

Editorial

Evaluating new tests for the diagnosis of food allergy

In 1985, the *Journal of Allergy and Clinical Immunology* published an outstanding editorial by Charles May, the father of the modern concept of food allergy, entitled: "Are confusion and controversy about food hypersensitivity really necessary?" (13). May stated that the only procedure able to establish a correct diagnosis of food allergy is the double-blind, placebo-controlled food challenge (DBPCFC), as clinical history and skin prick tests (SPT) alone have poor diagnostic efficacy.

Little has changed in the ensuing 10 years, as no new diagnostic tests are available, and in routine allergy practice large numbers of patients are still "labeled" as food allergic merely on the basis of positive SPT and unspecific symptoms, such as chronic urticaria or gastrointestinal disorders, without any objective procedure.

The diagnosis of food allergy by history and SPT is hampered by two main factors. First, clinical history of adverse reactions to foods offers a low level of reliability, because of the vast difference between patients' self-perception of being allergic to a food and the demonstration by objective procedures of whether that food actually causes a clinical reaction. For instance, a recent epidemiologic study conducted in the UK found that about 20% of 20000 subjects surveyed by a questionnaire complained of adverse reactions to foods, but only 1.4% were demonstrated to be really allergic by DBPCFC (23). Even in carefully selected populations of adults and children entering clinical trials, only about 30–40% of clinically suspected allergic reactions to foods are confirmed by DBPCFC (2, 5, 7–9, 11, 14–16, 18, 20). Clearly, in most cases of suspected food allergy, the cause-and-effect relationship the patient assumes between a food and a clinical symptom basically reflects particular human feelings about foods (6).

Taking these considerations into account, we have to conclude, with May, that adverse reactions to foods can be demonstrated only by objective procedures which eliminate bias on both the patient's and the physician's part.

Secondly, in establishing a correct diagnosis of

food allergy, we have to remember that the presence of specific IgE antibodies to a food is not necessarily associated with clinical symptoms, unlike the diagnosis of inhalant allergy in which positive skin tests and *in vivo* IgE tests usually correspond to a clinical reaction. This difference has not so far been explained, but we can assume the existence of certain factors underlying the unsatisfactory reliability of these tests for foods. Allergenic food extracts are mostly inadequate, as the relevant allergens for many foods are still unidentified and may not be represented in the diagnostic material. In some cases, the allergens of foods are labile and the only reliable material is fresh food, as has been demonstrated for fruits and vegetables, for which the prick and prick technique (10) has detected higher sensitivity and specificity than commercial extracts (17). Recently, also for foods such as peanut, seafood, egg, and milk, better results were obtained with fresh foods than with commercial material (19). If standardized allergenic food extracts were available, the outlook might improve for the diagnostic accuracy of SPT and *in vitro* tests, as demonstrated by Aas & Lundkvist, who achieved 100% sensitivity and specificity using allergen M of codfish (3).

On the other hand, positive SPT and RAST results may be unrelated to clinical symptoms, being simply due to cross-reactivity between allergens present in foods and in other sources. Some structures in particular can be regarded as panallergens, being found in a large series of sources. This is true of profilin, which is represented throughout the vegetable kingdom (21); of tropomyosin, which is present in insects, crustaceans, and mites (22); and of common carbohydrate determinants identified in sources otherwise completely unrelated to each other (1). This clearly shows that IgE positivity to a food, while indicating sensitization to it, does not necessarily indicate a clinically important food allergy.

We may conclude that a certain diagnosis of food allergy must be based on the demonstration of clinical intolerance to a given food by DBPCFC and of the IgE-mediated mechanism by SPT and *in vitro* IgE tests.

Any new test in food allergy has to be measured against the internationally accepted standard, which currently is the DBPCFC. Any evaluation of diagnostic methods must assess the results in comparison to this.

The study by André et al. published in this issue of *Allergy* (4) sets out the meaning of total IgE measurement (by their Fc fragment) in stools as a first-step indicator of food sensitization. This investigation comprised 312 patients with positive SPT and RAST for many different foods and symptoms such as urticaria, atopic dermatitis, intestinal symptoms, and anaphylactic shock, historically related to foods. The authors found a significant difference between levels of total IgE in stools in healthy subjects and in the patients, and this led them to suggest that this test could serve as a screening test for food sensitization.

The role of intestinal mucosal immunity in allergy, particularly in food allergy, is still under investigation and there is, to date, no demonstration of different local and systemic IgE responses in food-allergic patients. Moreover, as levels of total IgE in blood after 2 years of age are considered to play a limited diagnostic role in allergic disorders, even for screening purposes (12), it would be interesting to see whether total IgE in stools is useful in diagnosis.

Of the 312 patients studied by André et al., 186 underwent DBPCFC: 121 were positive and 65 negative, the latter presumably being not allergic to foods. However, all the patients were included in the statistical analysis. As DBPCFC+ and DBPCFC- patients both had a positive result, we can conclude that the test is positive in a high percentage of patients with food-specific IgE in their blood, many of them without any true food allergy. It would have been interesting to know the behavior of the IgE in stools of patients with high levels of IgE for other allergens such as mites, grasses, molds, or latex in order to ascertain whether IgE is detectable in stools in these cases too.

As a rule, a new screening test must be evaluated in a population rigorously selected as having the disease under investigation, since only in this case can the sensitivity of the test be determined. In food allergy, the presence of IgE antibodies is only one element in the diagnosis, so any new screening test in this field must be based on the evaluation of a population with clinically well-characterized food allergy.

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