
Patterns of food hypersensitivity during sixteen years of double-blind, placebo-controlled food challenges

S. Allan Bock, MD, and F. M. Atkins, MD*

From the Department of Pediatrics, National Jewish Center for Immunology and Respiratory Medicine, Denver, Colorado

For 16 years the double-blind, placebo-controlled food challenge (DBPCFC) has been used at the National Jewish Center for Immunology and Respiratory Medicine to determine whether adverse reactions to foods do occur in children. The objective of these studies was to explore these reproducible adverse reactions and to characterize them. Although skin testing was performed on all subjects, a history of an adverse reaction to food and to subsequent DBPCFC were the only criteria for entry into this study. Of 480 children studied, 185 (39%) have had positive DBPCFC results. In these 480 children, 245 (24%) of 1014 DBPCFCs showed positive results. Egg, peanut, and cow milk accounted for 73% of the positive DBPCFC reactions, but many foods produced reactions. Skin test results were positive in most children with a positive DBPCFC reaction, but the large number of patients with asymptomatic hypersensitivity limited the accuracy of a positive skin test result alone as a predictor of clinical symptoms during food ingestion. Evaluation of results in this large number of children for a prolonged period revealed reproducible patterns of symptoms, timing, and incriminated foods. Placebo reactions were rare. The procedure was safe. Twelve youngsters with a negative DBPCFC result subsequently had positive reactions to open challenges when large amounts of the challenge food were used. In each of these cases the reactions were limited to areas of direct contact with the food or could be explained by the larger amount of food ingested during the open challenge. Multiple food hypersensitivity has been a rare finding. The DBPCFC should be the "gold standard" for both research and clinical diagnostic evaluations until it is superseded by methods that have yet to be developed. (J PEDIATR 1990;117:561-7)

In 1973, May^{1,2} began a systematic investigation of allergic reactions to foods by employing the double-blind, placebo-controlled food challenge as the "gold-standard" diagnostic test. Using this method, he was able to differen-

tiate factual histories of adverse reactions to foods from erroneous associations perpetuated by faulty observations. The study that he began continued prospectively as the standard diagnostic tool for evaluation of patients admitted

DBPCFC Double-blind, placebo-controlled food challenge

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Reprint requests: S. Allan Bock, MD, Department of Pediatrics, National Jewish Center for Immunology and Respiratory Medicine, 1400 Jackson St., Denver, CO 80206.

*In private practice in Washington, D.C.

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to the National Jewish Center for Immunology and Respiratory Medicine with histories of adverse reactions to foods; 480 children underwent 1014 food challenges. This report presents the data accumulated during these 16 years, which have been confirmed and extended by other authors,³⁻⁵ notably Sampson and McCaskill.³

Table I. Findings in 480 subjects up to age 19 years

	Findings by age of subjects		
	>3 Yr	<3 Yr	Findings in total group
Children challenged (No.)	315	165	480
Children with positive DBPCFC result (No.)	111	74	185*
Food challenges (No.)	669	345	1014
Positive reactions (No.)	133	112	245†
Positive skin test results/positive DBPCFC results	131/133	85/102‡	216/235§
Food			
Egg	30	32	62
Peanut	46	13	59
Milk	15	42	57
Nuts	23	2	25
Soy	3	12	15
Fish	5	3	8
Wheat	2	4	6
Pea	3	2	5
Shrimp	2	0	2
Chicken	2	0	2
Turkey	1	0	1
Banana	1	0	1
Rye	0	1	1
Squash	0	1	1
TOTAL	133	112	245

*Percentage of children challenged who showed positive DBPCFC result: 39%.

†Percentage of food challenges resulting in positive reactions: 24%.

‡Excludes late reactions.

§Percentage of positive skin test results for positive DBPCFC results: 92%.

METHODS

Subjects. The children evaluated ranged in age from 3 months to 19 years. The criteria for entry in the study was a history of adverse reaction to food and to a subsequent DBPCFC with the suspected food or foods. Once the history was obtained, food challenges were designed to reproduce the observations described by parents and patients.

