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Study of nutritional factors in food allergies and food intolerances

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Contractor

Prof. Claudio Ortolani

Head of Department for Prevention, Diagnosis and Treatment of Allergic Disease, Niguarda Hospital,
Milan, Italy.

Responsible for the study

Prof. Elide Anna Pastorello

Associate Professor of Allergy and Clinical Immunology, University of Milan-Policlinico Hospital,
Milan, Italy.

Collaborators

Dr Raffaella Ansaloni
Dr Cristoforo Incorvaia
Dr Marco Ispano
Dr Valerio Pravettoni
Dr Federica Rotondo
Dr Joseph Scibilia
Dr Giuseppe Vighi

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SUMMARY

The recent Position Paper of the European Academy and Clinical Immunology Subcommittee on Adverse Reaction to Food (ARF) divided the ARF into toxic and non-toxic.

The latter are subdivided in immunomediated (in clinical practice represented quite exclusively by the IgE-mediated reactions) and non-immunemediated (enzymatic, pharmacologic and undefined intolerances).

Toxic reaction to food affects all human beings exposed. The major sources of toxicity of foodstuffs are the toxic substances induced in food processing, contaminants and additives.

IgE-mediated food allergy is the most frequent, the best known and the easiest to be diagnosed of the ARF. However the diagnosis of IgE-mediated food allergy must be made only when the relationship between the ingestion of a particular food and the symptoms is well established.

An evident role in clinical food allergy of non-IgE-mediated food allergy (i.e. IgG responses to foods, immune complexes with food allergens, cell mediated immunity to food), at the moment has not yet been demonstrated, and this topic maintains only theoretical importance.

Enzymatic food intolerances, except for lactase deficiency, are rare conditions, mainly due to inborn errors of metabolism. The pharmacological food intolerance includes: (1) the effects of vasoactive amine contained in some fruits; (2) the effects of mediator released by non-immunologic mechanism and (3) the intolerances to food additives.

The symptoms of food allergy involve different organs. Oral allergy syndrome is frequent among patients with pollen allergy and it is provoked by sensitization to plant food allergens. This syndrome is frequently associated with birch or mugwort pollinosis. Rhinoconjunctivitis, asthma and otitis media with effusion are rarely due to food allergy. Acute orticaria/angioedema and atopic dermatitis frequently depend from food allergy.

Many foods have been reported to provoke fatal food-induced anaphylaxis: i.e. milk, egg, peanut, seafood, nut, legumes, spices and fruits. Hidden foods have been demonstrated to be frequently responsible for anaphylactic fatalities. Exercise-induced anaphylaxis may be related to a food allergy. In these patients the ingestion of the culprit food without exercise does not provoke symptoms.

Food allergy may provoke gastrointestinal reactions: gastrointestinal anaphylaxis is common in adults. In infancy, food intolerance may provoke some rare gastrointestinal syndromes, i.e. infantile colics, food-induced enterocolitis syndrome, food-induced colitis, food-induced malabsorption syndrome and food-induced hemosiderosis. Celiac disease and dermatitis herpetiformis are both gluten-related entero- and cutaneous-pathies in which a non-IgE mediated immune mechanism is probably involved. Allergic eosinophilic gastroenteropathy is a rare entity but only in some documented cases it is due to an IgE-mediated allergy. Lactose intolerance is a common disease due to acquired defect of intestinal lactase, more rarely the disease is dependent from an inborn lactase deficiency.

It is controversial whether clinical manifestations different from those listed above could be due to one food allergy. Medical knowledge and clinical studies provided by the literature do not justify the emphasis of some investigators and of the media in claiming the link between food allergy and unusual symptoms. Among atypical complaints migraine is the most suitable for a relationship with food intake. However the basic mechanism of the presumed food-adverse reaction is unknown and a true food allergy is unlikely.

Among the immunologically mediated reactions to foods, IgE-mediated food allergy is the most exhaustively investigated regarding the pathogenesis. An important role in development of food allergy is played by the break of oral tolerance, an immunologic mechanism mainly supported by T-suppressor lymphocytes leading to a systemic hyporesponsiveness but local IgA hyperresponsiveness to antigens ingested in early infancy. Thus, immaturity of the immune system might account for the higher prevalence of food allergy in children than in adults. Also the characteristics of some allergens, such as an enzymatic activity or the resistance to digestion, especially occurring with sequential allergens, may be important in determining food sensitization. In addition, recent studies showed that sensitization to cross-reacting allergens present in food and inhalant source may underlie the development of food allergy.

