

The natural history of peanut allergy

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Between 1973 and 1985, 114 children, aged 2 to 14 years, underwent double-blind, placebo-controlled, food challenge (DBPCFC) to peanut. Thirty-two of 46 children with symptoms produced by DBPCFC to peanut were included in this longitudinal evaluation. Contact was made with the 32 subjects 2 to 14 years after their positive DBPCFC to peanut. All 32 subjects had exhibited a positive puncture skin test to peanut at the time of the original evaluation. Sixteen subjects had experienced symptoms caused by accidental peanut ingestion in the year before contact. Eight subjects had reacted to accidental ingestion in more than 1 year but less than 5 years before contact. Eight subjects had completely avoided peanut since the original evaluation and positive DBPCFC. No subjects could be demonstrated to have "outgrown" their peanut reactivity. All subjects tested continued to have skin reactivity to a puncture skin test with peanut extract. It appears uncommon for peanut-sensitive patients to lose their clinical reactivity, even after many years have elapsed. In addition, data were collected concerning reactions to other legumes and other (nonlegume) nuts. Only two patients with DBPCFC to peanut reacted on DBPCFC to soy or pea (one each). None of the subjects with a positive DBPCFC to peanut reacted to nonlegume nuts. (J ALLERGY CLIN IMMUNOL 1989;83:900-4.)

Accurate data concerning the natural history of peanut allergy are scant. Information obtained from adult patients with allergic reactions to peanut supports the notion that peanut-allergic reactions that begin at an early age may persist for many years.¹ The few previous studies available suggest that peanut allergy is "lost" infrequently.² Accurate information about this problem is important so that allergists may give patients, diagnosed as having peanut allergy, proper information about avoidance, treatment of accidental ingestion, and particularly about the length of time the problem is likely to persist, thus, making precautions necessary. Recent articles in both newspapers and the medical literature reveal that fatalities from peanut ingestion occur apparently even after long periods of abstention from peanut exposure.³ This study was designed to investigate the persistence of peanut allergy years after the diagnosis had been unequivocally confirmed by double-blind, food-challenge testing in a controlled setting and accompanied by skin testing to support the involvement of IgE.

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Abbreviation used

DBPCFC: Double-blind, placebo-controlled, food challenge

SUBJECTS AND METHODS

All children in this study were part of the larger ongoing studies of food allergy begun in 1973⁴ at the National Jewish Center for Immunology and Respiratory Medicine. Some of these youngsters participated in an earlier natural history study²; thus, it was particularly interesting to obtain further information about their subsequent exposure to peanuts. The subjects in this study were aged 1 to 14 years at the time they were originally evaluated. Each youngster had been referred to National Jewish for investigation of asthma and/or other atopic disorders, including food allergy. Children selected for study had an impressive history of adverse reaction to peanut and underwent a DBPCFC to peanut.

At the time of each patient's original evaluation at National Jewish, acquisition of the history and performance of skin testing was followed by administration of DBPCFC with incriminated foods as described previously.^{4,5} Skin testing was performed to all foods incriminated in the history and also to a standard battery including, but not limited to, pea, soy, nuts (walnut, almond, cashew, filbert, pecan, and pistachio), egg, milk, wheat, and corn. The extracts used for skin testing were commercially available, 1:20 wt/vol concentration, and were applied by the prick/puncture technique. The extract diluent was used as the negative control, and histamine, 1 mg/ml, was used as the positive control. The skin test site was examined after 15 to 20 minutes, and

the mean wheal diameter was measured and recorded. A skin test was considered to be positive if it produced a mean wheal diameter 3 mm or larger after subtraction of the mean wheal diameter of the diluent control.

Contact was made with these subjects and their parents in 1987 (1988 for patient No. 32), 2 to 13 years after their DBPCFC to peanut at the time of their initial evaluation. Telephone interviews were conducted recording information concerning (1) precautions taken to avoid peanut ingestion, (2) the most recent ingestion of peanut (accidental or intentional), (3) the symptoms that occurred, (4) the treatment required, (5) any other symptomatic ingestion since the original DBPCFC, and (6) any further evaluation including skin testing or subsequent deliberate challenges with peanut under medical supervision. (There were none, and all patients declined an offer to arrange further oral challenges.)

