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Double-blind, placebo-controlled food challenge (DBPCFC) as an office procedure: A manual

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There is now enough experience with the use of double-blind, placebo-controlled, food challenge (DBPCFC) to recommend its use as an office procedure for most patients complaining of adverse reactions to foods. This manual discusses the practical methods required for the allergist to undertake DBPCFC in the office. Thorough histories supplemented by food allergen skin testing are used to design a DBPCFC that carefully attempts to reproduce the history of food-induced symptoms described by the patient. Precautions that must be taken are delineated before challenge, as is treatment that may be required if a reaction occurs. For those foods to which challenges are positive, longitudinal evaluation with repeated challenge at appropriate intervals help to determine whether or not the problem will resolve over a period of time. (J ALLERGY CLIN IMMUNOL 1988;82:986-97.)

The purpose of this article is to share the authors' experience using DBPCFC in outpatient settings. As such, it was designed to outline the stepwise procedures useful in evaluating the validity of a history of

Abbreviation used

DBPCFC: Double-blind, placebo-controlled food challenge

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adverse reactions to foods. The procedures as presented here have been endorsed in principle by the Adverse Reactions to Foods Committee of the American Academy of Allergy and Immunology.

The DBPCFC is the state-of-the-art technique to confirm or refute histories of adverse reactions to foods.¹⁻¹⁰ Although this is the "gold standard" by which all studies of food allergy should be judged, it is also a practical procedure by which practicing al-

TABLE I. Results of DBPCFCs from various centers

	NJC	JHU/DUKE	UCSD	MAYO	TULANE	NIH
No. Pts DBPCFC*	407	190	47	11	30	25
No. Pts + DBPCFC†	157	118	23	6	9	10
No. DBPCFC‡	826	539	59	24	125	38
No. + DBPCFC§	204	222	29	6	12	8
Foods producing a positive DBPCFC						
Peanut	48	34 (18)	4	2		2
Egg	53	90 (5)	14	1		1
Milk	47	32 (3)	7	1		
Nuts	21			2		
Soy	14	17 (1)	1			
Wheat	5	9	2			
Fish	6	13 (4)				
Shellfish (crustacea)	2	2			12	5
Chicken	2	4				
Pea	2	2				
Turkey	1					
Banana	1	2				
Rye	1	3				
Squash	1	0				
Potato		3 (1)				
Rice		2				
Beef		4				
Corn		2	1			
Other		3				

NJC, National Jewish Center; JHU/DUKE, Johns Hopkins University/Duke University; UCSD, University of California—San Diego; Mayo Clinic; Tulane University; NIH, National Institutes of Health; +, positive.

This table represents the cumulative experience with the technique of DBPCFC from the various centers of the authors of this article.

*Number of patients undergoing DBPCFC.

†Number of patients with positive DBPCFC.

‡Number of DBPCFCs performed.

§Number of positive DBPCFCs.

||Number in parentheses depict number of reactions based on convincing history of life-threatening reactions after ingestion (not included in total of 222 positive DBPCFC).

lergists can accurately diagnose adverse food reactions in their offices if some minimal preparation is undertaken. The ability to unravel food-related problems with the DBPCFC is only limited by the imagination of the physician and a clever dietitian. It is a useful outpatient procedure because much of what the physician is undertaking is the refutation of histories of adverse reactions, since even in studies of highly selected patients, 60% or fewer of the subjects are found to have reproducible reactions in DBPCFC (Table I). The procedure is a diagnostic, not a therapeutic challenge. Therefore, each challenge procedure is designed with a particular patient in mind, much as skin tests should be selected for each individual patient rather than evaluating all patients by the same protocol. Although each of the authors has used somewhat different protocols for studies in his individual institution, the procedures presented in this discussion

have all been used in clinical settings, and they have been found to be useful and practical in attaining patient compliance and in determining the true nature of an individual patient's food reactions. We hope that our colleagues in this specialty will find this article a practical guide in adapting DBPCFC to their individual practices.

