FOOD ALLERGY: CURRENT KNOWLEDGE
AND FUTURE DIRECTIONS 0889–8561/99 $8.00 + .00

# SKIN TESTING AND FOOD CHALLENGES FOR EVALUATION OF FOOD ALLERGY

Larry W. Williams, MD, and S. Allan Bock, MD

In recent decades, significant progress has been made in understanding allergic reactions to foods. The predictive value of skin testing to foods is much better understood now than in the 1970s, and at least one of the in vitro diagnostic techniques may emerge as an additional aid to management (CAP-FEIA, vide infra). The double-blind, placebo-controlled food challenge (DBPCFC) continues to be the only tool able to prove definitively the presence of food allergy (short of anaphylaxis); however, there remains a place for open food challenges. With the simple tools of skin tests and challenges, typical IgE-mediated food allergy can be fairly simply characterized. Unusual complaints related to foods may also be investigated by modification of these techniques. In this article, we provide a practical approach to the use of skin tests and challenges for diagnosis of food allergy. Use of these techniques should minimize patient risk both from diagnostic procedures and from inappropriately restrictive diets.

## APPROACH TO ADVERSE FOOD REACTIONS

Before discussing the details of testing procedures, we briefly consider the indication for such tests. Most patients are evaluated because of symptoms that are temporally related to ingestion of a food. Some

From the Department of Pediatrics, Division of Pediatric Allergy and Immunology, Duke University School of Medicine, and Duke University Medical Center, Durham, North Carolina (LWW); and the Department of Pediatrics, University of Colorado Health Sciences Center, Denver, Colorado (SAB)

patients are studied because of suspicion that a food is involved in the pathogenesis of the patient's atopic dermatitis. Appropriate testing can only be chosen by reference to an accurate and complete history. IgE-mediated reactions are usually characterized by a threshold dose of only a few grams of food (often much less), reaction on each exposure, and reaction rapidly on exposure; the history should seek to confirm or refute these features for putative allergens. Reactions with onset more than 2 hours after the ingestion are unlikely to have an IgE-mediated mechanism, but exceptions occur.[4, 15] Reactions that involve skin, the gastrointestinal tract, and respiratory tract are frequently IgE-mediated; the authors have not personally confirmed any behavioral or neurologic reactions that involved an allergic mechanism. Frequently, the history alone will clearly eliminate sensitivity to a food that the patient has assigned as a cause of symptoms. A common example is the mistaken assignment of symptoms to milk ingestion in a child who develops no symptoms on ingestion of other milk products such as ice cream or yogurt. Similarly, in infancy, sensitivity to egg is often mistakenly attributed to multiple items when the offending allergen is the egg in prepared foods. Thus, if symptoms are attributed to a food, the history should include inquiries for tolerated foods that might contain the supposed allergen in amounts sufficient to produce symptoms.

The history is also important in avoidance of potentially dangerous challenges.[5] As a rule of thumb, foods that have caused life-threatening reactions when consumed in isolation (so that no confusion exists as to the offending food) are not challenged. The major exception is the need for eventual challenge in infants who have experienced anaphylaxis to milk or egg. These infants can be expected to eventually tolerate these foods, usually within 3 years of avoidance.[14] For safety reasons, challenges are undertaken in a medical care setting, but in a few situations challenge in the office is not necessary. The authors' referral practices provide examples when challenge is not necessary. Often patients are seen who have had foods eliminated from the diet on the basis of a positive prick skin test (PST) to a member of the same botanical family or on the basis of low-grade radioactive allergosorbent test (RAST) (class 1 or 2) to the food; however, the patient has eaten and never reacted to the designated food. Such patients need not be challenged. Also, foods for which there is no history of reaction despite repeated consumption and for which the skin test is negative may be simply added back to the diet. This exception is most applicable to foods unlikely to be allergenic, such as vegetables and fruits. The safest site for reintroduction of highly allergenic foods (egg, peanut, milk, soy, nuts, wheat, fish, and other seafoods) eliminated without history of reaction, but for which the PST is positive, might still be the clinic.

## SKIN TESTING

The value of skin tests is well documented in the literature. For the protein-rich foods that most commonly induce IgE-mediated sensitivity,

the most clinically useful statistical descriptors of PSTs are the positive predictive accuracy (PPA) and the negative predictive accuracy (NPA).[15] These statistical measures are dependent on the sensitivity and specificity of the tests and on the prevalence of the disorder in the population studied, as the formulas below indicate:

$$\text{Positive predictive accuracy} = \frac{sP}{sP + (1-f)(1-P)}$$

$$\text{Negative predictive accuracy} = \frac{f(1-P)}{f(1-P) + (1-s)P}$$

where s = sensitivity, f = specificity, and P = prevalence (number of confirmed positive cases divided by the number of cases under study).