Skin testing. Before food challenge, skin testing was performed with the prick-puncture technique and a 1:20 wt/vol concentration of food extracts, as previously described.^{1, 6, 7} Skin test results were not a criterion for entry into the study. A panel of preselected foods was sometimes used, but for some patients only those foods under suspicion were tested. Food extracts were obtained from Greer Laboratories Inc., Lenoir, N.C., Center Laboratories, Port Washington, N.Y., and Miles, Inc., Hollister-Stier Division, West Haven, Conn. Because of the lengthy duration of this study, it was not possible to use the same lots of extracts throughout. We defined a positive skin test result as a wheal 3 mm or greater in net diameter (after subtracting the diameter of any wheal

produced by the diluent control). Controls for skin testing were the diluent and histamine, 1 mg/ml, applied by the same technique.

Food challenge procedure. The history was elicited as an undirected account of symptoms associated with food ingestion. Special emphasis was placed on determining the timing between ingestion of the food and onset of symptoms, the quantity of food required to produce symptoms, the number of occurrences, and the most recent occurrence. After skin testing was performed, the patient was admitted to the pediatric special care unit, where the challenge was performed under continuous observation. The exact procedure has been described.^{1, 2, 8} Briefly, the food suspected of causing the adverse reaction was administered to the patient in opaque capsules (or was hidden in another vehicle for children too young to ingest capsules). The challenge vehicle or capsules were administered by one of the investigators or by one of the nurses. The person administering the challenge and the subject were unaware of the contents of the challenge. The parents were excluded from the pediatric special care unit while the challenge was in progress. The challenge was administered in graded amounts beginning with an amount approximately half of that reported to be the lowest quantity producing symptoms. The amount was increased in doubling increments at intervals slightly longer than those reported to be required to produce symptoms. Challenge and placebo days were initially separate. After several years, during which the initial experience demonstrated that unequivocal symptoms during challenge made the placebo challenge unnecessary, we sometimes omitted the placebo step. However, when the reaction was at all equivocal, the placebo was always used. Subjective symptoms (abdominal pain, pruritus, nausea) were not accepted as confirming the history, and the challenge was continued until observable signs were produced or 8 gm of dried food was given in a single dose. In patients having diarrhea as the only symptom after a milk challenge, a lactose tolerance test was performed and patients with lactase deficiency were eliminated from the study.

Food products. Food products were usually obtained from commercial grocery sources, either by the investigators or by the dietary department of the center. The majority of the foods were available in dried form, either from grocery stores or from local camping outlets. A few foods were lyophilized in the laboratory. Foods administered in lyophilized form were at times hidden in other foods by the dietary department for those subjects unable to swallow capsules. For example, shrimp has been administered as lyophilized powder in capsules or hidden in another food such as hamburger. For young children, foods have been disguised in formula, applesauce, or another vehicle as described elsewhere.⁸ The list of foods suspected and thus

Table II. Usefulness of skin tests for selected foods studied

Food	Predictive accuracy	Predictive accuracy before and after 3 yr of age and in total group		
		>3 Yr	<3 Yr	Total group
Egg	v	0.40	0.80	0.75
(n = 168)	g	0.96	0.91	0.95
Peanut	v	0.45	0.72	0.49
(n = 167)	g	1.00	1.00	1.00
Milk	v	0.81	0.80	0.64
(n = 206)	g	0.83	0.83	0.89
Nuts	v	0.43	0.50	0.45
(n = 64)	g	1.00	1.00	1.00
Wheat	v	0.17	0.39	0.27
(n = 64)	g	1.00	1.00	1.00
Fish*	v	0.17	1.00	0.25
(n = 64)	g	1.00	1.00	1.00

The following formulas were used to calculate predictive accuracy: $v = sP/sP + (1 - f)(1 - P)$ and $g = f(1 - P)/f(1 - P) + (1 - s)P$, where s = sensitivity, f = specificity, P = prevalence (number of confirmed reactions divided by total number of challenges); data not shown for these values.

n , Number of food challenges; v , positive predictive accuracy; g , negative predictive accuracy.