Compared with the vast number of aeroallergens as yet identified, only a few food allergens are known, mainly because of the difficulty to recruit sufficient patients with positive IgE test and DBPCFC and to perform the laboratory technique for detecting allergens. So far, food allergens have been identified in cow's milk (α-lactoalbumin, β-lactoglobulin, caseins), in hen egg (ovomucoid, ovalbumin, ovotransferrin in egg white, livetin in egg yolk), in fish (Gad c 1), in shrimp (Pen a 1, Pen a 2), in peanut (Ara h 1, Ara h 2), in soybean (Gly m 1), in cereals (a series of proteins with m.w. from 26 to 79 kd as yet not named), in apple (Mal d 1), in celery (Api g 1), in fruits belonging to prunoideae (an allergen of 13 kd proposed as Pru p 1).

Because of the importance of psychological factors in food allergy, great differences are observed between the 'self-perception', accounting for 15-20% of suspected allergy in the general population and the real prevalence of food allergy as established by DBPCFC. Recent studies reported that the prevalence of true food allergy in adults was 1.4-1.8% in the United Kingdom, and about 1% in the Netherlands. In children a prevalence as high as 8% was reported, with major importance for sensitization to cow's milk. As cow's milk allergy tends to outgrow with age, the findings on children and adults seem to be consistent.

The diagnosis of food allergy should be based on clinical history and results of *in vivo* and *in vitro* tests, but a number of factors make their value questionable. In fact, clinical history is biased by the high 'self-perception' of food allergy, and skin tests and *in vitro* test have the drawback of unsatisfactory sensitivity and specificity due to the lack of standardized food allergen extracts. Thus, the 'gold standard' of diagnosis is the double-blind placebo-controlled food challenge (DBPCFC), the only test assessing the patient's reactivity to a suspected food in conditions free from patient's and physician's subjective influences.

Epidemiological data on food allergy are few and incomplete, and there are no figures on the changing prevalence of allergic reactions for each individual food. Particularly, there are no studies on how food allergy has changed with respect to the changes in dietary habits. However an increased risk for food allergy should be expected for several reason: (1) An increasing use of

domestic items within the household (e.g. freezer, microwave oven, frying devices, etc.); these items inevitably lead to the increased consumption of prepackaged food products, particularly frozen products and baked goods; (2) changes in life styles and work schedules facilitate the consumption of meals outside the household (e.g. fast-food restaurants, snack bars, etc.); (3) the increased distribution and availability of widespread food goods has reduced the boundaries of regional cooking habits and introduced new food products; (4) the food industry's expanding market of products that are processed and handled on an industrial scale.

Methods that are not shown to be effective and safe by proper clinical trials should be considered 'unproven methods' or 'non-validated methods'. Non-validated methods are not recommended in clinical practice, because the literature does not provide convincing data on the reliability of these methods and, in some cases, well-conducted studies do not show any difference between the investigated method and the placebo. The most commonly employed non-validated methods are discussed in Chapter 12.

The only preventive measure able to interfere with development of food allergy is to postpone as much as possible the introduction into the child's diet of foods containing known allergens, such as cow's milk, egg, fish, and others. This is mainly done by prolonged breast-feeding; the preventive effect is improved by eliminating these foods from the mother's diet. Because of the difficulty to maintain such conditions it is not recommended to prolong breast-feeding over six months. As yet, there are not enough data to use hydrolyzed cow's milk formulas as a measure alternative to breast-feeding.

Food allergic patients need to change their eating habits, to a varying extent. Once diagnosed, the treatment of a food allergy is the avoidance of the sensitizing food in order to prevent further episodes of ARF. This measure is easy for foods not predominant in the diet, like exotic fruits. However, the interaction with the eating habit is stronger when patients have to eliminate from the diet predominant foods or foods which may be masked and hidden in food products and preparations. However food allergens, especially in an occupational setting, may induce allergic reactions even when inhaled or after skin contact. Foods most commonly involved in occupational food allergy are: cereal flour, egg, milk, seafoods and legumes. The most effective measure to prevent occupational diseases due to exposure to food allergens is primary prevention, that is prevention of exposure to food-related substances that can induce allergic reactions. A second step is secondary prevention, that is the detection of diseases at an early stage. The earlier the diagnosis is made, the more likely workers are to recover. Tertiary prevention consists in appropriate medical care of diseased workers. Due to that mentioned above, it is clear that any effort should be directed to primary and not to tertiary prevention.