The positive predictive accuracy estimates the probability that a skin-test positive patient will react when given the food in a DBPCFC. The negative predictive accuracy estimates the probability that the skin-test negative patient will not react when similarly challenged. Inspection of the formulas shows that the PPA varies directly with the prevalence. Note that prevalence is a fractional number, the proportion of cases studied that can be confirmed by DBPCFC. Thus for foods that have a low prevalence of positive challenge, the positive skin test is poorly predictive because of the small value of P (much less than 1.0) in the numerator. The positive predictive accuracy, even in a high-prevalence population, is never more than about 70% for the most predictive skin test (egg) and is lower for other foods.[16] Because the NPA varies with inverse of the prevalence, in a low-prevalence population the negative predictive accuracy is very high. Even in a population with a relatively high prevalence of food allergy, the negative predictive accuracy for the common food allergens (egg, peanut, milk, wheat, soy, and fish) remains quite high, generally greater than 95%.[15]

Published calculations of PPA and NPA become valuable in the clinic, allowing rapid determination of foods for which there is very little chance of reaction on challenge (those with negative PST) and those for which some possibility of reaction exists (those with positive PST)[3]; however, the published values are dependent on the population studied. Most reported calculations of the positive and negative predictive accuracy of PST are based on study of patients with very severe atopic dermatitis[16] using 1:10 or 1:20 glycerinated extracts. This population may differ from that in most allergy office practices, but sufficient similarity exists to make valid inferences that may guide in management of a typical office population. The office population is likely to have an overall prevalence of food allergy significantly lower than in the studies cited previously. In the office, a negative PST becomes an even more powerful predictor that the patient will tolerate the food in question. On the other hand, the positive PST in the same low-prevalence office population has even less power to predict reaction on challenge than in the studies previously cited. In the study of very severe atopic dermatitis

patients, however, the previously calculated NPA and PPA are probably valid.

As the previous discussion should illustrate, some of the common perceptions of skin tests to foods are in error. Specifically, patients, and many physicians, commonly assume that a positive skin test to a food proves allergy to the food; indeed, skin test data in isolation is anything but diagnostic. Much inappropriate, long-term food elimination is begun because of this false assumption. Therefore, food elimination should be thought of as a step in the diagnostic path, not as a definitive therapy to be prescribed after any positive skin test.

The studies that defined these statistical parameters employed PST techniques. There is no role for intradermal skin testing (at this time) in evaluation of food allergy because it has been well demonstrated that only false positives (clinically irrelevant IgE) are found by adding intradermal skin testing to PSTs.[4] In addition, the risk of anaphylaxis is increased compared with that of PST. The reader should also carefully note the definition of a positive PST. Studies in the 1970s demonstrated that reactions to PST less than 3 mm larger than the negative control were not predictive of reaction on DBPCFC and are considered negative.[4, 15] The testing device used appears not to be critical, but comparison to the negative control is.

Because of the low predictive value of positive skin tests, indiscriminate, multiple food skin tests in patients suspicious that they have a food allergy are likely to be more confusing than helpful. The skin tests should be chosen based on the history. Certainly, patients whose history is suspicious for immediate reaction to a specific food or foods may be tested. Children with atopic dermatitis who require daily medications for more than a few months should also be tested because they have about a 30% prevalence of food sensitivity proved by DBPCFC.[7] By the same criteria, children with very severe atopic dermatitis have an even higher probability of food sensitivity, as high as 65%.[13] More than 80% of reactions to foods are caused by common foods: milk, egg, peanut, wheat, and soy.[3, 6] Even in the setting of atopic dermatitis, where the expectation of food allergy is probably highest, a recent publication suggests that PST with seven foods (milk, egg, peanut, wheat, soy, cod/catfish, and cashew) will detect 99% of children with provable food allergy.[6] When no specific food is implicated by history, testing to a broad panel of foods in hopes of finding a cause for symptoms is seldom helpful, except possibly in very severe atopic dermatitis. Occasionally, testing with the high expectation of a negative result may be considered in the patient with a concern of food allergy but a nonsupportive history. The negative skin tests may be helpful for reassurance of the patient; however, in atopic patients such testing may uncover clinically irrelevant positive skin tests that may foster further patient anxiety.

