Peanut allergy: Recurrence and its management

David M. Fleischer, MD,[a] Mary Kay Conover-Walker, MSN, RN, CRNP,[a] Lynn Christie, MS, RD, LD,[b] A. Wesley Burks, MD,[c] and Robert A. Wood, MD[a]

Baltimore, Md, Little Rock, Ark, and Durham, NC

Background: Although peanut allergy may recur, the frequency with which this occurs is unknown.
Objective: The goals of this study were to determine the rate of peanut allergy recurrence, identify risk factors for recurrent peanut allergy, and develop specific recommendations for the treatment of patients with resolved peanut allergy.
Methods: Children who outgrew peanut allergy were evaluated with questionnaires, skin tests, and peanut-specific IgE levels. Patients were invited to undergo a double-blind, placebo-controlled food challenge (DBPCFC) unless the history of a possible recurrence reaction was so convincing that a challenge would be potentially dangerous.
Results: Sixty-eight patients were evaluated. Forty-seven patients continued to tolerate peanut, of whom 34 ingested concentrated peanut products at least once per month and 13 ate peanut infrequently or in limited amounts but passed a DBPCFC. The status of 18 patients was indeterminate because they ate peanut infrequently or in limited amounts and declined to have a DBPCFC. After excluding 12 patients originally diagnosed with peanut allergy based solely on a positive skin prick test or peanut-specific IgE level, 3 of 15 patients who consumed peanut infrequently or in limited amounts had recurrences, compared with no recurrences in the 23 patients who ate peanut frequently ($P = .025$). The recurrence rate was 7.9 (95% CI, 1.7% to 21.4%).
Conclusion: Children who outgrow peanut allergy are at risk for recurrence, and this risk is significantly higher for patients who continue largely to avoid peanut after resolution of their allergy. On the basis of these findings, we now recommend that patients eat peanut frequently and carry epinephrine indefinitely until they have demonstrated ongoing peanut tolerance. (J Allergy Clin Immunol 2004;114:1195-201.)

Key words: *Peanut allergy, recurrence, food challenge, RAST, food hypersensitivity*

Peanut allergy is common, affecting about 1% of the population,[1] and it was once thought to be a lifelong problem. Fortunately, we now know that about 20% of children outgrow their peanut allergy.[2] There is now a new concern, however, for this group of patients with resolved peanut allergy: the possibility of a recurrence of their allergy after introduction of peanut into the diet. Recurrence of peanut allergy appears to be uncommon because there have been only a few reported cases in the literature of children becoming resensitized to peanut after previously passing a peanut challenge.[3,4]

In a study we recently completed,[5] a follow-up questionnaire was given to patients who had passed a peanut challenge to determine whether peanut had been reintroduced into the diet, how frequently it was consumed, and whether there was any evidence of recurrence. We found that although 97% of the 64 patients surveyed had consumed peanut after passing their challenge and only 2 patients had reactions suspicious for a recurrence, more than 70% of these patients consumed peanut infrequently or in small amounts, making it impossible to assess accurately the rate of recurrence. In this study, we sought to define more clearly how often peanut allergy recurs, identify any risk factors for this recurrence, and develop more specific follow-up recommendations for the treatment of patients who have outgrown their peanut allergy.

Abbreviations used
DBPCFC: Double-blind, placebo-controlled food challenge
FEIA: Fluorescent-enzyme immunoassay
kU_A/L: Kilounits of antibody per liter
PN-IgE: Peanut-specific IgE
SPT: Skin prick test