HISTORY AND PHYSICAL EXAMINATION

As with most disorders, the patient history is invaluable in initiating the evaluation of an adverse food reaction. A thorough history directed toward several pertinent facts is extremely important because the physician's task is to attempt to reproduce the patient's story. A description of the complete symptom constellation must be obtained. One must direct the questioning so that the history focuses on (1) the suspected foods, (2) the timing between the ingestion of the food

and the onset of symptoms, (3) the smallest quantity of food that the patient suspects will produce the symptoms, (4) the frequency and reproducibility of the reaction, (5) whether exercise was associated with the reaction, (6) the most recent occurrence of the putative food reaction, and (7) a description of signs, such as rhinitis, urticaria, eczema, nasal discharge, cough, asthma, sputum production, vomiting, diarrhea, and colic.

The physical examination should emphasize the cutaneous, respiratory, and gastrointestinal systems. In particular, skin rashes, abnormalities of the nose and ears, unusual auscultatory findings, and abdominal discomfort should be noted. Obviously, the behavior of the patient can be observed during the history and physical examination. This may be particularly important in young children of whom the parents are complaining about behavioral problems. Some physical findings may direct the physician to other considerations in the differential diagnosis and away from the patient's emphasis on foods.

Although innumerable symptoms caused by food have been claimed by patients, the symptoms and signs that have been reproduced in DBPCFC constitute a remarkably short list. These symptoms and signs include gastrointestinal complaints, such as abdominal pain, nausea, vomiting, diarrhea, bloating, cramps, and gas. Cutaneous symptoms and signs have included pruritus caused by eczema, urticaria, angioedema, and some nonspecific erythematous rashes that have been reproduced but have not been characterized because of the lack of biopsy material. Respiratory symptoms and signs that have been reproduced in blind challenges include sneezing, ocular injection, serous rhinorrhea, laryngeal edema, cough, bronchorrhea, and wheezing. (Respiratory symptoms as the sole manifestation of adverse food reactions are unusual and are most frequently observed in conjunction with gastrointestinal and/or cutaneous symptoms.) Cardiovascular symptoms and signs have included tachycardia, arrhythmias, and hypotension. It should be noted that these latter problems are unusual if patients with histories of severe systemic reactions are excluded from challenge and if care is taken to perform challenges in a dose-response fashion.

Allergy skin testing for foods

Skin testing for foods is useful if a few simple principles and facts are kept in mind.^{2, 4, 7, 8, 10-14} The confusion of the past with regard to food skin testing has arisen from problems of interpretation. A food skin test, like any other immediate skin test, is used in the evaluation of immediate hypersensitivity reactions, detects the presence of IgE antibody, and does

not by itself confirm a diagnosis. If allergists were required to prove that every positive *inhalant* skin test was responsible for a patient's symptoms before being included in an extract for allergy-injection therapy, there probably would be as much confusion and conflict about inhalant skin tests as there is about those for foods. The main difference lies in the fact that patients generally know the foods that they consume but not the allergens that they inhale. Since specific food consumption can be controlled by specific diets, the allergist and patient must determine whether a food associated with a positive food skin test truly causes a reaction when it is ingested. Therefore, food skin testing is limited to those foods suspected of provoking symptoms based on the history. Generally, skin testing with panels of foods is not advised, but if panels are used, they should be limited to a few foods that have been frequently associated with symptoms during double-blind food challenges. However, a food panel of likely causative foods may be necessary in the evaluation of idiopathic anaphylaxis.¹⁴

At the present time, food skin tests may be reliably performed by the prick/puncture test with extracts of a 1:10 or 1:20 wt/vol concentration that have been demonstrated to detect antibody in patients known to be sensitized. A positive skin test is indicated by the development of a wheal that is 3 mm or larger in diameter than a diluent control wheal measured within 10 to 30 minutes. The prick/puncture test has been well studied, whereas, at this time, intradermal skin tests for foods have not been demonstrated to have a high degree of clinical correlation and should not be used.^{11, 12}

Prick/puncture skin tests at the noted concentrations have been found to be helpful before challenge as a guide in designing the evaluation. Detailed statistical analysis of skin test data has revealed that the negative predictability of a properly performed food skin test is about 99% in a population in which the prevalence of food allergy is 5%.⁴ Thus, when the food skin test is negative, the food tested may be administered openly unless (1) the adverse reaction is believed not to be IgE-mediated, (2) the patient has a strongly held belief that symptoms will occur despite the physician's assurances that a reaction is highly unlikely, or (3) the physician believes the skin test to be incorrect. If the food skin test is positive (a wheal 3 mm or larger in diameter than the diluent control wheal) and is accompanied by a history of recent probable adverse food reaction, then the physician should proceed with food challenges as described below.

