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Value and limits of diagnostic tests in food hypersensitivity

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The treatment of food hypersensitivity is essentially based on complete elimination of the offending foods (6, 25, 38). However, a diet is always an obstacle to a normal life. It may cause nutritional inadequacies, interference with social life and psychological problems. Thus an elimination diet should only be prescribed on the basis of a confirmed food allergy after a well-conducted diagnosis.

For the diagnosis of food hypersensitivity, several *in vivo* and *in vitro* methods are available, among which are food challenges, skin test and RAST, histamine release and the study of changes in intestinal permeability.

On the basis of studies to date, American authors consider double-blind food challenges the only valid and definite method for diagnosis (21, 33). These tests are time-consuming, demand skill, and are also risky because they are based on the administration of food doses that may elicit symptoms. The search is on for alternative valid but simpler and less risky tests. Thus, we shall try to analyze all the tests available on the basis of published studies.

Skin tests and RAST

Skin tests (SPT) and RAST (radioallergosorbent test) that demonstrate the presence of specific IgE for food items often cause confusion; many positive results do not correlate with clinical symptoms and these tests may be negative in the face of clear clinical sensitivity. For this reason, years ago these tests were abandoned for testing for food allergy because they were considered of little help. Later, however, they were re-assessed after May and Bock's studies with double-blind food challenges (DBFC) in children (9, 22, 23). These authors found a high percentage of positive skin prick tests and RAST results in patients with positive challenges.

To evaluate the diagnostic accuracy of SPT and RAST, Sampson (34) recently made a study in 40 children suffering from atopic dermatitis; the results of these two tests were compared with those of double-blind placebo-controlled food challenges (DBPCFC) for eight food antigens frequently eliciting reactions. Sensitivity, specificity and predictive value of the two tests compared to DBPCFC were similar; the two tests showed an overall concordance of 73%. Values were different only for wheat with a positive predictive accuracy of 75% for SPT and 20% for RAST. The predictive indices varied according to the allergen considered, though the negative predictive accuracy of both tests was very high for all allergens (from 82 to 100%). On the whole, this study showed that if these tests are negative it is very likely that children with atopic dermatitis have no food hypersensitivity.

The value of SPT and RAST has not been well-determined in adults. However, from the available studies it appears that these tests have no definite diagnostic role in adults because of the higher number of positive food challenges with negative SPT in adults than in children.

The only condition in adult subjects in which an IgE-mediated mechanism is almost always involved is hypersensitivity to fruits and vegeta-

Table 1

The main published studies conducted with DBFC

Authors	date publication	population considered	No. pat.	No. DBFC	No. (%) + DBFC**	No. (%) pat. with + DBFC
May (22)	1976	children	38	70	14 (20%)	11 (29%)
Bock (10)	1986	children 3y	206	431	96 (22%)	81 (39%)
		children 3y	131	220	69 (31%)	51 (39%)
Aas (2)	1978	children	84	446	119 (27%)	not specified
Ford & Fergusson (18)	1980	children	40	54	26 (48%)	26 (65%)
Sampson (37)	1983	children	26	104	22 (21%)	14 (54%)
Sampson (35, 36)	1987-88	children	160	514	180 (35%)	98 (61%)
Bernstein (8)	1982	adults	22	46	13 (28%)	10 (45%)
Atkins (5)	1985	adults	15 (24)*	25 (71)*	0 (12)*	0 (10)*
Onorato (26)	1986	children & adults	20	35	13 (37%)	11 (55%)

*cumulative results of double-blind and open food challenges.
** + DBFC = Positive double-blind food challenge

bles. This kind of food hypersensitivity is the most frequent in adults and can be due to a cross-reactivity between minor pollen allergens and allergens from vegetable foods. We assessed the diagnostic accuracy of SPT (with commercial extracts and with fresh foods) and RAST for seven vegetables in 100 patients suffering from oral allergy syndrome due to fresh fruit and vegetables (28). DBFC were not possible in these patients because symptoms are elicited only locally by the specific contact. We found the predictive accuracy for the different foods varied depending on how the SPT was made. Thus, negative predictive accuracy was high for apple when the skin test was done with fresh material (80%) but low when it was done with the commercial extract (42%). For peanut, we found a negative predictive accuracy of 60% for the fresh food and 78% for the commercial extract. The sensitivity of SPT with fresh food was generally higher than with commercial extracts for all the foods considered. With the RAST method, sensitivity was highest for apple (71%), and less than 50% for the other foods. These tests made in a control group of normal non-atopic subjects were absolutely negative, thus demonstrating their specificity. However, in atopic subjects with allergy to birch, grass pollen, or mugwort, positive results for fruits and vegetables were more frequent despite the absence of symptoms. In this population in which pollinosis indicates the presence of specific IgE to some allergens, skin test and RAST may be less valuable because there might be a cross-reactivity which decreases the clinical sensitivity of the tests.