RESULTS

Peanut reactions

The summary of results of challenges and contacts in the youngsters involved in this investigation are presented in Table I. Between 1974 and 1985, 114 children, aged 1 to 14 years, were evaluated by double-blind peanut challenge because of a history of adverse reaction to peanut. Of these children, 68 had a negative double-blind peanut challenge and were able to eat peanuts without a problem. Forty-six children had a positive double-blind peanut challenge. Their adverse reaction consisted of gastrointestinal, cutaneous, and/or respiratory symptoms. (No children exhibited cardiovascular changes during challenge.)

Of the 46 children with positive double-blind peanut challenge, 10 could not be located, four had died of asthma (not asthma induced by peanut ingestion), and 32 children were contacted. All 32 patients attempted to avoid peanut ingestion. However, 16 children had experienced an accidental ingestion in the year before contact that led to symptoms less than, or as significant as, those symptoms produced by the double-blind challenge. No patient contacted had experienced anaphylaxis requiring emergency measures. Eight patients had accidentally ingested peanut more than 1 year but less than 5 years before being contacted. The interval between the initial evaluation and a reaction on subsequent peanut ingestion was 7 years or more in 19 patients, 3 years in five patients, and 2 years in one patient. Eight patients managed complete avoidance of all peanut since the double-blind peanut challenge in the hospital.

The details of the 32 patients included in this study are presented in Table II. Several important points should be noted. All children had a positive puncture skin test at the time of the original evaluation. The

TABLE I. Summary of results

Total No. of patients undergoing peanut DBPCFC 1974-1985	114
No. of patients with negative DBPCFC to peanut	68
No. of patients with positive DBPCFC to peanut	46
No. of patients lost to contact	10
No. of patients deceased (of asthma)	4
No. of patients contacted	32
Attempts of 32 patients to avoid peanut ingestion	
Accidental ingestion in the last year	16
Accidental ingestion 1 or more year but 5 or fewer years	8
Completely avoided since original DBFC	8

DBFC, Double-blind food challenge.

range of mean wheal diameters accompanying a positive double-blind peanut challenge was as small as 3 mm and as large as 25 mm. Examination of the skin test column in Table II strongly suggests that there is not a linear correlation between the size of the peanut skin test and the probability of a positive double-blind peanut challenge. Seven patients did have subsequent puncture skin tests at National Jewish as noted, and the skin test in all continued to be positive 2 to 10 years after the original skin test and double-blind peanut challenge.

Patient No. 11 did consent, in 1980, to undergo another double-blind peanut challenge that was positive and produced symptoms similar to the challenge in 1977. Patient No. 32 is perhaps the most interesting child in the study. He originally entered these studies in 1976 when he was evaluated and followed for anaphylaxis to milk. He gradually lost this severe reactivity, as has been previously reported.⁶ In 1978, his mother noted gastrointestinal symptoms on ingestion of peanut, and it was removed from his diet. In 1980 he was found to tolerate a small amount of peanut butter and was reported previously to have lost his sensitivity to peanut.² Between 1980 and 1987, the quantity of peanut consumed was not documented but was quite small and infrequent since the family was always concerned that a more severe reaction might occur. Then, in 1987, an accidental ingestion produced a symptomatic reaction, and peanut has been avoided since that time.

Other legumes

Because claims have been made concerning the cross-reactivity of legumes by skin testing, by in vitro laboratory methods, and clinically,⁷ and because patients with peanut allergy often report reactions to nuts

TABLE II. Positive peanut double-blind food challenge in patients

No.	Age (yr)	Initial evaluation			Subsequent exposure			Comment
		DBPCFC yr	DBPCFC Sx	PST*	Age	Yr	Sx	
1	14	1974	GI, S	7	26	1986	GI, S, R	PST-7 (80)
2	11	1974	R, S	6	24	1987	R	
3	10	1974	GI	10	18	1982	S	
4	13	1974	GI, S	7	24	1985	S, R	
5	6	1975	GI	5	15	1985	R	
6	8	1976	GI, S	11	Avoided exposure			
7	7	1977	GI, R, S	25	15	1984	R, S	
8	2	1977	R, S	22	12	1987	R, S	PST-6 (80)
9	11	1977	GI, R	12	21	1987	R, S	
10	12	1977	GI, R, S	8	Avoided exposure			
11	13	1977	GI, S	5	16	1980	GI, S†	PST-8 (80)
					Avoided since 1980			
12	2	1977	R, S	8	9	1984	R	PST-5 (80)
13	11	1978	GI	5	Avoided exposure			
14	1	1978	S	9	9	1985	S	
15	11	1978	GI	9	20	1987	R	
16	5	1978	R, S	6	12	1987	GI, R	PST-5 (87)
17	5	1979	S	8	14	1987	GI, R, S	
18	6	1979	S	12	14	1987	R	
19	14	1979	GI	7	22	1987	R	
20	8	1979	GI, R	8	Avoided exposure			
21	7	1979	GI, R	12	Avoided exposure			
22	3	1980	GI, R, S	9	10	1987	GI, R	
23	10	1980	S	4	17	1987	R	
24	12	1980	GI	10	Avoided exposure			
25	10	1980	GI	16	17	1987	S	
26	2	1984	GI, R, S	7	Avoided exposure			
27	6	1984	GI	12	9	1987	R, S	
28	4	1984	R, S	9	7	1987	R, S	
29	3	1984	GI, R, S	20	6	1987	GI, R	PST-10 (87)
30	1	1984	GI, R, S	3	3	1987	R	
31	5	1985	GI	12	7	1987	GI	
32	3	1978	GI	7				
	5	1980	Tolerated small amount PST-8 (80)					
	12	1987	GI (accidental ingestion) PST-5 (88)					