The immediate food skin test will be negative if the adverse reaction to a food involves physiologic re-

FOOD CHALLENGE CLINICAL MANIFESTATIONS

Name:					NO.:					Date:				
TIME														
T														
P														
R														
BP														
Abdom. pain														
Nausea														
Vomiting														
Diarrhea														
Rhinitis														
Asthma														
Rash														
Eczema														
Pallor														
Headache														
Change in:														
behavior														
mood														
activity														
(describe)														
Other:														
(describe)														
Rx for Symptoms														
P.E.														
Wheezing														
Rhinitis														
Other														

Chart bronchodilator or epinephrine under Rx for symptoms.

Present = +

Absent = 0

FIG. 1. An example of a food-challenge recording sheet that may be modified to suit the needs of the individual administering the DBPCFC.

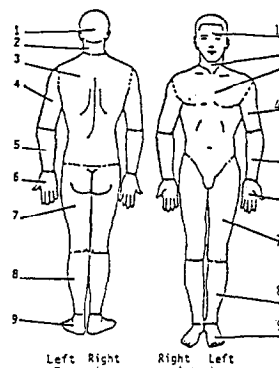
actions other than IgE-mediated mechanisms. In these unusual situations, the negative food skin test does not eliminate the food as a cause of the reported symptoms.¹⁵⁻²³ The results obtained by history, physical examination, and food skin testing should be recorded on a systematic form. Examples of food-challenge recording sheets are depicted in Figs. 1 and 2 and in Table II.

RAST has been demonstrated to be an effective means of identifying food-specific IgE. However, RAST is no more effective than skin tests and requires

more time and expense. Therefore, for almost all clinical situations, and in accord with American Academy of Allergy and Immunology recommendations, skin tests are the preferred method for identifying food-specific IgE. RAST is useful if food reactions have been so severe as to suggest that skin testing with food extracts is a risk to the patient. However, properly performed skin tests should not cause symptoms in patients, even those with a history of anaphylaxis, since the extracts may always be diluted to low concentrations before testing if this is appropriate. In

TABLE II. Food-challenge symptom score sheet

Possible reactions	
I. Skin	
A. Erythematous rash (% area involved)	
B. Rash	
0, absent	
1, mild: few areas of faint erythema	
2, moderate: areas of erythema, macular and raised rash	
3, severe: generalized marked erythema (>50%); extensive raised lesion (>25%); vesiculation and/or pilgrection	
C. Pruritus	
0, absent	
1, mild: occasional scratching	
2, moderate: scratching continuously for >2 min at a time	
3, severe: hard continuous scratching, → excoriations	
D. Urticaria/angioedema	
0, absent	
1, mild: <3 hives	
2, moderate: <10 hives to >3	
3, severe: generalized involvement	
II. Nasal	
A. Sneezing/itching	
0, absent	
1, mild: rare bursts	
2, moderate: bursts <10; intermittent rubbing of nose and/or eyes	
3, severe: continuous rubbing of nose and/or eyes; periocular swelling and/or long bursts of sneezing	
B. Nasal congestion	
0, absent	
1, mild: come hindrance to breathing	
2, moderate: nostrils feel blocked; breathes through mouth most of time	
3, severe: nostrils occluded	
C. Rhinorrhea	
0, absent	
1, mild: occasional sniffing	
2, moderate: frequent sniffing, requires tissues	
3, severe: nose runs freely despite sniffing and tissues	
III. Chest	
A. Wheezing	
0, absent	
1, mild: expiratory wheezing to auscultation	
2, moderate: dyspnea, inspiratory and expiratory wheezing	
3, severe: dyspnea, use of accessory muscles, audible wheezing	
IV. Abdomen	
A. Subjective complaints	
0, absent	
1, mild: c/o nausea or abdominal pain; no change of activity	
2, moderate: frequent c/o nausea or pain; decreased activity	
3, severe: patient in bed, crying, or notably distressed	
B. Objective complaints	
0, absent	
1, mild: 1 episode of emesis or diarrhea	
2, moderate: 2-3 episodes of emesis or diarrhea or 1 of each	
3, severe: >3 episodes of emesis or diarrhea or 2 of each	