The clinical meaning of cross-reactivity is not completely known. It has yet to be determined whether positivity to allergenically related substances is necessarily related to symptoms. This could be a problem because the members of some botanical families are numerous and widespread (25). For example, the *Leguminosae* family contains many vegetables and fruits present in a normal diet, such as peanuts, soy and beans. In a recent *in vitro* study in subjects allergic to peanuts, wide cross-reactions inside the *Leguminosae* family were shown by RAST

inhibition (7). However, Sampson's study with DBPCFC found only one case of intrabotanical cross-reactivity with clinical expression (35).

More specific results could be attainable with identification and purification of the most important allergens in each food item involved in food hypersensitivity. For instance, Aas used the codfish allergen he had purified for RAST and obtained positive results in all subjects sensitive to fish and negative results in all patients who tolerated it (1). However, on the basis of knowledge to date, we can only conclude that SPT and RAST have different roles in different situations in children and adults. In children, when SPT and RAST are negative it is reasonable to exclude immediate food hypersensitivity; positive results of these tests are useful to select foods for testing by DBFC. In adults, SPT and RAST are useful to confirm the diagnosis of oral allergy syndrome, which is IgE-mediated. In all other cases of food hypersensitivity, they have a role to clarify the underlying pathogenic mechanism after first establishing a reaction to food by DBPCFC.

Intestinal permeability

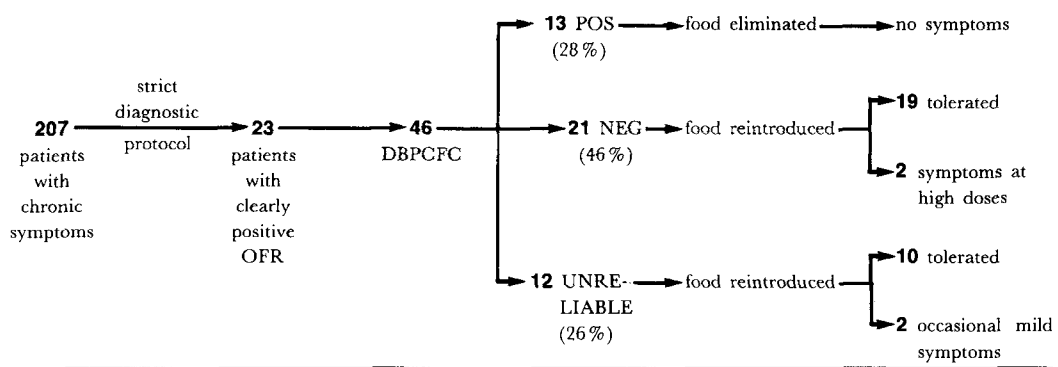
The study of intestinal permeability has been proposed as a test for the diagnosis of food hypersensitivity, but has not gained unamimous acceptance (3).

The rationale for the use of this procedure is based on the assumption that symptoms arise as a result of altered intestinal permeability, which allows the passage of macromolecules able to act as allergens. The techniques which have given the best results to date for *in vivo* study of intestinal permeability use molecules that differ in size and physicochemical properties and are therefore absorbed with different mechanisms at different levels.

Whereas small molecules diffuse through the aqueous pores of the gastroenteric epithelium (14), larger ones, which behave like food macromolecules, are normally absorbed only in minimal amounts. Thus, the percentage of an orally administered solution of macromolecules excreted in the urine can be a useful indicator of intestinal absorption in a given clinical situation. To date the techniques for evaluating intestinal permeability have been mainly applied to the study of gastroenteric diseases with malabsorption such as coeliac disease, in which absorption of the smallest molecules is often concurrently reduced (4, 11, 12). This reduced absorption is due to a reduction of mucosal surface and amplitude of aqueous pores caused by the disease.

Table 2

Results of DBPCFC and clinical follow-up in patients with chronic urticaria and/or perennial rhinitis



OFR = open food reintroduction
DBPCF = double-blind placebo-controlled food challenge
POS = positive
NEG = negative

In food hypersensitivity patients André (3) using a solution of mannitol (as low-molecular-weight molecule) and lactulose (as macromolecule) found normal absorption in basal conditions and an increase in lactulose absorption after challenge with the offending food. Swedish authors (15, 16, 17) in similar studies on food allergy, evaluated the intestinal permeability with polyethyleneglycol (PEG) at different molecular weights, following the Chadwich and coll. protocol (11). These studies confirmed that absorption was normal in basal conditions, but permeability changes in various ways after challenge with the offending food (milk) (17).