METHODS

Study population

Patients diagnosed with peanut allergy who had undergone and passed an oral peanut challenge from January 1997 to April 2003 were identified from the Johns Hopkins Pediatric Allergy Clinic, the Arkansas Children's Hospital Pediatric Allergy Clinic, and the private practice of 1 of the investigators (R. A. W.). A total of 96 patients were identified, and letters describing the study were mailed to these families. All patients were 4 years or older at the time of initial challenge, and these peanut challenges, either open or double-blind, placebo-controlled food challenges (DBPCFCs), were performed as part of the routine clinical care of these patients or as part of ongoing research studies. Patients had been initially diagnosed to have peanut allergy if they met 1 of the following criteria: (1) a history of an acute reaction after ingesting peanut and a positive skin prick test (SPT), a positive peanut-specific IgE (PN-IgE) level (>0.35 kilounits of antibody per liter [kU_A/L]), or a positive food challenge, or (2) no

From [a]the Department of Pediatrics, Johns Hopkins University School of Medicine, Baltimore; [b]the Department of Pediatrics, University of Arkansas for Medical Sciences and Arkansas Children's Hospital; and [c]the Department of Pediatrics, Duke University School of Medicine, Durham.
Supported by National Institutes of Health training grant T32 AI 07007 from the National Institute of Allergy and Infectious Disease, the Eudowood Foundation for the Consumptives of Maryland, the Myra Reinhard Family Foundation, and General Clinical Research Center grants M01-RR000052 and M01-RR14288.
Received for publication July 16, 2004; revised August 18, 2004; accepted for publication August 24, 2004.
Reprint requests: Robert A. Wood, MD, Johns Hopkins Hospital, CMSC 1102, 600 N Wolfe Street, Baltimore, MD 21287. E-mail: rwood@jhmi.edu.
0091-6749/$30.00

doi:10.1016/j.jaci.2004.08.035

history of peanut ingestion but a positive SPT or PN-IgE level. The study protocol was approved by the investigational review boards of the Johns Hopkins University School of Medicine and the University of Arkansas for Medical Sciences.

Patients accompanied by their parents were seen in the General Clinical Research Centers at the Johns Hopkins Hospital or the Arkansas Children's Hospital. A questionnaire was administered to establish a detailed history of peanut ingestion since passing the peanut challenge, including whether families still read food labels looking for peanut, whether patients had eaten peanut products since passing the challenge, what types of peanut products they ate, how frequently they ate them, and whether there was any evidence of a recurrence of their peanut allergy. The types of peanut-containing foods were broken down into the following categories: (1) those that "may contain peanut," ie, foods that do not explicitly contain concentrated forms of peanut, such as products labeled "may contain peanut," ice creams, Asian foods, and baked goods; and (2) foods that contain concentrated forms of peanut such as candy (including Reese's products, peanut M & M's, and Snickers), peanut butter, and shelled peanuts. Information about the presence of other food allergies, whether still present or outgrown, and the presence of other atopic diseases was also obtained.

Medications, including antihistamines (short-acting, 72 hours; long-acting, 7 days), β-agonists (12 hours), and cromolyn (12 hours), were restricted before the first visit when skin testing was performed and before food challenges.

Laboratory studies

SPTs. Skin prick tests were performed through a standard technique with Sharp-Test applicators (Panatrax, Placentia, Calif). A glycerinated peanut extract (1:20; Greer Laboratories, Lenoir, NC), a positive control (histamine; Hollister-Stier Laboratories, Spokane, Wash), and a negative control (saline solution; Hollister-Stier Laboratories) were applied. The mean diameters of both the wheal and erythema were measured after 15 minutes. To be considered positive, the wheal had to be at least 3 mm greater than that of the negative control. A scoring system was used that compared each patient's peanut result to the histamine result as follows: 0, no wheal present; 1+, wheal less than half of the histamine diameter; 2+, wheal greater than or equal to half of the histamine diameter; 3+, wheal equal to the histamine diameter; 4+, wheal greater than the histamine diameter but less than 2 times the histamine diameter; and 5+, wheal greater than or equal to 2 times the histamine diameter.

CAP system fluorescent-enzyme immunoassay (FEIA). Venous serum samples were analyzed for circulating IgE to peanut with the CAP System FEIA (Pharmacia, Uppsala, Sweden). The assay had a lower limit of detection of <0.35 kU_A/L and an upper limit of >100 kU_A/L.