There are testing options other than PST. RAST testing has been evaluated in comparison to skin testing. Sampson showed that RAST for the common childhood food allergens had no specific advantage over skin tests to predict reactions on DBPCFC.[15] If a Class 3 RAST

result is defined as positive, the RAST yields about the same positive and negative predictive accuracy as the PST but fails to detect a few who react on challenge. Definition of Class 2 RAST as positive greatly increases the false-positive rate.[15] Recently this group has published another analysis of in vitro tests in similar patients with severe atopic dermatitis. They report an improved predictive value for the Pharmacia CAP-FEIA for allergen-specific IgE.[16] This test detects allergen-specific IgE over a range from 0.35 to 100,000 kU/L. In an analysis of several hundred patients studied with CAP-FEIA and DBPCFC, CAP-FEIA results for egg, peanut, milk, and fish could be calculated that were associated with more than a 95% probability of a reaction on DBPCFC. Unfortunately, for most of these foods a value that was even 90% predictive of failure to react on challenge could not be determined (e.g., a significant risk of reaction remained even when the food-specific IgE was less than 0.35 kU/L). These calculations have not yet been replicated by other groups; however, it is likely that eventually such tests will allow estimation of patient risk with fewer challenges and will aid in appropriate timing of challenges to foods that typically are eventually tolerated.

The preceding discussion of the predictive value of testing for IgE to foods demonstrates one of the basic principles of food allergy: IgE to the food is necessary for an immediate hypersensitivity reaction, but it is not sufficient in isolation for a reaction. Thus unequivocally positive skin tests or RAST may be seen in patients who tolerate the tested food. In addition, for foods to which infants typically lose sensitivity, the skin test is frequently still positive even when the patient has lost sensitivity on challenge. Factors that are not yet understood control mast cell degranulation even in the presence of cell-bound IgE on cutaneous mast cells.

A distinctly different picture of the value of skin testing has developed for patients with the complex of symptoms termed *oral allergy syndrome*.[1, 11] These patients typically report oral itching or discomfort, and sometimes oral and lip swelling, related to consumption of foods that are rarely implicated in the food allergy studies described previously. Common inciting foods are fruits and vegetables. This area continues to be problematic because of overlap with patients who experience systemic symptoms and because investigators have not uniformly adopted a blinded challenge protocol to confirm the symptoms (that are often subjective). Nevertheless, it appears clear that some patients have IgE antibodies to aeroallergens that cross-react to proteins in fruits, as demonstrated by in vitro tests.[9] Common patterns include ragweed sensitivity and oral symptoms with melons[10] and birch sensitivity and oral symptoms with apples.[9] These patients are typically negative on PST with conventionally prepared extracts of the implicated fruit but are often skin-test positive if tested with a drop of fresh juice from the fruit or by the prick–prick technique[12] (prick device first used to prick into the flesh of the fruit, then to prick the patient). Investigators have assumed that a very labile allergen is being detected by the prick–prick

testing. Estimates of the positive and negative predictive accuracy of prick–prick testing for oral allergy syndromes have been published.[12] However, the values were derived without blinded challenges. Our knowledge in this area would benefit from better methods of confirming the diagnosis (more objective challenge techniques) and a uniformly applied case definition.

## FOOD CHALLENGES

Often symptoms are ascribed to a food without any proof. Although this method may be harmless, in many patients there is potential harm from false assignment of sensitivity to a food. The harm may be physical, by failure to avoid a true food allergen when symptoms are assigned to the wrong food, or psychological, when an unfounded fear of reactions is allowed to unnecessarily limit the patient's activities (often in the setting of secondary gain from the diagnosis of food allergy). Challenge procedures add the precision needed to avoid these adverse outcomes of overly casual diagnosis. A positive DBPCFC not only unequivocally assigns the diagnosis to a real allergenic culprit but allows an estimate of the dose required to induce symptoms. This dose threshold is also useful information; the patient who reacts to a DBPCFC after 50 mg of peanut is clearly a more difficult avoidance problem than the one who reacts only after 10 g of peanut. A negative challenge (open or blinded) allows liberalization of the diet and reduces difficult avoidance measures. All these considerations demonstrate the value of challenges in diagnosis and management of the potential food-allergic patient.

The clarification of sensitivity that a challenge offers is especially useful in the school-aged child. School children are often falsely labeled as food allergic; since many such children obviously tolerate the food in question, the school staff is led to pay little attention to "food allergy." The child who is indeed anaphylactically sensitive to a food then needs extra information to compel attention by the staff to the dietary restriction. Confirmation that the patient has had a reaction on challenge is often the evidence compelling the school to develop a management plan. Schools in the United States are required by several statutes to make reasonable accommodations to such medical problems. These laws include the Rehabilitation Act of 1973, the Individuals with Disabilities Education Act, and the Americans with Disabilities Act (further information is available from the Food Allergy Network, Fairfax, VA, 800-929-4040, www.foodallergy.org).