We studied a group of patients presenting food specific-IgE, demonstrated by SPT and RAST, in order to evaluate intestinal absorption of a PEG solution (PEG 300 and PEG 1000) in basal conditions and after challenge with the specific food (30). Healthy subjects were used as controls. The 12 patients (three males and nine females) with food-specific IgE were divided into two groups, symptomatic and asymptomatic, on the basis of a positive or negative DBPCFC. We determined the percentage of urinary PEG excretion by thin layer chromatography in all patients. In basal conditions, no differences in absorption of PEG 300 and PEG 1000 were found between symptomatic and asymptomatic patients and healthy controls. After challenge, only symptomatic patients showed increased permeability to higher molecular weight molecules (PEG 1000), significant compared to basal values (11.6% vs 4.59%, $P < 0.01$) and to the values of asymptomatic patients after challenge (11.6% vs 6.38%, $P < 0.05$). The opening of the gastrointestinal barrier to higher molecular weight molecules therefore seems to be connected with the occurrence of symptoms.

These results suggest that changes in absorption after food challenge are specific and therefore may have a diagnostic value. However, controlled studies to detect similar changes in permeability at various food doses (particularly not eliciting symptoms) are needed before these tests become useful in routine clinical practice.

Leucocyte histamine release (LHR)

This test is based on determination of the percentage of histamine released from peripheral basophils on contact with the antigen.

On the basis of previous observations (20) that this test showed good sensitivity in food hypersensitivity, Frick et al. (19) tried to apply it for the diagnosis of both immediate and delayed-onset reactions. As they found a high percentage (24%) of positive results in a group of 21 healthy non-atopic controls, they concluded this test was not useful in the diagnosis of food hypersensitivity. Recently, Lessof conducted a study of LHR in 12 patients allergic to egg, diagnosed on the basis of provocation tests and positive SPT (13). The LHR was positive in ten of the 12 patients (83%) and negative in all the negative controls. Thus the diagnostic role of this test seemed useful in atopic food hypersensitive patients.

We evaluated the utility of this test in 33 patients allergic to birch with apple-specific IgE, of whom 24 were apple-intolerant and nine apple-tolerant (28). LHR with apple was positive in 16 out of 24 (66%) symptomatic patients, thus showing good sensitivity. However, it was also positive in four (44%) of the nine patients who tolerated apple though they had apple-specific IgE. Thus a positive result of LHR is more related to the presence of specific IgE than to the presence of symptoms.

This hypothesis seems to be confirmed by the results of Bernstein's study in which LHR was tested in patients with food-related symptoms proved by DBPCFC (8). In these patients the presence of IgE was determined only in four out of 13 positive food challenges and the LHR test was positive only in a few cases (two out of 13 positive challenges).

On the basis of these findings, the basophil degranulation test does not seem to have much real diagnostic value for food hypersensitivity in adult patients. However, better knowledge of the mechanisms that can modify spontaneous histamine release by basophils may make it clearer in what circumstances the test can be used. In a recent work, Sampson showed that the actual clinical situation can radically modify

the degree of spontaneous histamine release (36). He observed that basophils of peripheral blood from children with atopic dermatitis and food hypersensitivity, not under any dietary restrictions, showed enhanced spontaneous histamine release *in vitro*. Such release is normal in atopic children in whom skin lesions have cleared-up after a diet free of the sensitizing food allergens.

These results, confirming analogous observations by May (24), do suggest that high spontaneous histamine release from leucocytes *in vitro* is a constant feature of subjects hypersensitive to foods, and that this test may have a possible future diagnostic role.

Double blind food challenges

In 1976 May (22) first proposed DBPCFC for the diagnosis of food hypersensitivity in routine clinical practice. These challenges are currently considered the "gold standard" for the diagnosis of food allergy.

Table 1 summarizes the results of the main studies in the literature in which DBFC have been used for the diagnosis of food hypersensitivity. Only about 30-40% of foods suspected on the basis of clinical history or open food challenges are in fact positive on DBPCFC. The reason for this discrepancy is not known but probably it can be ascribed to the psychological interferences often present in reactions believed to be due to foods. The clearest evidence of the importance of psychological conditioning is the large number of positive reactions to placebo found in several studies (8, 32). In Bernstein's study 2 out of 10 patients (20%) tested with placebo gave positive results (8). In Pearson's study, 6 out of 8 patients (75%) submitted to DBPCFC reacted to placebo on more than one occasion (32). In our study too, 7 out of 23 patients (30%) gave positive responses to the challenge with placebo (29).

From these results, it is clear how important it is to do DBPCFC. However these tests present technical difficulties because they are not standardized. It is very important to analyze the procedure because mistakes in methodology can affect the results. Procedures vary depending on the authority consulted (5, 8, 22, 26, 37). However, certain methodological features are common to all and there are some main differences, summarized here:

1. At the moment of the challenge patients must be asymptomatic or have attained a stable baseline of disease with medication stabilized.