There are two main problems that arise from food processing and preparation: (1) food processing may alter content and/or properties of food allergens, both reducing and increasing the allergenicity of the starting material; (2) most processed, packaged and canned foods contain additives and other 'hidden' ingredients of both natural and synthetic origin. Common food allergens such as milk, egg, soya, and wheat are constituents of a wide variety of prepared foods, and in most cases labelling is incomplete and often misleading. This can have devasting consequences for a food-sensitive person. In fact almost all patients who died from food anaphylaxis had a history of allergic reactions to the food allergen responsible for the death, but they were unaware that the allergen was present in the food they ate. Therefore it is imperative that all processed foods sold

in the European Community be clearly labelled with the list of the ingredients and of the starting materials.

Hypoallergenic formulas (HF) may be used to treat allergic symptoms induced by cow's milk in sensitized children or to prevent food allergies in infants at high risk for the development of allergic disease. The important role that HF may play in the treatment of cow's milk allergy has been defined. *In vitro* and *in vivo* studies show that extensive casein hydrolysates are the less allergenic formulas in cow's milk allergic children. An elemental formula (Neocat) seems to be a good alternative as well. However it should be underlined that these formulas are hypoallergenic and not non-allergenic, because some highly sensitive milk-allergic infant may react adversely to being fed such formulas.

The role of HF in the prevention of allergic diseases is still controversial. Although some studies indicate a protective role of some HF in preventing allergic diseases in high-risk babies, further studies are needed to elucidate this point. *In vitro* and animal studies should select new formulas suitable for milk substitutes in cow's milk allergic children. Preclinical screening of these hydrolysates should demonstrate the absence of intact proteins and more than 99% of the peptides with molecular weight < 1.5 Kd, and non-anaphylaxis in animals challenged with the formula under investigation.

Hydrolysates selected by preclinical studies should then be screened by DBPCFC and open consumption, showing to be tolerated in cow milk allergic infants, in which the diagnosis of allergy to milk has been documented by positive DBPCFC.

The optimal treatment of food allergy is to avoid the culprit food, but this may be very difficult as masked foods are present in a number of preparations, exposing the allergic subject to unaware consumption. A series of fatal reactions derived from eating apparently unsuspected foods has been reported. In recent years, specific immunotherapy was considered as a treatment of food allergy and a first double-blind placebo-controlled study performed in patients allergic to peanut with a defatted peanut extract demonstrated, by a marked reduction of symptoms scores to DBPCFC and decrease of skin sensitivity to peanut extract in actively treated patients, that this treatment may be effective.

A new idea of prevention in food allergy must take into account the production of hypo- or non-allergenic food. Current means used to induce hypoallergenicity are heating, enzymatic hydrolysis and selection of vegetable stocks which synthesises little or no major allergenic protein (e.g. wheat deficient in gliadins). This last goal could be obtained by the biogenetic engineering with the production of transgenic plants.

Public health's role will be to make more effort than in the past to spread correct information on food allergy to the medical profession and to the public so as to provide an authoritative bulwark to the spread of unorthodox practices which are the main source of controversies on this topic. Measures will have to be taken to prevent or deal with serious allergic reactions, instructing those in charge of restaurants, hotels and school canteens on what should be done in cases of severe anaphylactic reactions. Constructive relations must be established with the food industry to make sure the user receives accessible information on food products, and jointly to promote studies to set in motion the farthest-reaching positive approaches.

1. CLASSIFICATION AND TERMINOLOGY OF ADVERSE REACTIONS TO FOOD

SYNOPSIS

The recent Position Paper of the European Academy and Clinical Immunology Subcommittee on adverse reaction to food (ARF) divided the ARF into toxic and non toxic.

The latter are subdivided in immunomediated (in clinical practice represented quite exclusively by the IgE mediated reactions) and non-immune mediated (enzymatic, pharmacologic and undefined intolerances).

The document, entitled 'adverse reactions to food' prepared by the American Academy of Allergy and Immunology Committee on Adverse Reactions to Foods and the National Institute of Allergy and Infectious Diseases in 1984, suggested an up-to-date terminology in the field of adverse reactions to food, with the aim of establishing a definite common meaning of all terms generally used by the medical community for food allergy and intolerance[1,2].

Recently the European Academy of Allergy and Clinical Immunology (EAACI) Subcommittee on Adverse Reactions to Food presented a Position Paper with a new classification for adverse reactions to foods, based on pathomechanisms, that is the development of the American manual[3] (Figure 1.1).