Food challenges may be open, single-blinded (when only the patient is unaware of the food ingested), or double-blinded (when physician, staff, and patient all are blinded).[5] The advantage of the double-blinded challenge is the great reduction in false-positive challenges. In open challenges, patient anxiety frequently induces the physician to judge the challenge positive-based on only trivial and coincidental symptoms. Indeed, the power of suggestion and emotional bias is so great that quite

convincing reactions are often not confirmed on DBPCFC. Approximately 50% of positive open challenges are not confirmed on repetition by double-blinded technique.[4, 8, 13] On the other hand, a negative open challenge is definitive proof that the patient is not sensitive to the food challenged. In general, these problems require that positive open challenges be confirmed by DBPCFC. The DBPCFC has very favorable diagnostic accuracy as judged by false-negative and false-positive results. The two largest series, reported by Sampson and by Bock, suggest that false-negative DBPCFC occurs in between 1.8% and 4.6% of challenges.[5, 14] Of the 12 false-negative challenges in Bock's series, seven were caused by inadequate dose in the original DBPCFC. Five other patients had contact urticaria or oral symptoms only (itching or swelling) on open consumption of the food but no systemic symptoms. False-positive reactions (calculated from reactions to placebo) are quite uncommon in the DBPCFC, 0.5% to 0.9% in the two series quoted previously.

The decision to challenge by open or blinded technique is influenced by several clinical factors. An open challenge may be favored if there is statistically little probability of a positive result (that would require a DBPCFC for confirmation). Such a situation might occur with a patient who wants to add the food to his or her diet and has very little evidence of sensitivity (e.g., negative skin test or poorly suggestive history). Patients who have had numerous positive skin tests without confirmatory history might also be screened rapidly for these foods with open challenges. A DBPCFC would be the better initial choice in settings in which the patient and his or her family have centered their existence around food avoidance and may have a strong psychological bias toward positive challenge. Also, if the food tested is relatively likely to be positive, as with egg, milk, and peanut in the young, skin-test positive patient with atopic dermatitis, the DBPCFC is often preferred because it will detect positives without requiring confirmation of multiple positive open challenges by DBPCFC.

The nature of the food challenge material is important. For open challenges, any form of the food the patient will eventually eat is acceptable. It is helpful if the food is in a form that lends itself to measurement so that the challenge can be recorded in quantitative fashion. A challenge is typically administered in increments over approximately 1 hour, beginning with a small dose and progressing to larger doses. Accurate control of the dose given is simplified if the food is in a form that can be measured. A total amount equal to a normal serving is given. Frequently, especially in young children, the most convenient challenge form is dried food suspended in a strongly flavored vehicle, such as Concord grape juice. The child who has not previously eaten a particular food may find the taste or texture unpleasant. Use of an acceptable vehicle can avoid this cause of refusal of the food. Dried egg white and dry powdered milk are easily given in a grape juice vehicle. Other commonly used vehicles are listed in Table 1.

The older child may prefer the actual food for an open challenge. Foods that are thought to have extremely labile allergens (as suggested

**Table 1.** CHECKLIST FOR ORAL FOOD CHALLENGES

1. Food to be challenged strictly avoided for 2 weeks or more?
2. Antihistamines (and drugs with antihistamine activity) withheld long enough to allow positive PST to histamine?
3. Bronchodilators, cromolyn, nedocromil, and inhaled steroid all withheld for 6 to 12 hours before challenge?
4. Equipment and drugs to treat anaphylaxis available?
5. Patient not fed for 2 to 3 hours prior to challenge?
6. First dose calculated to be less than amount previously thought to induce reaction? (Maximum of 400 mg if no history.)
7. Total dose of 8 to 10 g of dried food (or wet equivalent)?
8. Patient to be observed for 2 hours after completion of challenge (longer if history describes longer interval between ingestion and reaction)?

for the oral allergy syndrome) should be given in fresh form. Attention is usually focused on demonstrating that the food in its commonest form is tolerated.

## Open Challenge Techniques

The technique of open challenge may be as varied as the clinical situations for which it is employed. At its simplest, the open challenge is merely a serving of an implicated food, given under observation in the clinic. The techniques used are well described.[5] Table 1 is a checklist of safety and practical considerations for challenges. The challenge is ideally done in the fasting state. Prior to the challenge, antihistamines are withdrawn long enough to allow a positive histamine skin test. Beta-agonists, theophylline, and cromolyn should probably be avoided for 12 hours prior to the challenge. The food to be challenged should be strictly excluded from the diet for at least 2 weeks. As a general rule, the challenge is being done in the office because there is at least some chance of a reaction. Where this possibility of reaction exists, the challenge protocol should specify incremental administration of the food, beginning at about half the dose suspected to have caused a reaction. Because the reaction being sought is IgE-mediated, observation in the clinic for 2 hours after the food is completely consumed is sufficient. When reactions of other types are suspected, the length of observation may need to be prolonged, depending on the reported temporal relation (if any) of the food to the symptoms and the nature of the reported symptoms.