Peanut challenges. For the DBPCFCs, 8 g of peanut protein (fully defatted peanut flour from Nutrin Corp, Washington, DC) was disguised in either a chocolate brownie that contained vanilla extract or a ground chicken patty with ketchup. As texture and flavor control, ground oat flour (Old Fashioned Quaker Oats, Chicago, Ill) was used in the placebo food. Both the peanut flour–containing foods and the placebos were free of milk, egg, soy, and wheat. A physician, nurse practitioner, and/or nurse who were blinded to the testing materials administered the challenge in 6 divided doses. The first dose contained 0.4 g peanut protein (5% of the challenge), and subsequent doses were increased 0.8 g (10%), 1.2 g (15%), 1.6 g (20%), 2 g (25%), and 2 g (25%). The active and placebo challenges were performed either on the same day, with 3 hours between the last ingestion of food in the first challenge and the start of the next challenge, or on 2 separate days. After each challenge, the patients were observed for several hours. At any sign of objective or subjective symptoms deemed clinically significant, the challenge was terminated, and appropriate medical treatment was provided. The nutrition department of the Pediatric Clinical Research Unit of the General Clinical Research Center prepared and randomized each challenge.

Statistical analysis

For the purpose of analysis, patients were divided into the following 3 categories on the basis of questionnaire results regarding the type of peanut products eaten, the frequency with which they were eaten, and food challenge results: (1) patients who clearly tolerated peanut, as defined by 1 of the following criteria: (a) they consumed concentrated forms of peanut frequently, defined as at least once a month, or (b) they passed a DBPCFC to peanut regardless of whether they ate peanut frequently or infrequently; (2) patients whose tolerance of peanut was indeterminate, as defined by both of the following criteria: (a) they either consumed peanut in limited amounts, which meant eating foods that "may contain peanut," such as ice cream, ethnic foods, baked goods, and other foods that stated "may contain peanut" at any frequency; or they consumed concentrated forms of peanut rarely, defined as several times per year, and (b) they declined to undergo a DBPCFC to peanut; and (3) patients who had a recurrence of their peanut allergy, as defined by 1 of the following criteria: (a) they had a possible allergic reaction to peanut in an outside environment and subsequently failed a DBPCFC to peanut in the study, or (b) they had a convincing allergic reaction to peanut in an outside environment, and a DBPCFC was deferred because the PN-IgE level was dangerously high.

The Mann-Whitney *U* test was used for comparison of continuous variables, including PN-IgE levels, age, and skin test wheal size, whereas the χ^2 test was used to compare dichotomous variables, such as sex, current peanut consumption, history of other food allergy, and the presence of other atopic diseases. Negative PN-IgE levels, <0.35 kU_A/L, and PN-IgE levels >100 kU_A/L were arbitrarily assigned levels of 0.1 and 100, respectively, for the purpose of analysis. The Cuzick's test for trend was used to assess the interval time of follow-up across the strata of types of label reading.

RESULTS

A total of 68 of 96 possible patients (71%), 60 from Johns Hopkins Hospital and 8 from Arkansas Children's Hospital, participated in the study and are described in Table I. All 68 patients completed the questionnaire, and 21 patients underwent DBPCFCs. On the basis of these results (Table II), there were 34 patients who clearly continued to tolerate peanut because they consumed concentrated forms of peanut frequently. Thirty-one of the remaining 34 patients consumed only "may contain peanut" products, and the other 3 consumed concentrated peanut products, but only several times per year. Seven of the 21 patients who were challenged were in the category of consuming concentrated forms of peanut frequently, and all passed. The remaining 14 patients ate peanut in limited amounts, of whom 13 passed and 1 failed. Therefore, there were a total of 47 patients who continued to tolerate peanut: 34 patients who ingested concentrated peanut products frequently and 13 who ate peanut in limited amounts but passed a DBPCFC. Twelve of these 47 patients were diagnosed with peanut allergy solely on the basis of a positive SPT or PN-IgE level, 11 of whom ate peanut frequently, whereas the other did not but passed