*Fish and shellfish.

Table III. Distribution, by age, of symptoms produced during DBPCFC

Age (yr)	No. of patients	No. of positive DBPCFC reactions			GI, C, R	GI, C	GI, R	C, R	GI, C, R	Total
		GI	C	R						
>3	111	133	34	28	9	15	13	16	18	133
<3	74	112	25	37	4	11	7	13	15	112
TOTAL	185	245	59	65	13	26	20	29	33	245

GI, Gastrointestinal symptoms (abdominal pain, vomiting, diarrhea); C, cutaneous symptoms (eczema, urticaria, erythematous rash); R, respiratory symptoms (sneeze, rhinorrhea, nasal obstruction, wheezing, cough, ocular sign).

tested included almost every constituent of the American diet.

RESULTS

Findings in children 3 years of age or older. In the earlier publications from this study, children were divided into two groups because of selection criteria, foods to which they reacted, and apparent differences in some findings.^{1,2} At this time, 315 children 3 years of age and older have been evaluated. Symptoms have been evoked during DBPCFC in 111 (35%) of 315 children (Table I). The 315 children have undergone 669 food challenges, and 133 (20%) of the challenges have produced symptoms. Of these 315 subjects, 14 (4%) were examined for gastrointestinal or behavioral symptoms, had no positive skin test results, had negative DBPCFC results, and thus would be considered nonatopic. Those foods confirmed as causing symptoms composed a relatively short list (Table I).

Prick or puncture skin test results were positive in 131 (98%) of 133 positive food challenge reactions. Table II presents the positive and negative predictive accuracies of

prick or puncture skin testing for egg, peanut, milk, nuts, wheat, and fish.

Despite many histories of delayed-onset reactions to foods in this group, none was confirmed by a positive DBPCFC result. Symptoms appeared within 2 hours of ingestion of the challenge food. Reactions occurred with as little as 20 mg and as much as 10 gm of dried food. When there was no reaction to a single challenge dose of 8 to 10 gm of dried food (often requiring a total dose of up to 22 gm in one day), the food was introduced openly into the diet and consumed under observation so that we could be certain that it was tolerated. Twelve subjects with negative DBPCFC results had a positive reaction to the open food challenge (see below).

Findings in children less than 3 years of age. One hundred sixty-five children less than 3 years of age have been examined. During DBPCFC, symptoms have been evoked in 74 (45%) of 165 children. These 165 children have undergone 345 food challenges, and 112 (32%) of the challenges have elicited symptoms. In 66 youngsters, 102 food challenges produced prompt onset of symptoms and were accompanied

Table IV. Number of subjects reacting to more than one food

Foods eliciting reaction	No. of subjects
Two foods*	
Peanut and egg	13
Milk and soy	3
Milk and egg	12
Other combination	14
TOTAL	42
Three foods†	
Milk, egg, peanut	2
Milk, egg, pea	1
Milk, peanut, pea	1
Peanut, egg, soy	1
Egg, wheat, rye	1
TOTAL	6
Four foods	
Egg, milk, peanut, trout	1
Egg, milk, peanut, cod	1
TOTAL	2
More than 4 foods‡	
General	1
Milk and soy plus other foods	1
TOTAL	2
Milk plus one or more other foods	
Milk and soy	4
Milk and one or more other foods, including soy	54

*Subjects less than 3 years of age: 17; subjects 3 years of age or older: 25.

†All patients were less than 3 years of age.

‡One of these subjects reacted to milk and soy as well as other foods.

by 85 positive reactions (83%) to prick or puncture skin tests (Table I). For the 17 reactions not accompanied by a positive skin test result, seven occurred in youngsters who might be considered nonatopic because they had only gastrointestinal symptoms during challenge and no positive skin test reaction to any allergen tested.