Sx, symptoms; PST, puncture skin test; S, urticaria, angioedema, and atopic dermatitis; GI, nausea, vomiting, diarrhea, and abdominal pain; R, ocular pruritus, erythema, swelling, rhinorrhea, sneezing, oral pruritus, laryngeal edema, wheezing, and cough.

*Mean wheal diameter of PST in millimeters (after subtracting diluent control).

†During DBPCFC in 1980.

(nonlegume) or avoid nuts entirely, we examined data concerning these issues. Each of 32 patients with a positive double-blind peanut challenge had been skin tested to pea and soy. Fifteen patients had a positive skin test to pea, 17 had a positive skin test to soy, 10 had a positive skin test to both, and 10 patients had a negative skin test to both. Despite the frequency of positive skin tests, only one patient with a positive double-blind peanut challenge had a positive double-blind soy challenge; only one (different) patient had a positive double-blind pea challenge.

Two subjects from the overall food studies had positive DBPCFC to pea; one subject also had a positive

DBPCFC to peanut, as noted above. Fourteen patients from the overall food studies had positive DBPCFC to soy; only the one subject mentioned in the above paragraph was found to have a positive DBPCFC to peanut.

Other (nonlegume) nuts

Despite histories to the contrary at the time of hospitalization, no patient with a positive double-blind peanut challenge had a positive challenge to any other nut during the hospitalization. Nineteen of the 32 subjects in this study with a positive double-blind peanut challenge were skin tested to one or more nuts; 12 of

these 19 children had a positive skin test to one of more of the other nuts (walnut, 11; filbert, 10; cashew, 9; almond, 6; pecan, 6; and pistachio, 6). To examine skin test responses in these 32 atopic children another way, skin test reactions by the same technique with the same concentration of extract performed at the same time were examined to egg, milk, wheat, and corn. Twenty-two subjects had a positive skin test reaction to egg, 12 to milk, six to wheat, and two subjects to corn. Only two of these positive skin tests were accompanied by a positive DBPCFC, and both positive tests were to egg. The remainder of these skin tests represent the documentation of immunologically detectable antibody, which is clinically unimportant during usual ingestion conditions (asymptomatic sensitivity).

During the same time period, 14 different children were evaluated for adverse reactions to nuts. Eight of these subjects reported no symptoms on peanut ingestion, and the other six subjects who were avoiding peanut had a negative DBPCFC to peanut. A positive DBPCFC occurred during 19 challenges with nuts. The nuts producing the 19 positive DBPCFC in these 14 children were walnut, 7; cashew, 6; pecan, 3; pistachio, 2; and filbert, 1. One patient reacted to five nuts, one patient, to two nuts, and the other 12 patients reacted to a single nut each.

DISCUSSION

This longitudinal study has resulted in some very useful information and clarified some important points about the natural history of peanut allergy. Previously, most longitudinal studies of the natural history of food allergy had been performed in younger children whose problem foods were egg and milk,^{2, 8-12} whereas our knowledge of the natural history of reactions to nuts, peanuts, and shellfish is very limited. This study suggests that peanut allergy is rarely outgrown; in fact, no children in this group who were exposed to peanut by ingestion have been able to tolerate peanut 2 to 14 years after an unequivocal diagnosis with double-blind food challenge to achieve objective results. Obviously, it would be optimal to have undertaken peanut DBPCFC in each of these subjects at the time of follow-up. Clearly, longer term studies of larger numbers of patients will be required to confirm these results. In fact, the ability of two subjects to tolerate peanut ingestion subsequent to an earlier symptomatic DBPCFC has been demonstrated (Sampson HA. Personal communication). However, the fact that in this study subjects retained marked reactivity to peanut ingestion for more than a decade supports the conclusion that peanut allergy is long lasting.