If there is not a reliable history from which an initial dose may be determined, a first dose in the range of 100 to 400 mg of dried food would be reasonable. If dried food is not used, rough equivalents to this rule of thumb would be 3 mL of milk, one quarter of a peanut, or about one twentieth of the white of a hard-boiled egg. Other conversions of dried and wet foods are available.[5] The total to be administered should approximate a serving of the food. Increments may progress by doubling for several steps. The largest increment is chosen to allow administration

of the challenge over about 1 hour with 10 minute intervals between doses. If no reaction is seen during ingestion or the observation period, the challenge is judged negative. If the challenge has used dried food in a vehicle, the authors' practice is to then feed more of the food in conventional form to further demonstrate that it is tolerated. If the challenge ends with an equivocal result, usually because of subjective complaints, a follow-up challenge by DBPCFC is necessary to clarify the status of the patient. Open challenges that cause florid urticaria or repetitive vomiting are likely to be confirmed on DBPCFC. Challenges judged positive because of a few small, transient hives limited to the face or hands, but not accompanied by any gastrointestinal or respiratory symptoms, often are negative on blinded challenge. These hives may be the result of contact urticaria and result from cutaneous mast cell response to allergens contacting the skin,[18] rather than being a systemic response to ingested and absorbed allergen.

Several problems are commonly encountered in open challenges. Contact urticaria may confuse grading of any challenge; if the patient is a small child, attention must be paid to keeping the food off the hands and face. Small children often resist consuming an adequate dose of a food that has been eliminated from the diet and is thus unfamiliar. Administration of an unfamiliar food (such as milk or peanut) that has a distinctive flavor or texture may meet resistance and sometimes vomiting on an emotional basis. In addition, some patients with a previous adverse experience with a food will have a profound aversion to the food that limits the ability to challenge unless the food is disguised. It may be impossible to determine whether a young child refuses the food because of aversion to a new taste or because of a conditioned response to a previous adverse experience. Thus, especially with younger children, challenge with a palatable vehicle as for a blinded challenge is routinely advisable. In older children and adults, if the challenge is likely to be confused by issues of aversion, administration of 8 to 10 g of dried food in capsules may be advisable. The patient is also more likely to consume the food as normally served if the dried food has induced no symptoms.

## Blinded Challenge Techniques

The blinded challenge adds a little complexity to the challenge scheme, but this small effort is rewarded with a great increase in certainty of diagnosis. The physician performing blinded challenges must have a process for producing and blinding the material for challenge. Clearly the physician and nursing staff administering the challenge may not prepare and label the challenge material. Offices might have skin testing or immunotherapy personnel prepare challenge material. In an institutional setting, a dietitian may be available to perform these tasks. The selected staff should understand the absolute necessity to adequately label and record challenge material and to prepare the prescribed

materials exactly. The possibility of cross-contamination in the challenge preparation area should be controlled by allowing only one challenge material to be in preparation at a time. This rule also decreases the possibility of mislabeling and administration of the wrong food. Disposable containers, weigh boats, and transfer devices are preferable to decrease the possibility of cross-contamination. A scale capable of accurately weighing gram quantities is necessary (an inexpensive triple beam balance is sufficient) as are a few graduated cylinders for measurement of liquids. A magnetic stirrer may be helpful for getting dried foods into suspension but is not critical. A blender or coffee grinders may be used to convert dry solids to powders; again, care must be taken to prevent cross-contamination.

The challenge technique is similar to an open challenge except that two coded portions (active and placebo) of challenge material are given, separated by several hours of observation. The code should be immediately available if needed. Antihistamines, other drugs, and the food to be challenged are withheld as noted for open challenge. The challenge is administered in increments, starting at a dose less than that thought to have induced a reaction. A challenge of 100 mL of liquid might be conveniently given over 1 hour by giving an initial 5 mL, waiting 15 minutes, and then giving doses at 10 minute intervals of 10 mL, 20 mL, 20 mL, 20 mL, and 25 mL. After the first challenge is given, a 2-hour wait should precede administration of the second challenge material. The exact timing of the challenges may depend on the office schedule. A possible routine would have the first challenge begin at 8:30 AM, with the observation complete by 11:30 AM. The patient might then have a break with a light lunch and begin the second challenge at 12:30 PM. If no reaction is seen after completing the second challenge material, the blinded portion of the challenge is judged negative. It is important to then follow with open administration of the food in a form in which it will likely be eaten. This open administration confirms that the food is indeed tolerated (that the challenge material was not somehow reduced in allergenicity) and that there is not a reaction with a high-dose threshold. Once again, for small children who have not previously consumed the challenged food, some allowance may have to be made to avoid refusal of a strange food. Thus a milk shake rather than whole milk or an egg in a pudding rather than a fried or boiled egg may be needed in the open challenge phase. The published data showing the impressive power of these challenges is predicated on inclusion of the open consumption of the food at the end of the challenge.[5, 7, 15]