Eight children had the onset of symptoms after 4 hours. Six of these eight youngsters had milk (4/6) or milk and soy (2/6) protein enteropathies. One of the eight had biopsy-proven gluten-sensitive enteropathy. One of the eight had an evanescent but reproducible erythematous skin rash that occurred 6 to 12 hours after ingestion of milk. Parental permission to take a biopsy specimen of the rash was refused. Skin testing to detect IgE antibodies for the 10 foods was not helpful in these eight children, who should be viewed as being nonatopic.

Symptoms produced. Table III displays the symptoms produced during DBPCFC. For peanut, milk, and egg, the three foods responsible for 73% of the DBPCFCs, gastrointestinal symptoms accounted for the largest number of observed responses, followed by cutaneous symptoms. However, cutaneous reactions were the most frequent symptoms (for all foods tested), followed by gastrointestinal symp-

toms. Respiratory manifestations were recorded less frequently; asthma (wheezing) as the *sole* manifestation of an adverse reaction to food was noted in only four positive reactions to DBPCFC. Wheezing, with either gastrointestinal or cutaneous symptoms, occurred in 36 youngsters (all ages included); 64% of these children had either active atopic dermatitis or a history of atopic dermatitis. Although patients with histories of laryngospasm and a decrease in blood pressure were examined, challenges were performed with sufficient care that only four children had reactions that required injections of epinephrine. Despite precipitation of asthma requiring treatment in these youngsters, none had a significant decrease in blood pressure or compromise of the airway.

Subjects reacting to more than one food. Of 480 children, 52 (11%) reacted to two or more foods (Table IV). Foods producing the largest number of individual reactions (Table I) also contributed to symptoms in subjects with multiple hypersensitivities.

Fifty-four children in this study reacted to milk. Only four of them also had symptoms when ingesting soy. One of these four had biopsy-proven enteropathy, and another reacted to multiple foods.

Of the two children reacting to more than four foods, one reacted to five tree nuts but not to peanut or other foods, and one was a young child who, when originally examined, seemed to "react to everything" with such severity that at the time of the initial evaluation her growth was retarded. A prolonged diet of elemental formula and rice brought about a significant improvement in her growth and general well-being.

Subjects with negative DBPCFC and positive open food challenge results. Twelve subjects have had a negative DBPCFC result and a subsequent positive reaction to an open food challenge (Table V). Dose-response considerations were not satisfied by the blind challenge because the dose given during DBPCFC to 7 of 12 of these youngsters was too small to elicit symptoms. When a larger amount of food was given during the open challenge, symptoms occurred. This observation was confirmed by repeating the blind challenge with more food than was used in the initial DBPCFC. Five other patients had contact urticaria or complaints of oral pruritus and edema; contact of the food with the skin produced urticaria, and contact of the food with the oral mucosa elicited oropharyngeal symptoms. Skin test results were positive for all of these reactions.

DISCUSSION

For those skeptics who do not believe that food hypersensitivity exists, these objective observations and those of other authors^{3-5, 9, 10} demonstrate the ability of food proteins to produce immunologically mediated reactions.

Table V. Subjects with negative DBPCFC results* and positive open food challenge results

Patient No.	Age (yr)	Food	Wheal † (mm)	OFC dose	Symptom	Interpretation
1	7	Milk	5	16 oz	GI, R, C	Dose-response‡
2	6	Walnut	7	15 gm	C	Dose-response
3	2	Peanut	8	12 gm	GI	Dose-response
4	15	Milk	5	4 oz	R, C	Dose-response
5	6	Walnut	5	18 gm	C	Dose-response
6	12	Peanut	8	10 gm	GI, R, C	Dose-response
7	3	Milk	12	4 oz	GI, R	Dose-response
8	9	Peanut	5		CU	Contact reaction§
9	9	Fish	8		OS	Contact reaction
10	5	Egg	9		CU	Contact reaction
11	6	Milk	5		CU	Contact reaction
12	16	Shrimp	12		OS	Contact reaction

GI, Gastrointestinal symptoms; C, cutaneous symptoms; R, respiratory symptoms; CU, contact urticaria; OS, oral symptom.