The frequency of accidental ingestion is at once fascinating and frightening. All subjects made an ef-

fort to avoid all peanut ingestion, eight succeeded, and 24 subjects failed, demonstrating how many ways an apparently obvious food can be hidden in our diet. Each of these youngsters had been instructed about peanut avoidance at the time DBPCFC was positive while they were in the hospital. An attempt was made to educate the subjects about the variety of disguises in which peanut could appear. Clearly, the success of this educational process was limited. Fortunately, none of the accidental exposures resulted in catastrophe. An attempt was also made to acquaint these patients with the advisability of carrying and using, when it was appropriate, emergency epinephrine. Clearly, we need more effective methods of educating truly food-allergic individuals in both avoidance and treatment. Further studies in the area of the natural history of food allergy should determine which foods are a long-lasting problem and which food reactions are likely to resolve with time.

The sensitivity of peanut-sensitive individuals to peanut oil was addressed in four patients of this study. Each of these patients received 30 ml of commercial peanut oil by DBPCFC without reaction. None of the other patients in our study reported convincing histories of reactions after ingestion of products containing peanut oil. These results, and the awareness of the study by Taylor et al.¹³ in which 10 patients with histories of systemic reactions to peanut did not experience symptoms on DBPCFC with peanut oil, convinced us that further challenges with commercial peanut oil in these patients were unnecessary. As reviewed by Taylor et al.,¹³ virtually all peanut oil sold for both commercial and domestic uses in the United States is processed by one manufacturer and contains no detectable protein. However, peanut oil and other oils used to fry peanut-containing foods could retain peanut allergens and pose a potential risk to peanut-sensitive individuals.

The question of the persistence of allergic reactions to foods raises the issue of the ethics of repeated challenge of subjects with a history of a marked reaction and especially the propriety of the initial challenge of subjects with a history of a potentially life-threatening reaction to food. There are two sides to this question, both brought out by the present investigation. On the negative side of rechallenge is the advisability of making patients ill, particularly with a history of severe reaction to confirm the presence and subsequently the continuation of a food reaction. In fact, the major reason that so few patients in this study were deliberately rechallenged was that they declined the opportunity. This was more likely with peanut-sensitive patients than with subjects reacting to other foods, as experienced in the earlier study, which included some of these same subjects.²

The positive side of challenge is the importance of confirmation of the history under observation in a controlled setting in which proper emergency care may be provided if it is necessary. Controlled challenge allows the provision of a graded dose beginning with a very small amount of the suspected food and increasing the amount in small increments so that severe reactions should be avoided. It is crucial to confirm the original suspicion to educate patients about avoidance of the correct food. Willingness to use this approach resulted in the gratifying observation that young children lost their life-threatening reactivity to egg, milk, and soy in some cases.⁶ Perhaps future studies will demonstrate that the persistence of severe reactions to some foods is so unlikely to remit that they should be avoided permanently, but until this information is firmly established, the argument can be advanced that periodic challenge under controlled observation will demonstrate the continuing need for and reinforcement of avoidance of foods that can produce significant symptoms.

Finally, the other area of interest revealed by this investigation is the lack of clinically significant cross-reactivity between peanut, other legumes, and, particularly, nuts. The general lack of cross-reactivity in peanut-allergic patients between peanut and nuts underscores the conclusion that each food stands alone, and instructing patients to avoid all foods in a food group (based on botanical relationships rather than immunologic relationships) is a disservice that complicates an already trying problem. It is the frequent habit of peanut-allergic patients to avoid all nuts despite a lack of history of reaction in many cases. This would not appear to be necessary or at least any suspicious history should be confirmed by DBPCFC. Whether or not there is frequent clinical or immunologic cross-reactivity between nuts remains an area in need of study. However, of the 14 nut-sensitive patients mentioned above, one reacted to two nuts and one reacted to five nuts during DBPCFC with suspected nuts. The other 12 patients only reacted to a single nut. It is interesting that there are accumulating studies of immunologic cross-reactivity between foods that are apparently botanically unrelated.¹⁴⁻¹⁸ These findings will be placed on a firmer foundation when the immunologic information is correlated with the results of DBPCFC. Meanwhile, these studies point to areas in need of further investigation with respect to immunologic cross-reactivity and the natural history

of symptomatic reactions to ingested, inhaled, and contacted allergens.

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