likely that the diet accounts for the patient's complaints. Several variations of the elimination diet may be used, depending on the patient's history. The simplest diet is elimination of one or two suspected foods. The resolution of symptoms after such avoidance coupled with positive prick/puncture tests is strong supportive evidence of specific food hypersensitivity that should be verified by controlled food challenge.

When the patient is concerned that foods cause symptoms, but no particular food is suspected or incriminated, then an elimination diet similar to that listed in the Appendix may be undertaken for 7 to 14 days. In this instance, a highly restricted elimination diet for 1 to 2 weeks is preferable to attempting to establish the diagnosis by eliminating one or two foods at a time, since this approach may take months and may still not be rewarding. Patients have been found to be quite compliant with short duration elimination diets. In many instances, elaborate food diaries may be cumbersome and burdensome for patients and rarely useful to the physician. In contrast, after completion of 1 to 2 weeks on a strict elimination diet, most patients will be able to state unequivocally that the diet has been very helpful or useless. Very restrictive diets are admittedly unpleasant. Thus, if the patient reports an improvement in symptoms, this observation should be pursued by the methods that follow.

If the patient still reports symptoms after completion of the elimination diet, the allergist is left with two options. First, the patient can be told that foods are not implicated in the problem and other diagnoses should be explored. Second, if a food (or foods) in the elimination diet is suspected of being the culprit, then the patient should proceed to an elemental diet. Three elemental diets include Nutramigen and Pregestimil (Mead Johnson and Co., Evansville, Ind.) and Vivonex (Norwich-Eaton Pharmaceutical, Inc., Norwich, N.J.). (There are other diets on the market.) If the patient's symptoms do not vanish with an elemental diet, it is very unlikely that ingested substances are the problem. If the elimination diet has been helpful, then the physician should proceed to either an open food challenge, in selected circumstances, or directly to the DBPCFC. Suspected foods should not be reintroduced at home except under the direction of a physician.

Food-challenge precautions

Before performing any food challenge, a thorough discussion must be undertaken with the patient and/or parent or guardian. The purpose of the procedure must be explained, including a discussion of both beneficial and potential adverse reactions, in-

cluding anaphylaxis. Moreover, the patient/parent should be assured that reactions will be treated promptly as appropriate. Adequate time must be allowed to answer all questions.

Open food challenges

DBPCFC is the ideal method for definitely confirming histories of adverse reactions to foods; however, there are occasions when open food challenges may be useful. When the skin test is negative and the history of a reaction to that food doubtful, the food may be replaced in the diet at home with a 99% expectation that the food will be tolerated. Reintroduction of foods into the diet at home should *NEVER* be undertaken if there is even a remote chance of severe symptoms developing. Purported "false negative" skin tests are often associated with a patient's strongly held belief that a food will cause symptoms, but usually are only subjective ones. These patients will need a DBPCFC to determine the validity of their complaints.

Occasionally, open food challenges in the allergist's office may be instructive, particularly when objective symptoms can be elicited (rash, hives, decreased pulmonary function tests, vomiting, or diarrhea) in the reliable patient. Open challenges are especially useful when the symptoms are not reproduced, thus eliminating the incriminated food as a possible culprit. The open challenge may be administered in increasing increments during a period of hours, as specified below for DBPCFC. For convenience, occasionally the patient may bring the suspected food to the office and then be challenged with it in incremental portions. For most other circumstances, DBPCFC is the preferred technique.