Many practitioners have the impression that blinding foods for challenge is difficult. On the contrary, a common-sense approach is all that is necessary to adequately blind most challenges. For older children and adults, powdered food in capsules is a simple and effective blinding technique. Corn starch or dextrose are convenient placebo capsule fillers. If the food has a significant odor that might prevent blinding, another strong flavor or odor agent may be added to both the active and the placebo capsules. For example, if encapsulated peanut has a detectable

odor, addition of artificial almond flavoring to the peanut and to the placebo may aid blinding. Also, freezing the capsules until just prior to administration further reduces the odor. Shaking both the active and placebo capsules in flavored powdered sugar may also be effective. If a capsule challenge is impractical for the food or the patient, creation of a suspension in a strongly flavored liquid is frequently easy. For milk and egg, 8 to 10 g of dry powdered milk or dried egg white may be conveniently suspended in 100 mL of Concord grape juice. The strongly flavored juice overpowers the minimal flavor of either of these powders and is almost always accepted by children. Corn starch again is a convenient placebo in a 6 g quantity. Peanut is less easily disguised in liquid, but 10 g of roasted peanuts finely powdered in a grinder is adequately disguised in 6 to 8 oz of chocolate pudding. Strongly flavored fish may be impossible to completely mask; however, almost all fish-sensitive individuals tolerate canned tuna because it has been essentially denatured by the canning process.[2] Fish or placebo (canned tuna) may be mixed into hamburger patties, which will have similar taste and texture for use in blinded challenge, or the fish being challenged may be mixed directly into the tuna. Hamburger patties are also useful to hide cereal grains for challenge. Shrimp may be hidden in ice cream flavored with grape syrup. Table 2 includes several common vehicles for blinded challenges.

The placebo arm of the challenge may also be tailored to the challenge and the patient. As noted, special effort may be needed to produce an adequate placebo for a few strongly flavored foods. Use of similar-tasting, tolerated foods in the placebo is useful, as is the use of strongly flavored vehicles.

Testing for the oral allergy syndrome need not differ much from those previously mentioned. In this syndrome, capsule challenges are probably contraindicated because contact of the food with the oral mucosa may be required. Although the oral allergy literature does not discuss the issue, the authors believe that 15 to 30 g of pureed fruit may be used in a lemonade base (or Neocate if a stronger masking taste is required) in the active arm of a challenge, and a nonimplicated bland fruit in the placebo arm. Artificial flavoring to mimic the tested fruit may be added to both the placebo and active arm for blinding. The diagnostic accuracy of this maneuver has not been tested. If the symptoms are entirely subjective, several repetitions of both the active and placebo arms may be necessary to validate the challenge. Because the

**Table 2.** COMMON VEHICLES FOR BLINDING

| | | |
|---|---|---|
| Capsules | Chocolate pudding | Ice cream |
| Infant formula | Tapioca fruit mixture | Popsicles |
| Neocate | Grape juice | Lentil soup |
| Applesauce | Hamburger | Mashed potatoes |
| Milkshake | Canned tuna | Cereal |

literature suggests at least some risk of systemic reaction, incremental administration is advised.

## Challenges for Unusual Symptoms

The challenges discussed previously have centered on detection of immediate hypersensitivity reactions. Many symptoms that patients describe are very unlikely to involve an IgE-mediated mechanism because they are purported to occur many hours to days after the consumption of the food begins. The techniques described previously may be modified to investigate such atypical symptoms attributed to foods. Several principles are involved in appropriately altering these protocols. Because prolonged administration is required, preparation of challenge materials for home use is usually necessary. Because the symptoms being investigated are often subjective, several cycles (probably at least three) of placebo and active are necessary to avoid a 50% random choice rate for a single pair of placebo and active. Administration should continue at least as long as the purported interval to symptoms and probably twice as long if practical. Materials for challenge should be issued one arm at a time to avoid any ability to directly. compare the challenge materials. A wash-out period between challenge arms is advisable to ensure no carry-over of effects from one arm of the challenge to another. Unless the challenge food has been recently eaten and clearly causes no immediate reaction, an initial challenge of the type described above is often indicated.