TABLE I. Patient characteristics

	Clearly tolerate (n = 47)	Indeterminate (n = 18)	Recurrence (n = 3)	Total (n = 68)
Male	28 (60%)	12 (67%)	0	40 (59%)
Female	19 (40%)	6 (33%)	3 (100%)	28 (41%)
Age at initial diagnosis	(n = 47)	(n = 18)	(n = 3)	(n = 68)
Range, y	0.5-2.9	0.8-2.5	0.83-1	0.5-4
Median, y	1.2	1.05	0.83	1.1
PN-IgE, initial diagnosis	(n = 17)	(n = 5)	(n = 2)	(n = 24)
Range, kU_A/L	<0.35-8.96	<0.35-52.9	2.79-10.4	<0.35-52.9
Median, kU_A/L	1.1	0.83	6.6	1.15
Number diagnosed by history	35 (74%)	14 (78%)	3 (100%)	52 (76%)
Number diagnosed by SPT or PN-IgE level	12 (26%)	4 (22%)	0	16 (24%)
Age, initial challenge	(n = 47)	(n = 18)	(n = 3)	(n = 68)
Range, y	3.5-17.7	4-14.1	4.5-5.5	4-17.7
Median, y	5.8	5.9	4.8	5.8
PN-IgE, initial challenge	(n = 47)	(n = 18)	(n = 3)	(n = 68)
Range	<0.35-8.37	<0.35-4.13	0.66-1.9	<0.35-8.37
Median	<0.35	<0.35	1.1	<0.35
Current age	(n = 47)	(n = 18)	(n = 3)	(n = 68)
Range, y	5.1-21.4	6.5-17.8	6.3-8.9	5.2-21.4
Median, y	8.3	8.9	6.9	8.5
Follow-up	(n = 47)	(n = 18)	(n = 3)	(n = 68)
Range, y	0.3-5.8	1.1-5.3	1.4-4.1	0.3-5.8
Median, y	1.8	2.25	1.8	1.95
PN-IgE at follow-up	(n = 32)	(n = 10)	(n = 3)	(n = 45)
Range	<0.35-54	<0.35-4.85	4.92 to >100	<0.35 to >100
Median	0.61	<0.35	19.8	0.61

a DBPCFC in this follow-up study. There were 18 patients whose ongoing tolerance of peanut was indeterminate because they ate peanut only in limited amounts and declined to have a DBPCFC. The remaining 3 patients had recurrences of their peanut allergy and are described in more detail.

Patient 1, a 6.9-year-old girl who presented at age 10 months with urticaria and facial angioedema immediately after eating a part of a peanut butter sandwich, passed an initial peanut food challenge at age 5.5 years with a PN-IgE level of 0.66 kU_A/L. She subsequently occasionally ate ''may contain peanut'' products only. Approximately 1.4 years after the initial challenge, she ate a cookie that contained peanut, and within 15 minutes, she developed throat and abdominal pain and vomiting. Her repeat PN-IgE level was 4.92 kU_A/L, and her SPT to peanut was positive, with a wheal of 9 mm (4+). After consuming 15% of the nonplacebo food (unblinded after the DBPCFC was completed), she developed abdominal pain with emesis, congestion, rhinorrhea, sneezing, and facial erythema. She was given diphenhydramine with initial resolution of symptoms, but 20 minutes later, she developed total-body erythema and again vomited. She was then given intramuscular epinephrine and oral prednisolone with prompt resolution of all symptoms.