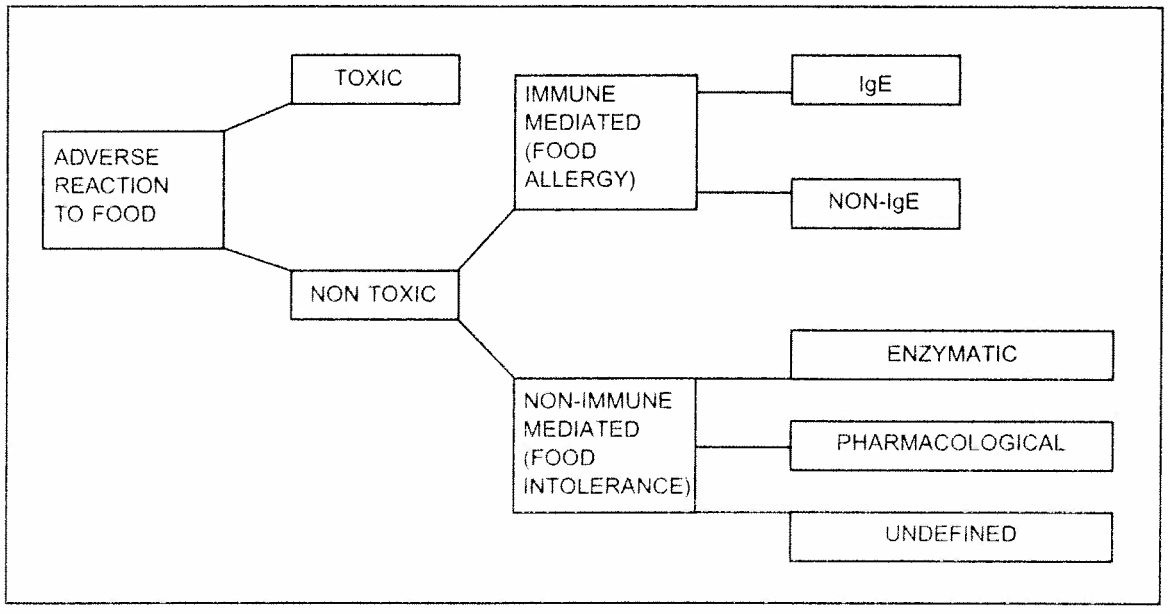

Figure 1.1.

According to this classification, adverse reactions to foods are divided into toxic and non toxic food reactions.

1.1. *Toxic food reactions*

Toxic food reactions are due to some substances that contaminate foods or that are naturally present in them, e.g. poison in non-edible mushrooms. Toxicity affects all human beings exposed to high doses of a certain toxin with the same mechanism and is not connected to an individual susceptibility. Allergists must be aware of toxic food reactions on account of their prevalence among adverse reactions to foods, in order to make a correct differential diagnosis, particularly when these reactions may mimic in some way an allergic symptomatology (e.g. scombroid syndrome).

1.2. *Non-toxic food reactions*

Non-toxic food reactions are due to an individual's susceptibility to certain foodstuffs and they are divided into immune-mediated and non-immune mediated reactions. Food allergy is the term commonly used for immune-mediated reactions, while food intolerance includes all non-immune mediated reactions. According to the immunological mechanism involved in the adverse reactions. Food allergy is defined IgE-mediated and non-IgE-mediated.

1.2.1. IgE-mediated reactions

IgE-mediated reactions can be diagnosed in atopic patients when IgE antibodies specific to food, that significantly correlate with the symptoms and/or the provocative tests, are detected by *in vivo* and/or *in vitro* tests.

1.2.2. Non-IgE-mediated food allergy

Non-IgE-mediated food allergy includes: (a) immune reactions caused by, other than IgE, specific to food allergen/s; (b) food immune-complexes; (c) cell-mediated immunity specific to food. Also in this case, a correct diagnosis needs the demonstration of the existence of an immune mediated mechanism (other than IgE) against the suspected food by *in vivo* and/or *in vitro* tests and the clinical evidence of a correlation between the symptoms evoked by the ingestion of the suspected food and the immune reaction. Up to now no clear demonstrations exist in respect of food allergy mediated by (a) and (b). Food intolerance, that is non-immune-mediated food adverse reactions, is a term used when the causative role of a food in provoking complaints is irrefutable, as clearly shown by the history and/or the provocative tests, but there is no evidence of an immunological mechanism. Two mechanisms are likely to explain these reactions; they are enzymatic defects and pharmacological actions of drugs or other pharmacological active substances added to the food or naturally present in it. In this case the reactions are therefore subdivided into enzymatic and pharmacological reactions; while the non-immune mediated food adverse reactions due to an unknown mechanism are classified in the group of undefined reactions.