The algorithm for analysis of unusual symptoms (Fig. 1) describes this approach for patients whose symptoms are not of an immediate nature. Frequently, patients read lay literature that leads them to suspect foods as a cause of multiple symptoms; however, they cannot assign symptoms to any particular foods. Some patients suspect symptoms related to multiple foods. In these situations, an elimination diet may clarify if the food is inducing the symptoms. If a diet eliminating all suspect foods does not improve symptoms, the foods may be ruled out as the cause of symptoms. A few patients will be so certain of a food-related cause that a hypoallergenic or elemental diet is needed to demonstrate lack of relation to symptoms (and a few will actually have objective changes related to this extreme dietary maneuver). Adequate elimination diets are described elsewhere.[5] If symptoms resolve on the elimination diet but recur on reinstitution of regular diet, elimination is re-instituted and foods added openly by groups. Typically a short list of implicated foods will be generated. If the symptoms reported are possibly IgE-mediated, skin testing may then be indicated for guidance. If reported symptoms have the timing or characteristics of IgE-mediated reactions, caution should be used in returning eliminated foods to the diet. If the symptoms are not typical for IgE-mediated sensitivity, blinded challenges are required to determine if the foods are indeed causing symptoms.

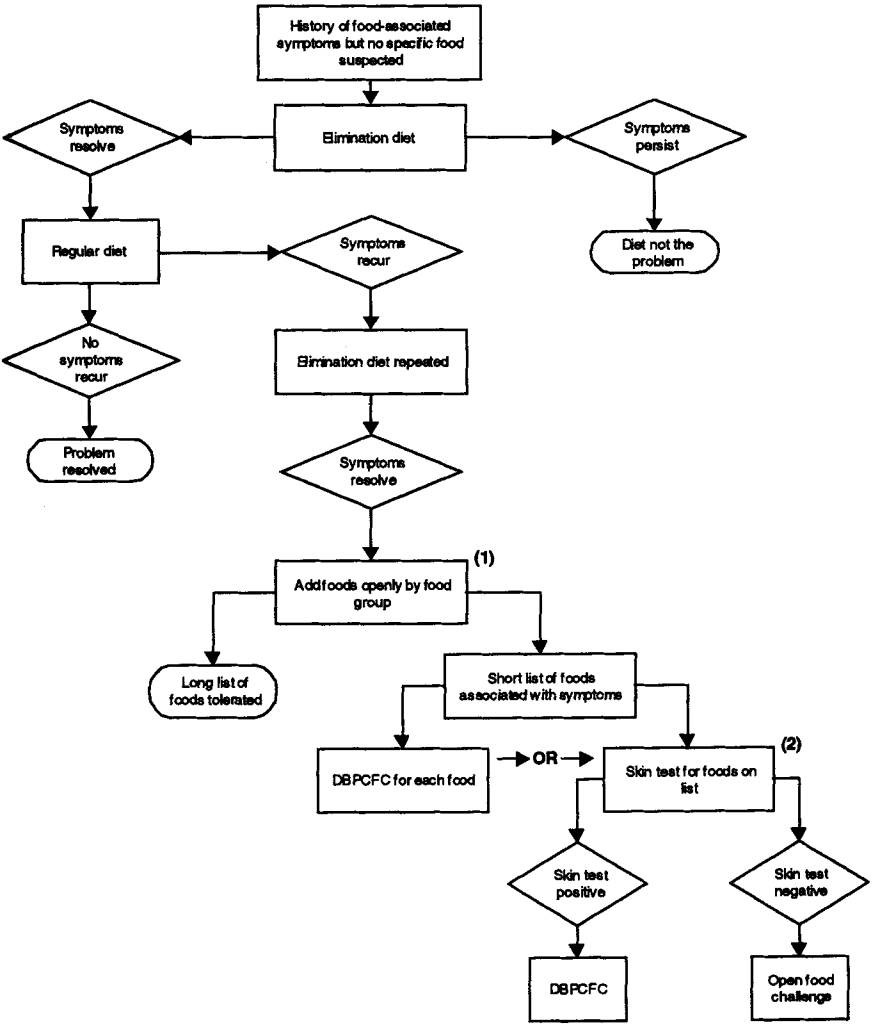



**Figure 1.** Unusual reactions to foods. This analysis applies to situations that are not likely to be IgE-mediated, and may be generalized to all food reactions if appropriate steps are taken to avoid dangerous, immediate reactions. (1) Foods are added openly at home only if history does not suggest an IgE-mediated or other potentially life-threatening reaction. (2) Skin prick tests may be employed if it is believed that the reaction seen is IgE-mediated. DBPCFC = double-blind, placebo-controlled, oral food challenge.