Double-blind, placebo-controlled food challenges

Preparation of foods. The advantages of dehydrated or dried foods cannot be overstated because of their convenience and easy storage. Such foods as grains (wheat, oat, rye, rice, barley, corn, soy, etc.) are available as flour or meal. Nuts and legumes may be purchased and powdered with a simple mortar and pestle, or blender. Dried milk and usually dried egg white are not difficult to find. Acquisition of fruits, vegetables, and some meats has been enormously simplified because of the popularity of camping in this country. What the grocery store is lacking, the camping store often has in a freeze-dried pouch. It may be surprising to find how little many of these products have been adulterated with additives and preservatives. On rare occasion, it may be necessary for the allergist to find a friendly local biochemist with a

TABLE III. Sample weight equivalents

Food	Wet weight (gm)	Dry weight (gm)	Wt/capsule (gm)
Egg	2.36	0.59	0.59
Milk	6 (ml)	0.61	0.61
Peanut	1.83	0.44	0.44
Wheat	0.90	0.90	0.90
Soy	2.83	0.68	0.68
Corn	8.25	0.66	0.66
Beef	4.10	0.57	0.57
Shrimp	3.28	0.59	0.59

lyophilizer to freeze-dry sufficient quantities of some foods to last a year or more. Fish, crustacea, and mollusks are still a problem to prepare; they may be dried in a microwave oven and then encapsulated or hidden in a vehicle listed below. Because of their strong taste and unmistakable texture, masking may be incomplete. However, freezing capsules often helps mask the taste.

Vehicles. A multitude of vehicles have been used to hide foods for DBPCFC. Remember that the principle is to administer the challenge to the patient objectively to duplicate the conditions of timing and quantity noted in the history. Therefore, any vehicle used must allow for a truly blind challenge, masking smell, flavor, and texture of the food. The vehicle must be able to accommodate enough food in a small quantity so that multiple challenges during a few hours may be administered. Any procedure which deviates from absolute blinding is to be regarded as suboptimal because it introduces subjective biases of the patient and observer; alternative procedures should be sought to assure that the challenge is blind.

Capsules (00 white, opaque gelatin, tinted with titanium oxide)* are the preferred vehicle of most investigators. Capsules have the advantage because a fairly large amount of food can be thoroughly hidden in a small space. For example, a whole egg, when it is dried, weighs about 5 gm, and this amount can be placed in about 10 to 15 capsules. Eight grams of powdered milk is approximately 2 ounces of reconstituted nonfat powdered dry milk. Foods are packed into capsule by hand, and excess food wiped from the outside of the capsule. Placing all capsules in powdered sugar before wiping clean assures a similar taste of both food and placebo capsules. A simple but accurate balance is used to weigh the capsules needed to undertake each challenge. The dried weight of foods in individual capsules, as used at Johns Hopkins Uni-

versity School of Medicine, is presented in Table III. The appropriate wet-weight equivalent is also presented for these examples.

A pharmaceutical company (Dura*) has recently marketed encapsulated dried foods that are ready for food challenges. These food-containing capsules are not approved by the Food and Drug Administration for use in the diagnosis of food hypersensitivity. They have been criticized for containing small quantities of food in each capsule. Therefore, large numbers of capsules are required for some challenges.

Vivonex, especially when it is iced and flavored with vanilla or another of the available flavor packets, can disguise almost anything, especially items that cannot be freeze-dried, such as liquids. For example, items such as vinegar, various oils, wine, and fruit juices can be hidden undetectably in iced, flavored Vivonex. Children's formulas can be hidden in Vivonex, in each other (e.g., soy in cow's milk and cow's milk in soy), or in one of the elemental formulas. The dried foods may be weighed and mixed into individual portions used for challenge. Alternatively, a large quantity may be weighed and mixed into the challenge vehicle, and then portions of the vehicle may be used for challenge in increasing increments.