Psychosomatic food-adverse reactions are not truly food dependent but are related to a primary mental disorder; therefore they are excluded in the EAACI classification. However, in clinical practice, most patients, who think they are allergic to some food, belong to this category[4,5].

Unfortunately the individual beliefs of patients suffering from vague, recurrent symptoms, wrongly ascribed to some particular food, often find confirmation in many articles published in non-specialized newspapers, that attribute a lot of symptoms to food allergy simply on the basis of non-validated hypothesis and anecdotal reports. Moreover many of these patients find their assumptions guaranteed by physicians who apply unorthodox non-validated diagnostic procedures. In order to avoid these mistakes, official international allergy associations have published diagnostic protocols to be followed to diagnose adverse reactions to food[3,6].

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2. GENERAL OUTLINE OF THE ROLE OF FOOD COVERING THE DIFFERENT HYPOTHESES

SYNOPSIS

Toxic reactions to food affects all human beings exposed. The major sources of toxicity of foodstuffs are the toxic substances induced in food processing, contaminants and additives.

IgE-mediated food allergy is the most frequent, the best known and the easiest to be diagnosed of the ARF. However the diagnosis of IgE-mediated food allergy must be made only when the relationship between the ingestion of a particular food and the symptoms is well established.

An evident role in clinical food allergy (i.e. IgG responses to foods, immune complexes with food allergens, cell mediated immunity to food) has not been demonstrated conclusively, and this topic is still the object of investigation.

Enzymatic food intolerances, except for lactase deficiency, are rare conditions, mainly due to inborn errors of metabolism. The pharmacological food intolerance includes: (1) the effects of vasoactive amine contained in some fruits; (2) the effects of mediator released by non immunologic mechanism and (3) the intolerances to food additives.

2.1. *Toxic reactions*

Many toxic substances may occur in foodstuffs. However, the amounts of these toxic substances are generally too small to cause symptoms, and habitual dietary variety keeps down the intake of any single toxin; this could explain the low prevalence of toxic reactions. Toxic substances in foodstuffs are:

1. Naturally occurring, both endogenous and exogenous;
2. Induced in food processing;
3. Contaminants;
4. Additives.[1]

Some examples of naturally occurring toxins in animal and vegetal foods are shown in Table 2.1.

Food toxicity mainly affects the CNS (headache, hallucination, incoherence and at times convulsions), liver and blood. Toxins induced in food processing, contaminants and additives are the major source of toxicity of foodstuffs today. Modern food technology enables us to produce, preserve and distribute large quantities of foods but there are frequent risks of breakdown in the food production and distribution chain, exposing many individuals to a high risk of food toxicity. The scombroid syndrome has become one of the major chemical food-borne illnesses reported in recent years.[2,3]

Table 2.1

Naturally occurring toxins in food (by C. May,[1] modified)

TOXIN	FOOD	SYMPTOMS
Cyanide	*Prunoideae* fruits	Neuropathy, mental confusion
Glucosinolites	Cabbage	Goiter
Atropine	*D. stramonium*	Hallucination
Pressor amines	Banana	Headache, hypertension
Solanine	Potato (raw), Jerusalem cherry, unripe tomato, etc.	Headache, CNS depression, gastrointestinal
Aflatoxins	Contaminants of corn, nuts and meats, hypoallergenic milk	Reye's syndrome, gastrointestinal, hepatic
Colza toxins	Colza oil	Gastrointestinal, CNS, muscular
Histidin & scombrotoxins	Spoiled fish	Scombroid poisoning
Paralytic shellfish toxins	Shellfish	CNS (paralysis), cardiovascular, gastrointestinal, respiratory

2.2. *Non-toxic reactions*

2.2.1. Immunological reactions (food allergy)

2.2.1.1. IgE-mediated food allergy

Type I, IgE-mediated, reactions in food allergy are the most frequent, the best known and the easiest to be diagnosed. The presence of IgE antibodies to specific offending food support the existence of an IgE mechanism, although clearly the diagnosis of IgE-mediated allergy can be made only when the relationship between the ingestion of a particular food and the onset of symptoms is well established. Double-blind placebo-controlled food challenge (DBPCFC) is the gold standard to demonstrate this relationship in order to exclude psychological reactions, and physician's and patient's prejudice. The result of DBPCFC is considered the only objective evidence in food allergy.

