are several milk-protein hydrolysates available as substitutes for cow's milk formulas on the market. In these products, the cow's milk proteins have been degraded to a varying degree, either by hydrolysis, enzymatic degradation, or ultrafiltration. These "hypoallergenic" infant formulas vary with regard to the remaining allergenicity (3).

The use of casein hydrolysate in infants with allergy to cow's milk proteins is well established in clinical experience. Recently, an extensively hydrolyzed whey-based formula has also become available. These hydrolysates are enzymatically highly degraded to molecular mass <1500 Da and have little allergenicity and antigenicity left. However, there are a few reports of reactions to these formulas in highly cow's milk-allergic patients (1, 9a, 10). As suggested by the European Society for Paediatric Allergy and Immunology (ESPACI), a skin prick

test with the material and an oral provocation under appropriate safety precautions are advisable before they are used for feeding (3). More recently, less extensively hydrolyzed infant formulas have been marketed. The main advantage of these products is better taste. This has been achieved by less extensive hydrolysis or by ultrafiltration. The molecular mass of the peptides has been reduced to about 20 and 10 kDa, respectively. These products are not to be considered hypoallergenic and should not be used for infants with allergy to cow's milk.

Soy-based formulas (9) are often considered as substitutes for regular cow's milk formulas in milk-allergic infants. They are less expensive than the hydrolysates. However, as many as 30–40% of cow's milk-allergic infants will develop allergy to soy if they are switched to this formula. To avoid the risk of sensitization to soy in infants, one may prefer a hypoallergenic hydrolysate if tolerated.

An optimal diet is particularly important in infants and children for normal growth. Any dietary changes should therefore be done under proper supervision, preferably in cooperation with a dietician. A prolonged elimination diet should be considered only in cases of confirmed food allergy. As most infants and young children outgrow their food allergy, the diagnosis should be reconsidered every year. If the patient tolerated an accidental exposure without problems, then the food may be safely eaten in the future. If there is no clear history of exposure, a skin prick test may yield more information. A decreasing wheal size and negative test for circulating IgE antibodies may indicate that tolerance is developing. Reintroduction of foods should always be preceded by a negative challenge or a convincing history of accidental exposure.

It should be borne in mind that many food-allergic infants develop later in life other atopic diseases, e.g., asthma and allergic rhinoconjunctivitis. Therefore, particularly in infants with a family history of allergic disease, it may be advisable to caution the parents that allergy to inhalant allergens may develop later. Certain preventive measures should be strongly encouraged, particularly avoidance of exposure to tobacco smoke.

In patients with celiac disease, the complete elimination of gluten from the diet should be lifelong, once the diagnosis has been conclusively established.

4.1.5. Food intolerance. Adverse reactions to lactose are common, as most of the world population is lactase deficient. The treatment is simply to limit the intake of fresh milk to the individually tolerated level. Cheese is well tolerated and usually also fermented milk products, e.g., yogurt. Lactase is commercially available and can be used by lactase-deficient individuals who are eager to drink milk.

In young children, both diarrhea and constipation may ensue from a diet rich in fiber and low in fat. While such a diet is recommended for adults, it may cause discomfort in children under 2 years of age and is a common cause of toddler's diarrhea.

4.2. Prevention of food allergy

For obvious reasons, primary prevention is possible only in infancy and early childhood. Early weaning to cow's milk-based formulas has been associated with an increased rate of allergic disease. Prolonged breast-feeding would thus protect against food allergy. This is, however, a controversial issue. The explanation of the conflicting results seems to lie in the selection of patients for the studies and in the fact that such studies cannot be truly randomized. Studies showing a protective effect of exclusive breast feeding have included infants with a genetic propensity to allergy, rather than an unselected group of infants (2). Moreover, in successful studies, breast-feeding was associated with avoidance of other foods, including egg, juices, and solid foods, for at least the first 6 months of life (7, 8). Breast feeding has many important advantages over formula feeding, including optimal nutrition, fewer infections, and psychological benefits. However, critical reviews indicate that even under the best circumstances the effect of breast-feeding on the development of food allergy is limited to risk individuals with genetic predisposition to allergic disease, and that it appears merely to delay, rather than prevent, the onset of food allergy.

In carefully performed studies, soy and partially hydrolyzed formulas based on cow's milk have not been shown to prevent food allergy. Such products are therefore not recommended for the prevention of food allergy.