Milk shakes are a good vehicle for some foods, as is ice cream flavored with some strong taste like grape flavoring. Applesauce is a superb place to hide powdered foods for young children. Children appear to like applesauce as long as it tastes like applesauce, no matter what it looks like. Therefore, hiding cereal grains in applesauce becomes a realistic alternative for toddlers. A clever dietitian, often available at local clinics and hospitals, may be able to offer ingenious methods for hiding food, especially if quantity is the issue. Even a hamburger may be hidden in tuna fish or tuna fish in a hamburger. Two other vehicles which

*Manufactured by Parke-Davis, supplied by ELANCO, subsidiary of Eli Lilly & Co.

*Dura Pharmaceutical Co., PO Box 28331, San Diego, CA 92128.

have been used are a mixture of tapioca with fruit and a lentil soup.

At least two situations exist in which liquid challenges may be preferable to capsule challenges. The first is the "oral allergy syndrome" in which all the reported symptoms are limited to the oropharynx (pruritus of the mouth and swelling of tongue or pharyngeal structures). These patients may benefit from both liquid and capsule challenges on separate occasions that will determine whether the reaction is due to local contact with oral mucosal tissue and/or systemic absorption. The second circumstance in which liquid challenges are preferred occurs in the patient suspected of being anaphylactically sensitive to a food. Administration of quantities of the suspected food in liquid may be more easily controlled and will not be subject to waiting for capsular dissolution.

Placebos. The placebo portion of the challenge may be arranged in several ways, depending on the vehicle chosen. If capsules are used, a good placebo is dextrose because of its commercial availability and ease of encapsulation. A food not under suspicion but available from the physician's supply may also be used as the placebo. Some foods are hard to disguise in capsules because of their color. The most notable of these is chocolate. However, mother nature has been kind to us and has created carob that has the virtue of being botanically unrelated to chocolate but has the same appearance. Many of the vehicles mentioned can be used as a placebo without adding anything to them. It should also be noted that since the patient is not sure what is taking place, one may occasionally omit the placebo entirely by giving the suspected food first and, if the reaction is negative or impressively positive, forego the placebo challenge. One must be certain that the blind observer, often a nurse, is unaware of this choice, or the observations may become biased. Regular use of the placebo should ensure that this does not occur.

Medication avoidance. Medications that need to be avoided before food challenge include antihistamines (96 hours*), β -agonists (12 hours), theophylline (12 hours), and cromolyn (12 hours). Modifications of this schedule may be needed, depending on the nature and severity of a patient's underlying medical problem, especially asthma. Withholding medications could result in confusion between symptoms occurring caused

by the food challenge versus those caused by inadequate medication. The placebo challenge should clarify the difference. It is optimal to administer challenges after an overnight fast to eliminate the possibility that previously ingested substances might alter the timing of the reaction.

Administration of the blind food challenge. A single-blind food challenge may be used when the objectivity of the observer (i.e., nurse) can be assured. However, for most single-blind challenges, the observer is the allergist in whom some bias usually exists. Often it is just as easy to do a double-blind challenge. If it can be arranged, the allergist should take the opportunity of being the blind observer periodically. Nevertheless, the allergist must be present during all challenges and should confirm suspected reactions.

Administration of the food during challenge should be done in a graded fashion. The starting quantity should be less than that estimated by the patient to be required to produce symptoms. The dose may then be doubled at intervals specified by the history or every 15 to 60 minutes. If the reaction is said to take 45 minutes to occur, the challenge interval could be 1 hour. The doubling doses should continue until the patient has convincing symptoms, or 8 to 10 gm of dried food, or 60 to 100 gm of the wet food has been ingested as a single dose. It is obvious that by the time incremental doses have reached the level of 8 gm of the dried food, the patient may have had a total dose of as much as 15 to 20 gm of dried food from the beginning to the end of the challenge.

If the double-blind challenge up to about 8 gm (dry weight) is negative, then the food must be reintroduced into the diet openly, preferably under observation in the allergist's office, so that the patient and doctor can observe that the patient can eat the food without the production of symptoms. The open consumption of the food eliminates many of the vagaries often raised about cooking, digestion, etc., that may alter the food.