A variety of symptoms, likely to be secondary to an IgE-mediated response, are reported in controlled trials:[4,5,6] anaphylaxis (associated with exercise in some cases); cutaneous manifestations, like urticaria-angioedema, atopic dermatitis and contact dermatitis; upper and lower respiratory symptoms, like rhinitis (rare), larynx edema and asthma; gastrointestinal disorders, like oral allergy syndrome (OAS), infantile colics, nausea, vomiting, diarrhoea and abdominal pain and neurological symptoms. However, in connection with these last complaints, there is no definitive evidence of a relationship between food and hyperactivity, depression or migraine.

Various foods have been found to cause most frequently IgE-mediated food allergy in a series of DBPCFC[7] in adults and children. The foods found responsible of IgE-mediated food allergy listed in order of prevalence are: egg, milk, peanut, nuts, fish and soya in children, and peanuts, nuts, fish and shellfish in adults.

The prevalence of reactions to specific foods may depend on the eating habits or other peculiarities of a given population. For example soybean allergy is more common in Japan and fish allergy is more prevalent in Scandinavian countries. Patients suffering from allergy to certain pollens more often react with OAS to certain fresh fruits and vegetables.[8,9] These patients with pollen allergy present very intense mucosal sensitivity to foods, such that local symptoms are evident within 15 minutes of food contact. OAS is IgE-mediated. The symptoms are generally localized in the oral cavity and pharynx, though more severe local or systemic manifestations may also occur, often within few minutes after the oral contact with the responsible food, they are angioedema of the oral cavity and pharynx, urticaria, conjunctivitis, orbital angioedema, asthma, gastrointestinal symptoms and even anaphylactic shock. The main foods inducing this IgE-mediated syndrome are apple, peach, cherry, nuts, celery, carrot, tomato and fennel.[8,9]

2.2.1.2. Non-IgE-mediated food allergy

Non-IgE-mediated food allergy provides the evidence that the adverse reaction is the consequence of an immune response, other than IgE-mediated specific for a certain food; immunoglobulins, belonging to a non-IgE class, food immune-complexes or cell-mediated immunity are directly involved in the mechanism provoking the symptoms. IgG4 to specific food antigens are frequently present in patients with adverse reactions to foods,[10] but these antibodies are also often detected in normal subjects or in patients with inflammatory bowel disease, and their pathogenetic role has not been demonstrated. Their presence is likely to be the consequence of prolonged exposure to ubiquitous antigens resulting in an IgG4 restricted response.[11] Circulating IgG and IgE immune-complexes containing food antigens may be found in patients with food allergy suffering from asthma and eczema,[10,12] but their pathophysiological role has been rarely unequivocally demonstrated. Furthermore there is no definitive evidence that either IgG or IgE food-immune complexes cause human disease.[10,12]

There is ample indirect evidence that celiac disease (CD) may be provoked by a cell-mediated food allergy to gliadin, a prolamine contained in gluten.[13,14] T cells appear to be involved in the pathogenesis of this disease,[15,16] although, so far, there is no exhaustive proof that these immune phenomena are the direct original cause of the human disease. Recently an over-representation of one TCR variant of the lymphocytes present in the gut mucosa in CD was found, suggesting a role for these cells in the disease.[17] Some experiments showed that the immune-mediated intestinal damage is similar to that provoked in the intestinal mucosa by the graft-versus-host reaction.[18,19] As yet the role of the increased IgA and IgG antigliadin antibodies in the immunopathogenesis of this disease is still unclear.[17,18]

reported in this syndrome.[20] Serum IgA and IgG antibodies specific to milk are elevated in cow's milk induced malabsorption.[21] These abnormalities suggest both type-III (immunocomplexes) and type IV (cell-mediated) immunopathogenesis.

The same mechanisms may be present in food-induced enterocolitis syndrome in infants.[22] The jejunal biopsy shows flattened villi, edema and an increased number of lymphocytes, eosinophils and mast cells. The most prevalent responsible foods are cow's milk, soya protein or both together. These foods are also involved in food-induced colitis that differs from the above infantile syndromes in its mild clinical picture, generally characterized by the presence of gross or occult blood in the stools and a prominent eosinophilic infiltrate in the colonic mucosa.[23] Heiner's syndrome, that is a food-induced pulmonary hemosiderosis, is very rare; it affects infants with non-IgE-mediated hypersensitivity to cow's milk; egg and pork have also been reported as the cause of this syndrome in some infants.[24]

2.2.2. Non-immune mediated adverse reactions to foods

2.2.2.1. Enzymatic food intolerance

Enzymatic food intolerance is present in patients affected by enzymatic defect that causes a clinically evident adverse reaction to certain foods or food additives. The most common conditions are: (1) disaccharidase deficiencies caused by a defect of lactase or sucrase; (2) galactosemia caused by a defect of galactose 1 phosphate uridyl transferase or uridine diphosphate-4 epimerase; (3) phenylketonuria due to phenylalanine hydroxylase deficiency; (4) alcohol intolerance consequent upon aldehyde dehydrogenase deficit; (5) favism due to a defect of glucose-6-phospho dehydrogenase (G6PD).