Dietary manipulation in pregnant women during the last trimester of pregnancy has been tried as a possible means to reduce the rate of allergic disease in their offspring (4, 5). Neither the incidence of food allergy and other allergic diseases, nor the appearance of IgE antibodies in the children was affected by the diet. Thus, manipulation of the diet during pregnancy has not been associated with any change in the prevalence of food allergy in infancy.

In contrast to the lack of effect of dietary manipulation in pregnant women, an elimination diet may be worthwhile during the period of breast-feeding of infants with a strong family history of allergic disease (6, 11). As there are many practical problems with such a diet, it should be considered only in families with a strong history of allergic disease and in highly motivated mothers.

4.3. Conclusions

Food allergy is best treated with avoidance of the offending foods. To secure this, as well as adequate nutrition, proper training of patients and their families is necessary. Treatment of extensive food allergy is therefore a matter of teamwork and should include a physician with proper training in allergology, gastroenterology, and nutrition, and a dietician. The team should preferably also include someone competent in psychology.

In infants with documented food allergy, extensively hydrolyzed formulas are recommended as substitutes for regular infant formulas if tolerated. If the mother is still breast-feeding, this should be continued, if possible, until 1 year of age. If the offending food is egg, milk, or fish, the mother should be instructed to avoid these foods for the remaining period of lactation.

The value of pharmacologic treatment of food allergy is not clearly documented and should only be considered in special cases when dietary exclusion is not feasible. Immunotherapy is not of documented value.

Primary prevention of food allergy is only feasible in infants. Preventive measures include breast-feeding for as long as possible and exclusively so for at least 3 months. If this is not possible, then extensively hydrolyzed infant formulas may be considered. In addition, antigenic foods such as cow's milk and egg should be excluded for the first 6 months of life. These precautions may temporarily reduce the incidence of allergic manifestations to these foods. Partially hydrolyzed infant formulas have not been documented for allergy prevention. Manipulation of the infant diet is not of documented value to prevent either other allergies, or allergic manifestations in the skin or respiratory tract late in life.

Manifestations of food allergy in infants are usually a forerunner of other atopic diseases later in life. Exposure to tobacco smoke is a potent factor in the development of respiratory allergy and asthma. Parents should therefore be strongly advised not to smoke at home.

4.4. References

1. BOCK SA. Probable allergic reaction to casein hydrolysate. *J Allergy Clin Immunol* 1990; 84: 272.
2. BJÖRKSTÉN B, KJELLMAN N-I. Does breast feeding prevent food allergy? *Allergy Proc* 1991; 12: 233-9.
3. BUSINCO L, DREBORG S, EINARSSON R, et al. Hydrolyzed cow's milk formulae. Allergenicity and use in treatment and prevention. An ESPACI position paper. *Pediatr Allergy Immunol* 1993; 4: 101-11.
4. FÄLTCH-MAGNUSSON K, ÖMAN H, KJELLMAN N-I. Maternal abstinence from cow milk and egg in allergy risk pregnancies. Effect on antibody production in the mother and the newborn. *Allergy* 1987; 42 (1): 64-73.

5. FÄLTH-MAGNUSSON K, KJELLMAN N-I. Allergy prevention by maternal elimination diet during late pregnancy: a 5-year follow-up of a randomized study. *J Allergy Clin Immunol* 1992; 89(3): 709-13.
6. HATTEVIG G, KJELLMAN B, SIGURS N, BJÖRKSTÉN B, KJELLMAN N-IM. Effect of maternal avoidance of eggs, cow's milk and fish during lactation upon allergic manifestations in infants. *Clin Exp Allergy* 1989; 19(1): 27-32.
7. KAJOSAARI M. Food allergy in Finnish children aged 1-6 years. *Acta Paediatr Scand* 1982; 71: 815-19.
8. KAJOSAARI M, SAARINEN UM. Prophylaxis of atopic disease by six months' total solid food elimination. *Acta Paediatr Scand* 1983; 72: 411-14.
9. KJELLMAN N-IM, JOHANSSON SGO. Soy versus cow's milk in infants with a biparental history of atopic disease: development of atopic disease and immunoglobulins from birth to 4 years of age. *Clin Allergy* 1979; 9: 347-58.
- 9a. SAMPSON HA, JAMES JM, BERNHISEL-BROADBENT J. Safety of amino-acid derived infant formula in cow's milk allergic children. *Pediatrics* 1992; 463-5.
10. SAYLOR JD, BAHNA SL. Anaphylaxis to casein hydrolysate formula. *J Pediatr* 1991; 118: 7.
11. ZIGER R, HELLER S, MELLON M, HELSEY J, HAMBURGER R, SAMPSON H. Genetic and environmental factors affecting the development of atopy through age 4 in children of atopic parents: a prospective randomized study of food allergen avoidance. *Pediatr Allergy Immunol* 1992; 3: 110-27.