Occasionally, the open challenge will be positive in the face of a negative blind challenge. Three possibilities may explain this observation. (1) The patient's threshold to respond may be higher than was achieved during the blind challenge, as suggested by the dose-response relationship. Such a possibility can be tested in a blind challenge with greater quantities of food. (2) The allergenicity of the food may be different because of the manner of preparation. This often raised explanation is rarely ever confirmed during blind challenges. (3) The reaction may be due to psychologic factors; that is, the patient may have a strongly held belief that the particular food in question

*Subjects taking hydroxyzine have been noted to have a persistently negative skin test for up to 10 days; therefore, it may be wise to use the histamine skin test to assure clearance of antihistamine from the tissues before challenging selected patients. These recommendations may need to be modified as newer, longer-acting antihistamines become available.

will cause a reaction and, thus, the symptoms are a self-fulfilling prophesy.

During the challenge a symptom-score sheet is maintained by the blind observer. (Samples are illustrated in Figs. 1 and 2; Table II.) If bronchoconstriction, secondary to the ingestion of a food or food additive is suspected, patients should be monitored by spirometry (unless this is prohibited by age) to detect early changes in airway function. Subjects should be monitored for 1 to 2 hours after the completion of the challenge, since most major allergic symptoms would occur within this period. The challenge is best initiated in the morning in the allergist's office with the patient having fasted overnight. For many of the patient's complaints, a morning of blinded challenges with the open challenge at lunch time will resolve the problem without putting undue strain on the physician or the office staff.

DBPCFC can be used in circumstances in which the reaction is said to occur hours to days after the food is ingested. Despite numerous claims and anecdotes, delayed onset food reactions caused by immunologic mechanisms are rare and limited, primarily, to diarrheal symptoms observed in young children, including gluten-sensitive enteropathy and cow's milk and soy protein enteropathies.¹⁵⁻²³ "Delayed-in-time" or true late-phase reactions in the intestine, skin, and respiratory system caused by foods may occur, but their existence must be confirmed and studied with objective techniques. Meanwhile, DBPCFC can still be used to help confirm or dismiss foods as a cause of delayed reactions.

If the patient reports that a single dose of food produces symptoms hours to days later, then this amount of food is administered blindly in the physician's office, and the patient is told to return when the symptoms occur. The challenge is arranged, if this is possible, so that the symptoms occur during the daytime. Use of a placebo in this situation is essential to confirm any reaction. At least two visits and two sets of challenges may be necessary. It is often optimal to crossover the placebo and food several times to ensure that the reaction is reproducible. This is crucial when the symptoms are subjective. Moreover, when the symptoms are subjective, it is important to repeat the challenge after several months to determine whether or not the problem has persisted.

When the patient claims that the food must be administered multiple times to elicit the symptoms, food and placebo capsules are taken home by the patient with instructions about when the capsules should be administered. These challenges must nearly always be performed with capsules. The allergist is cautioned not to undertake this type of challenge unless he be-

lieves the patient will truly be objective and not attempt to open the capsules to discern their contents. During this type of challenge, the patient will be required to maintain a symptom diary appropriate for the set of circumstances under study. It is paramount that if the patient has a strongly held belief about the outcome, it would be better for all concerned not to administer the challenge until it can be performed under direct observation. Anytime challenges are performed away from a physician's observation, positive results should be regarded with skepticism unless the symptoms can be confirmed objectively. Challenges at home should *NEVER* be performed if there is even a remote chance of a severe reaction developing.

The combined experience of the authors with DBPCFC is presented in Table I with a summary of the foods that were confirmed by challenge. Summary data from different investigators studying different aspects of food allergy are also presented in Table I. It is useful to observe the frequency with which DBPCFC confirms suspected food reactions and which foods are repeatedly responsible for objectively reproduced symptoms.