Except for lactase deficiency, these are very rare conditions or inborn errors of metabolism. However it is widely held that many undefined food intolerances may result from enzymatic defects. For example, a deficiency of diamine-oxidase has been postulated in patients with intolerance to histamine-containing foods,[25] but clear evidence of a clinical syndrome due to this enzymatic defect has never been found.

2.2.2.2. Pharmacological food intolerance

The main substances that may be responsible for pharmacological food intolerance are: (1) vasoactive amines like histamine, octopamine, phenylephine and other biogenic amines: tyramine, phenylethylamine (in chocolate), tryptamine (in tomatoes), 5-hydroxytryptamine (in banana and avocado), spermidina (in pork and cereal germs); (2) releasing factors present in foodstuffs causing indirect pharmacological reactions such as protamine, basic peptides, diamines and polyamines and peptones (histamine releaser foodstuffs);[26] (3) food additives.

histamine may be lowered in some individuals, e.g. as stated above, subjects affected by diamine oxidase deficiency. Selected foods containing relatively large amounts of histamine or histidine or both can pose problems in these intolerant subjects.[27] In scombroid poisoning factors potentiating histamine toxicity are involved and therefore this syndrome must be classified as a toxic food reaction.[28]

The largest amounts of histamine and tyramine are found in fermented foods, such as cheese, alcoholic beverages, tinned fish, fish autolysates (Nuoc-Mam), sauerkraut, tuna, dry pork and sausage.[29,30,31,32] Grapes, potatoes, and cabbage are rich in tyramine.[33]

Some studies indicate that tyramine may play a role in migraine and chronic urticaria, especially in patients treated with a MAO inhibitor.[27] In addition certain foods are said to have histamine releasing properties.[27,34] Examples include egg white, shellfish, strawberries, tomatoes, chocolate, citrus fruit, fish and pork. However there is no evidence of this effect *in vivo*. Studies generally quoted to support histamine release by these foods are non-controlled, very old and performed in laboratory animals. More appropriate studies are therefore necessary to validate this hypothesis.

Pharmacological food intolerance might be evoked for the food intolerance present in patients with poor sulphoxidation ability. A poor sulphoxidation ability has frequently been documented in patients with ascertained food intolerance.[35] The metabolism of foodstuffs containing sulphur, including thiophenes, sulphides and isothyocyanates might be impaired.

2.2.2.3. Additive intolerance

IgE-mediated additive allergy has been documented in some cases,[36] but additive intolerance caused by non-toxic reactions does not seem to depend on immune-mediated mechanisms. Some observations suggest that additive intolerance may be consequent upon an enzymatic inhibition (e.g. sulphites and azo dyes).[37] Other studies show non-specific mediator release *in vivo* induced by challenge with some additives (ASA, sulphites, etc.).[38,39] So far, however, the mechanisms of additive intolerance remains largely unknown, therefore it seems more appropriate to include the adverse reactions to additives in the group of undefined food intolerance.

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15. CONCLUDING REMARKS

Over the past few years public opinion has been showing increasing interest in food allergies. The lay press — in fact the mass media in general — has fuelled this curiousity. Unfortunately, however, the information published is not always entirely correct.

It is for instance widely believed that food allergy or intolerance can cause a variety of diseases and disorders, ranging from the classical allergic manifestations such as eczema or urticaria to symptoms not normally attributed to allergies, such as arthritis and irritable bowel syndrome. The layman also tends to accept the suggestion that, in addition to true food allergies, diagnosable on the basis of skin reactions and assays for specific IgE for certain foods, much of the pathology arising in connection with foods is caused by food intolerance, although this 'disorder' lacks a precise pathogenic reference except for some rare diseases caused by enzymatic deficits.

In 1995 the Subcommittee of the European Academy of Allergy and Clinical Immunology published a position paper, 'Adverse reactions to food' which set up a new classification and terminology for these reactions. Essentially this position paper gives priority to IgE-mediated reactions; while admitting that theoretically there could be non-IgE-mediated immune reactions, it indicates clearly that there is no real proof that they have any role in causing symptoms.