2. The food either lyophilized in opaque dye-free capsules (for most authors) or fresh hidden in a juice or milkshake, is given at increasing doses starting from a fixed minimum dosage (100-500 mg) or established on the basis of each single patient's clinical history. If no reaction occurs the dose is cautiously increased in two-fold to ten-fold increments, at regular intervals of 15-20 minutes until symptoms appear or a maximum dosage is reached. This, depending on the authority consulted, can be 8 grams of lyophilized food in children (May (22), Sampson (37)) or 11 grams (Bousquet (26)) or 15 grams (Bernstein (8)) in adults or the maximum amount of food that can be masked, in the case of fresh foods administered in milkshake. This amount is in fact very small (ranging from 5 g of peanut to 10 g of egg and shrimp), generally insufficient to elicit symptoms. Therefore, in the only study carried out following this method all the positive challenges were in fact open (5).

3. The placebo, presented as capsules containing dextrose, sucrose or cornstarch, or otherwise milkshake alone, must be administered the same way as the food. Most authors administer it on different days from the food; Sampson makes two challenges, one with placebo, the other with a food, at different times on the same day.

4. Appropriate medication and resuscitation equipment must be available in the challenge area.

5. At the end of the challenge patients must be kept under observation for at least 1-2 hours.

6. Patients with a history of severe anaphylactic reactions are generally excluded from the challenge. In such situations, when a challenge has to be done for particular reasons, an intravenous line should be placed before starting to make drug administration easier should a severe reaction occur.

The main difference among the methods lies in the characteristics of the administered foods, fresh or lyophilized.

The administration of lyophilized foods does ensure blind conditions and permits high doses; however, freeze-drying may alter or destroy some of the antigens in the foods, and administration in capsules, which bypass the oropharynx, could mean that local symptoms are missed (5). However it is not always possible to mask the high doses of food (often nearly 100 g) necessary to elicit symptoms when giving fresh foods in a milkshake.

We can thus conclude that in choosing a method, one must weigh the limitations against the advantages so as to carry it out correctly and obtain reliable results.

In fact, though different methods have been tried, most results are comparable showing that in both adults and children the impression received on the basis of the clinical history and the results of SPT and RAST are confirmed only in about 1/3 of the cases. However, whereas a positive DBFC clearly demonstrates the presence of food hypersensitivity, a negative result is more difficult to interpret, especially because in some cases the open challenge made after the DBPCFC to check a negative result has in fact elicited reactions. For instance, in Sampson's study (36), the ingestion of normal amounts of milk caused symptoms in three patients in whom DBFC was negative; one patient with a negative DBFC to peas presented reactions after a normal portion of peas. We followed up a group of patients with negative DBPCFC to verify the reliability of the results of this test. In our Allergy Center, patients suffering from chronic urticaria and/or perennial rhinitis in whom all other pathologies had been excluded, went through a strict diagnostic protocol for food hypersensitivity (29). Out of 207 patients (Table 2), we found 23 cases whose symptoms were clearly correlated to the reintroduction of at least one food. These underwent DBPCFC with the food in question freeze-dried in capsules, at increasing doses up to a maximum of 15 g. Each patient was also given a placebo in identical capsules. A total of 46 DBPCFC were made. Of these, 13 (28%) gave positive results, 21 (46%) were negative and 12 (26%) were considered unreliable as the patient had also reported reactions after taking the placebo. Patients with positive DBPCFC were placed on a diet without the offending foods. All the patients with negative results or reactions to placebo were informed of the outcome of their test, and were advised that a "psychological" cause or erroneous impression had probably led them to believe a food item was responsible for their symptoms (31). In cases of negative challenge, the patient was reassured that he had tolerated the equivalent of a normal portion of a food, and was persuaded to reintroduce it gradually into his diet. Patients were then followed-up for a year or more.

Out of 21 negative challenges, the previously suspected food item could be reintroduced in 19 cases, and was completely tolerated even in unlimited amounts. In two of the 21 cases, however, on increasing the dose of the offending food, the symptoms re-appeared. We repeated the DBPCFC in these two patients after an interval, using higher doses than we normally employ. Both reacted positively, one after 50 g and the other after 60 g, given over two days.

In the 12 cases with unreliable results, we showed the patient that a placebo had triggered the same - if not a worse - reaction than that induced by the food itself, and explained that the symptoms were probably unrelated to the food, and might be due to mental tension. We left these patients free to choose whether or not to re-introduce the food into their diet. These subjects were seen again after two years and all had been eating the foods in question. In 10 of the 12, symptoms totally disappeared and the food was well-tolerated. The two remaining cases reported occasional symptoms re-appearing perhaps in relation to their having eaten the suspected food item.

On the basis of this study, therefore, we can conclude that DBPCFC, if carried out by a correct method and reaching sufficiently high doses, is the sole valid method for the diagnosis of food allergy.

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