*Double-blind, placebo-controlled food challenge in capsules negative at 8 gm.

†Wheal diameter of prick-puncture skin test.

‡A dose of 8 gm was inadequate to elicit symptoms.

§Reaction occurred only when food contacted skin or mouth.

Atopic dermatitis, which is included in these reproducible patterns, should be accepted as a manifestation of food hypersensitivity in some children with eczema.^{1-4, 9, 10} For those "true believers" who seem to attribute every symptom to food allergy, these objective observations should encourage them to be more critical about their own conclusions. In this highly selected population of children, only 39% had historical complaints objectively reproduced during DBPCFC. When children do have food hypersensitivity, it does not involve as many foods as are usually suspected. Thus food hypersensitivity does exist but is overreported.

Foods. Foods purported to produce adverse reactions compose a long list, but those which regularly elicit symptoms form a much shorter list. Ninety-five percent of the food reactions objectively confirmed in this study were to egg, peanut, milk, tree nuts, soy, fish, and wheat. Seventy-three percent of the symptomatic reactions were triggered by egg, peanut, and milk. In an earlier article, we described two mother-infant pairs in whom maternal ingestion of cow milk, followed by breast-feeding, produced symptoms in the infant.² As these studies have continued, we have seen additional children react to peanut, soy, and egg proteins apparently transmitted to them through maternal milk.

Symptoms. Behavioral changes as the sole manifestation of an adverse reaction to food were sought but not found. We did recognize irritability in children in whom significant abdominal and cutaneous reactions developed.

Several children in this study with negative food reactions were under study for chronic ear problems, including serous otitis media and recurrent purulent otitis media. Even in the children sensitized to food (as detected by skin testing), we

were unable to effect any clinical alteration in their ear problem either by using elimination diets or during food challenges with food to which they were sensitized. We also did not produce changes in headache patterns, including migraine headache, with elimination diet and DBPCFC; migraine headache was the subject of another, more intensive study.¹¹

Food challenge did not apparently change the clinical reactivity of any subject to the food used in the challenge. Ongoing contact with our patients has taught us that once the food is tolerated, it can be eaten as often as the patient desires, and in the usual portions.

Timing. During the past 16 years, numerous children have been examined for delayed-onset (or late) reaction to foods. Only the eight children described in the results have had late-onset symptoms. It seems reasonable to suspect the existence of food-induced late-phase reactions in the gastrointestinal tract, skin, or respiratory system. Just why they have been so difficult to observe is unclear. However, the notion that millions of children are having delayed food reactions seems unlikely in view of the results of this and other studies using DBPCFC.¹⁻¹³ Hill et al.¹⁴ described children with late reactions to cow milk, some of whom share characteristics with the patients having late-onset reactions as described above. However, Hill et al. defined the time of the reaction as being the time from the first dose of the challenge to the onset of symptoms. We and others^{3, 4} have defined the time of the reaction as being the duration from the last dose to the onset of symptoms.

Skin testing. The usefulness of properly performed and properly interpreted skin tests has been well docu-

mented.^{6,7,9,10} We have found that in children past their third birthday, a high percentage (98%) of positive food reactions during DBPCFC have been accompanied by positive prick or puncture skin test results when a 1:20 wt/vol concentration of commercial extract is used and a wheal diameter of 3 mm or greater is the criterion for positivity. In youngsters younger than 3 years of age, the percentage of positive skin test results accompanying a positive DBPCFC reaction is lower (83%) but is still substantial enough to be helpful. However, as pointed out by Sampson and Albergo,^{9,10} a negative skin test result has excellent predictive accuracy and is the most useful finding. Our predictive accuracy data are similar to those published by Sampson and Albergo,^{9,10} despite the fact that their population of subjects was selected for the presence of atopic dermatitis and our subjects were selected for a history of any symptom associated with food ingestion. Thus the studies from both centers show that a negative skin test result nearly always eliminates the possibility of IgE-mediated food hypersensitivity. This conclusion is even more accurate in the general population, in which the incidence of food hypersensitivity is much lower than in the study populations.¹⁰