Treatment of adverse reactions during challenge

Since adverse reactions, some potentially severe, may occur during challenge, prompt management is necessary. Appropriate personnel and equipment should be available to treat anaphylactic reactions, as outlined in the Position Statement, "Personnel and equipment to treat systemic reactions caused by immunotherapy with allergic extracts," by the Executive Committee of the Academy of Allergy and Immunology.²⁴ Detailed description of the treatment of adverse allergen-induced reactions is beyond the scope of this article, but the allergist performing food challenges must be particularly trained in the treatment of anaphylaxis (see standard allergy textbooks). For any severe reaction to a food challenge, epinephrine (subcutaneously or intramuscularly) is the drug of choice. Antihistamines should be administered in addition. In situations in which shock is developing, appropriate intravenous fluid replacement should be begun promptly. If the symptoms do not promptly resolve, or if they recur after treatment, gastric lavage to remove remaining food antigen should be considered.

Longitudinal management after positive food challenges

At the present time, avoidance with a program of regular rechallenge is the appropriate way to care for patients with confirmed food reactions. Educating pa-

tients (parents) to read food labels has been found to be a good means of providing an appropriate avoidance diet. This involves teaching them words that will appear on food labels indicating the presence of specific food antigens, such as egg, milk, soy, etc.²⁵ An emergency kit with epinephrine (Epipen; Center Laboratories, Port Washington, N.Y., and Ana-kit; Hollister-Stier Laboratories, Seattle, Wash.) should be available to all patients with confirmed severe food reactions. Medications, such as cromolyn and antihistamines administered orally, have not been adequately or systematically proved to be effective for the prevention of proved adverse food reactions; therefore, their routine use cannot be recommended.²⁶ Eventually, a safe and effective preventative program may be developed to allow patients to consume foods to which they are sensitive, but for the present time, avoidance of foods proved to produce symptoms is strongly recommended. Injections with food antigens have never been demonstrated by properly controlled studies to have any efficacy for reducing clinical symptoms, and injections of food extracts into truly food-allergic patients may be especially dangerous at the present time.

Food allergy is a dynamic process that changes as patients age. The natural history of food allergy for each food has not been completely delineated, but what is presently known strongly suggests that children, especially younger children, may lose their clinical reactivity to selected foods (milk, egg, soy, and wheat). However, at the present time, it would appear that children and adults may never lose their symptomatic hypersensitivity reactions to peanut and probably nonlegume nuts.^{27, 28} Thus, repeated food challenges are recommended under circumstances appropriate for the severity of the previous reactions. These intervals may be as often as once per month, or as infrequent as every few years, depending on the allergen involved and the symptoms occurring during the most recent challenge. Allergists have an obligation to help patients with diagnosed food allergy determine when and if the problem has resolved or determine that, as in the case of nuts, the problems will never resolve and that care to avoid accidental ingestion will always be essential.

A final caveat concerns anaphylactic reactions to foods. Because accidental ingestion is a constant problem and because some young children can be observed to "outgrow" their frightening reactions to milk, egg, and soy, it becomes the responsibility of allergists to help families determine if these severe reactions are subsiding.²⁹ After potential morbidity and mortality are thoroughly discussed with patients (and/or par-

ents), these challenges *MUST* be undertaken in facilities equipped to handle anaphylactic reactions, including complete resuscitation equipment and well-trained personnel. If extreme care is exerted, the reactions should be mild and can be aborted. Far better for this to take place in a properly equipped medical facility than in a classroom of second graders.

In conclusion, the authors of this article hope that it will prove practical for allergists who recognize the usefulness of DBPCFC as a daily procedure. Included are many practical recommendations to cover the vast majority of situations observed in the research, clinic, and office practice settings. Allergists should find these techniques very useful for solving patient problems and, with a little time and experience, DBPCFC can become an every-day office procedure.

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APPENDIX

Sample elimination diet: Foods allowed at mealtime

Rice	
Puffed rice	
Rice flakes	
Rice krispies	
Pineapple	} (canned fruit)
Apricots	
Cranberries	
Peaches	} (also juice or nectar of these)
Pears	
Apples	
Lamb	
Chicken	
Asparagus	
Beets	
Carrots	
Lettuce	
Sweet potato	
Tapioca	
White vinegar	
Olive oil	
Honey, 2 oz a day	
Cane sugar (or beet)	
Salt	