The position paper is specific that food intolerance may be enzymatic or pharmacological; the first heading includes the rare reactions due to enzymatic deficits and the second heading those where the symptoms depend on the effects of certain amines that are either naturally present or develop in foods. The subheading of undefined food intolerance temporarily includes only celiac disease and adverse reactions to food additives.

The position paper stressed the importance in all clinical situations of applying the appropriate diagnostic procedure which should be based on DBPCFC, the only way of confirming food intolerance or allergy.

The new classification and particularly the general outline of the 'role of food in relation to the different hypotheses', presented in section 2 of this study casts ample light on the real problems of food allergy and intolerance. These are questions of public health relevance to which clinical and basic research must seek answers. Thus EC agro-industrial research projects developed in the future will have to take account of this approach and its related problems.

The main point is that the IgE-mediated pathogenic mechanism is by far the most frequent and is also the most important as regards the severity of symptoms, hence the danger posed by the culprit foods, which may cause harm even only as trace contaminants.

The next most important point is sensitivity to gluten, the main cause of celiac disease.

Enzymatic intolerance can usually be traced to inborn metabolic errors; diseases in this group are extremely rare and precise dietary rules can usually be formulated to avoid problems.

Lactose intolerance is an exception, since it is very widespread. However, it is a relatively bland condition and generally raises difficulties only in preparing milk formulas for infants in countries where its prevalence is high.

Pharmacological intolerance is another problem affecting limited numbers of people, and the foods containing the culprit amines have been clearly identified.

Focusing on IgE-mediated allergies, therefore, several important question are still open. First of all we have to improve our knowledge of alimentary allergens. Many allergenic molecules have been identified in recent years, some have been sequenced and some allergenic epitopes have been recognized, but this research field is still in its infancy. Correct methods must be established for identifying the main allergens and intermediates and these require sera from at least 50 individuals, correctly diagnosed on the basis of DBPCFC as being intolerant to the study food. If at last 50 are used the resulting allergogram should meet stringent criteria. It would nevertheless be advisable to select these allergic individuals in different parts of the EU, so as to allow for the possibility of genetic and dietary differences.

Identification of the major and intermediate allergens for the main foods should then be followed by purification of the major allergenic proteins and their immunological study, aimed at identifying the epitopes involved in the immune response.

Immunological research will then provide purified allergenic molecules or allergens produced by recombinant DNA technology, and these can be employed for research into characteristics of their immunogenicity.

From the practical viewpoint it is important if we are to prevent food allergies to reduce the allergenic potential of foods. In the past this has been tackled for cow's milk, the basic food item in infant formulas, and the market now offers a variety of hypoallergenic products. For milk and other animal proteins, egg and fish, the allergens are highly stable even to cooking and digestion, so reducing their allergenicity means breaking the molecule down so vigorously that the organoleptic attractions of the original food may be lost. Many plant allergens, however, are labile to heart and digestion, so methods will probably be found to reduce their allergenicity.

Identification of the major allergenic molecules in specific foods will lead to considerable improvements in the diagnosis of allergies, and *in vitro* diagnostic tests will then became possible with much better overall accuracy, so that it may eventually no longer be necessary to use the DBPCFC test.

Knowledge and availability of the allergenic molecules for certain foods will also enable us to standardize food allergens used for specific immunotherapy. Right now these methods are not available, and research is still awaiting better standardization of the allergens. Recognition of the T epitopes of certain food allergens may open new prospects for modulating the IgE response.

Identification of the allergenic molecules will boost research into the production of transgenic plants containing little or none of the allergens concerned.

While awaiting this scientific and technological progress we must draw on our current knowledge of the effects of food processing and preparation. This is particularly important for products prepared by new methods, such as the microparticulate proteins and certain additives; which may constitute a risk for people with allergies. The best policy for the EU is to make certain that the user receives correct and detailed information about each type of food and each ingredient in the final product, and that manufacturers respect these requirements.

Public health's role will be to make more effort than in the past to spread correct information on food allergy to the medical profession and to the public so as to provide an authoritative bulwark to the spread of unorthodox practices which are the main source of controversies on this topic. Measures will have to be taken to prevent or deal with serious allergic reactions, instructing those in charge of restaurants, hotels and school canteens on what should be done in cases of severe anaphylactic reactions. Constructive relations must be established with the food industry to make sure the user receives accessible information on food products, and jointly to promote studies to set in motion the farthest-reaching positive approaches.

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