5. Conclusions

This position paper illustrates the present state of knowledge of adverse reactions to food. It proposes a simple classification which is based on mechanisms and can be applied to different food reactions.

While the spectrum of adverse reactions to food may be wide, they all correspond to the classic allergic symptoms; i.e., systemic anaphylaxis, urticaria-angioedema, exercise-induced anaphylaxis, atopic dermatitis, contact dermatitis, rhinitis, asthma, vomiting, diarrhea, and oral allergy syndrome. Some manifestations, i.e., celiac disease and dermatitis herpetiformis, indicate gluten intolerance. Eosinophilic gastroenteritis, ulcerative colitis, and allergic vasculitis are supposed to be associated with food intolerance even if unequivocal demonstration of this association is still lacking. So far, there is no convincing evidence that hyperreactivity, headache, rheumatoid arthritis, chronic fatigue syndrome, and otitis media are due to an adverse reaction to food. The diagnosis of adverse reactions to food is problematic. The overall accuracy of skin prick tests and of specific IgE measurement is poor. Therefore, the only accepted test for supporting the diagnosis of adverse reactions to food is a properly performed DBPCFC. However, there are several practical problems with this test. A flowchart for diagnosis of nontoxic adverse reactions to foods is presented in the position paper.

Avoidance of the offending foods is the only reliable treatment of adverse reactions to food. In infants with documented food allergy, extensively hydrolyzed formulas are recommended as substitutes

for regular infant formulas. The value of allergen-specific immunotherapy has not been documented.

Primary prevention of food allergy is feasible only in infants. Preventive measures include breastfeeding for at least 3 months or extensively hydrolyzed infant formulas. In addition, antigenic foods should be excluded for the first 6 months of life.

6. Future directions

Although it is well known that IgE-mediated allergies constitute the only well-defined type of nontoxic adverse reactions to food, and there is considerable evidence that IgE-mediated food allergy is the most common of these reactions, accurate measurement of the prevalence of adverse reactions to food remains our most challenging task. This is indicated by the lack of epidemiologic studies. The absence of such studies is mainly due to the difficulty of performing the DBPCFC on large populations (a test that is necessary in order to substantiate suspected food intolerance).

A major objective is to improve the reliability and overall accuracy of the diagnostic material for skin tests and specific IgE to food; for example, by utilizing all the major allergens present in foods, thus surpassing the DBPCFC. Furthermore, in addition to carrying certain risks, the DBPCFC is not feasible for all foods, and it confirms the symptoms but does not illuminate the mechanisms.

Therefore, the characterization, isolation, and synthesis of the major allergens of the main allergenic foods constitute a prerequisite for advance in the diagnosis of food allergy. This step could clarify the clinical significance of cross-reactions in food allergy, make epidemiologic studies possible, and facilitate the preparation of nonallergenic foods that maintain their characteristic nutritional properties.

In this way, we can be in a better position to improve the prevention and treatment of IgE-mediated food allergy. Furthermore, greater diagnostic accuracy in IgE-mediated food allergy could shed light on the occurrence of other immune and intolerance reactions to foods.

Appendix

Members of the EAACI subcommittee on adverse reactions to food:

R. Aalberse	The Netherlands
K. Aas	Norway
C. Bindslev-Jensen	Denmark
B. Björkstén	Sweden
J. Brostoff	UK
C. Bruijnzeel-Koomen	The Netherlands
D. Cagnetti	Italy
W. Canonica	Italy

G. Ciprandi	Italy	K. Nekam	Hungary
P. Cortina	Italy	C. Ortolani	Italy
P. Falagiani	Italy	M. Pacor Corrocher	Italy
A. Helbling	Switzerland	R. Paganelli	Italy
M. Ispano	Italy	C. Palmieri	Italy
F. de Maat-Bleeker	The Netherlands	L. Sensi	Italy
G. Marchi	Italy	B. Wüthrich	Switzerland
D. Moneret-Vautrin	France	G. Zanoni	Italy

This document is a scanned copy of a printed document. No warranty is given about the accuracy of the copy. Users should refer to the original published version of the material.