A specific class of adverse food reaction frequently seen in younger children deserves special mention: the syndrome of food protein–induced enterocolitis. This disorder must be remembered especially in the evaluation of infants suspected of reaction to formula. Because this disorder is not IgE-mediated, skin testing is negative to formula proteins

(milk or soy). Yet, on challenge the patients may develop brisk diarrhea, to the point of hypovolemic shock, over the course of a few hours. Thus the negative skin test cannot rule out the occurrence of a brisk and potentially life-threatening reaction. Almost all children with this disorder present in the first six months of life with vomiting or diarrhea and are intolerant of milk or soy.[17] A few patients present later in childhood, again with vomiting or diarrhea, and may be intolerant of proteins other than milk or soy. On challenge, the patients usually react within an hour of administration of the implicated protein.[17] Thus infants with a history of isolated GI symptoms and without a positive skin test may react on challenge because of this disorder.

## SUMMARY

Skin tests by prick technique offer considerable guidance in the diagnosis of food allergy. Negative prick skin tests are powerful evidence against food allergy. Positive food skin tests are slightly to moderately predictive of reaction to a food on DBPCFC. Oral food challenge should be considered for confirmation of food allergy except when the history is overwhelmingly convincing. Open, incremental food challenge as described is diagnostic if negative, but only 50% of all positive open challenges are confirmed on blinded challenge. DBPCFC can be designed for any food with simple blinding techniques. The technique of DBPCFC can be modified for investigation of atypical symptoms.

## References

1. Anderson BL, Dreyfuss E, Logan S, et al: Melon and banana sensitivity coincident with ragweed pollinosis. J Allergy 45:310–319, 1970
2. Bernhisel-Broadbent J, Scanlon SM, Sampson HA: Fish hypersensitivity. J Allergy Clin Immunol 89:730–737, 1992
3. Bock SA, Atkins FM: Patterns of food hypersensitivity during sixteen years of double-blind, placebo-controlled food challenges. J Pediatr 117:561–567, 1990
4. Bock SA, Lee WY, Remigio LK, et al: Studies of hypersensitivity reactions to food in infants and children. J Allergy Clin Immunol 62:327–334, 1978
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 82:986–997, 1988
6. Burks AW, James JM, Hiegel A, et al: Atopic dermatitis and food hypersensitivity reactions. J Pediatr 132:132–136, 1998
7. Burks AW, Mallory SB, Williams LW, et al: Atopic dermatitis: Clinical relevance of food hypersensitivity reactions. J Pediatr 113:447–451, 1988
8. Burks AW, Sampson HA: Double-blind placebo-controlled trial of oral cromolyn in children with atopic dermatitis and documented food hypersensitivity. J Allergy Clin Immunol 81:473–480, 1988
9. Ebner C, Birkner T, Valenta R, et al: Common epitopes of birch pollen and apples. Studies by Western and Northern blot. J Allergy Clin Immunol 88:588–594, 1991
10. Enberg RN, Leickly FE, McCullough S, et al: Watermelon and ragweed share epitopes. J Allergy Clin Immunol 79:867–875, 1987

11. Eriksson NE: Food sensitivity reported by patients with asthma and hay fever. Allergy 33:189–196, 1978
12. Ortolani C, Ispano M, Pastorello EA, 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 83:683–690, 1989
13. Sampson HA: Role of immediate food hypersensitivity in the pathogenesis of atopic dermatitis. J Allergy Clin Immunol 71:473–480, 1983
14. Sampson HA: Adverse reactions to foods. *In* Middleton E, Reed CE, Ellis EF (eds): Allergy: Principles and Practice, ed 5. St. Louis, Mosby, 1998, pp 1162–1182
15. Sampson HA, Albergo R: Comparison of results of skin tests, RAST, and double-blind placebo-controlled food challenges in children with atopic dermatitis. J Allergy Clin Immunol 74:26–33, 1984
16. Sampson HA, Ho D: Relationship between food-specific IgE concentration and the risk of positive food challenges in children and adolescents. J Allergy Clin Immunol 100:444–451, 1997
17. Sicherer SH, Eigenmann PA, Sampson HA: Clinical features of food protein-induced enterocolitis syndrome. J Pediatr 133:214–219, 1998
18. Winston G, Lewis C: Contact urticaria. Int J Dermatol 21:573–578, 1982

*Address reprint requests to*
Larry W. Williams, MD
Division of Pediatric Allergy and Immunology
Duke University Medical Center
Box 3559
Durham, NC 27710