Multiple food hypersensitivity. During our years of study, many children have come to us with complaints that numerous foods exacerbate their asthma or cause other symptoms. Despite these often impressive histories, only 11% of the subjects in this study (Table IV) reacted to more than one food. Perhaps most remarkable is that the number of children reacting to a large number of foods is so small. Only two subjects in this investigation reacted to more than four foods; one of these reacted to five types of nuts but to no other food. The other reacted to many foods as confirmed by DBPCFC; as she has grown, the number of forbidden foods has diminished but remains considerable. In many children, more than one food to which they were sensitized (positive skin test result) could be ingested simultaneously without producing symptoms.

Positive reaction to open food challenge after negative DBPCFC result. Twelve children in this study had negative DBPCFC results but reacted when the food was fed openly. The first 7 (1%) of these 480 children are of greatest concern because their symptoms were systemic. These observations illustrate the importance of administering an open challenge under observation even after a negative blind challenge result. If this is not possible, parents (or patients) should be instructed to add the food to the diet in small but increasing increments for several days.

The five other patients had oral symptoms (pruritus, sensation of swelling without detectable change in physical examination), urticaria or angioedema, or a combination thereof, where the incriminated food contacted the skin or

mucous membranes. To determine whether oral symptoms are due to direct contact or systemic absorption, one may need to conduct a blind challenge both with capsules and with the food placed in another vehicle. The double procedure allows contact of the suspected food with oral mucosal and pharyngeal tissues as well as a challenge in which the food bypasses the mouth. Our results suggest that the "oral allergy syndrome" required contact of the food with oropharyngeal structures; none of these children complained of oral symptoms during the blind challenge with capsules. This "syndrome" is in need of further objective, blind evaluation, probably in adults, in whom the problem seems to be more frequently reported. Too many of the studies of cross-reactivity between food and pollen have accepted patient reports as confirmation of the history of "oral allergy syndrome."¹⁵⁻¹⁸

The phenomenon of contact urticaria, especially contact angioedema, in children can be especially disconcerting to parents if the reaction occurs in the early years of life, before the child has had a chance to ingest the food in usual portions. Parents are frequently concerned about the likelihood of their child's having a systemic reaction when the food is ingested for the first time (usually away from home). The answer can be determined only by a careful food challenge.

Placebo foods or dextrose was administered for 82% of the positive DBPCFC results. The remaining reactions were so unequivocally positive or negative (food tolerated openly) that the placebo was unnecessary. Less than 10 reactions to placebo have occurred in these subjects; all of the associated symptoms were subjective—primarily vague abdominal discomfort or headache. Sampson and Albergo⁹ reported that placebo reactions were also unusual in their series. Most children probably do not believe that there are foods that they should avoid unless the evidence is strong. An occasional but unusual problem has been overcoming food aversions in children in whom histories of food reactions cannot be confirmed or who have lost their hypersensitivity to foods as they have grown.

This study was designed with practical matters in mind. No one protocol fits all situations. In fact, DBPCFC should be regarded as a diagnostic challenge, not a therapeutic trial as in a drug study. Thus, within certain predictable guidelines, each challenge is designed for each individual history. Early in these studies, all challenges were placebo controlled, with the placebo being administered in a similar manner to the challenge food but on a separate day. As the years have passed and our staff has been trained in these procedures, we have at times been able to eliminate the placebo or combine it with the food challenge. The observing nurse (or physician or both) and the patient know only that a challenge is being administered but are unaware of the

contents, so an unequivocal negative or positive result obviates the need for the placebo, especially because a negative result is followed by open administration of the food. The placebo must be used often enough to ensure that the observer or observers never assume that the placebo will not be used. We do not anticipate that primary care physicians will begin doing food challenges, but hope that eventually each community will have an allergist skilled in this procedure to whom patients with potential food hypersensitivity may be referred.

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