Patient 2, a 6.3-year-old girl, presented at age 1 year with generalized urticaria and facial angioedema within 5 minutes of eating a peanut butter cracker. Her PN-IgE level at diagnosis was 2.79 kU_A/L, and she had no history of other food allergies. She passed a challenge at age 4.5 years with a PN-IgE level of 1.1 kU_A/L. She ate ''may contain peanut'' products frequently until approximately 1.8 years after the initial challenge, when she had 2 bites of Butterfinger ice cream and within 15 minutes developed urticaria, coughing, difficulty breathing, throat tightness, abdominal pain, vomiting, and diarrhea. She was given diphenhydramine, and her symptoms gradually resolved. A repeat PN-IgE level was >100 kU_A/L. A SPT was not performed, and a DBPCFC was deferred because of the severity of the reaction and the high PN-IgE level.

Patient 3, a 9-year-old girl, ate a small amount of peanut butter at 11 months and developed generalized erythema and hives 15 minutes later. Her initial PN-IgE level at diagnosis was 10.4 kU_A/L, and she had no other food allergies. After passing a peanut challenge at age 4.8 years with a PN-IgE level of 1.9 kU_A/L, she continued to avoid all peanuts. Four years later, she developed urticaria on her

TABLE II. Questionnaire results: eating frequency

	May contain peanut products* (%)	Concentrated peanut products† (%)
Never	0	0
Occasionally‡	8 (12)	3 (4)
Frequently‡	13 (19)	13 (19)
Regularly‡	10 (15)	16 (24)
Daily‡	0	5 (7)

*Products labeled as such, ice cream, ethnic foods, and baked goods.
†Peanut candy, peanut butter, shelled peanuts.
‡*Occasionally*, Several times/y; *frequently*, at least once/mo; *regularly*, approximately once/wk; *daily*, approximately every day.

TABLE III. Patients with possible allergic reactions and outcomes

Patient number	Age of initial reaction (y)	Sensitization history	Age passed initial challenge (y)	Age at possible recurrent symptoms (y)	Symptoms of possible recurrence	Current PN-IgE and SPT	Outcome
1	1.4	Angioedema, total body erythema at first reaction; SPT^+ at 1.4 y; PN-IgE <0.35 at challenge.	4.8	7.8	Throat tightness	SPT^-; repeat PN-IgE not performed	Eaten PN M & M's since without problem
2	2	Urticaria, emesis, and wheezing at first reaction; SPT^+; PN-IgE <0.35 at diagnosis and challenge	9.6	12	Pruritic, papular rash	PN-IgE <0.35; SPT not performed	Continues to eat
3	2	Eczema flare at first reaction; SPT^+ at 1.4 y (wheal 4 mm); PN-IgE 8.37	5.5	9	Urticaria	PN-IgE 7.27; SPT 2+	Passed challenge
4	2	Urticaria, vomiting at first reaction; PN-IgE 1.21 at 6.2 y, <0.35 at challenge	5.1	7.7	Urticaria, emesis	PN-IgE 1.88; SPT not performed	Passed challenge
5	2.1	Facial angioedema; SPT^+ at 2.5 y; PN-IgE <0.35 at 2.5 y and at challenge	4.7	5.5	Skin and oral pruritus	PN-IgE 0.46; SPT 1+	Passed challenge
6	1.1	Erythematous rash at first reaction; SPT 4+ and PN-IgE 2.33 at 1.2 y; PN-IgE <0.35 at challenge	5	5.5	Urticaria and oral pruritus	PN-IgE <0.35; SPT negative	Passed challenge
7	0.9	Urticaria at first reaction; PN-IgE 5.42 at 1.3 y, PN-IgE <0.35 at challenge	6.5	8.2	Oral pruritus	Declined repeat PN-IgE and SPT	Declined challenge
8	1.1	Never ate before challenge; SPT^+; PN-IgE 1.1 at diagnosis and challenge	4.4	5.8	Urticaria around mouth; oral tingling	PN-IgE 0.6; SPT 5+	Declined challenge

TABLE IV. Questionnaire results: label reading

	Always	Sometimes	Never
Number that still read labels for peanut	19* (28%)	24 (35%)	25 (37%)
Age at follow-up, y			
Range	5.2-12	5.7-21.4	5.2-17.8
Median	7.2	7.9	9
Interval time of follow-up, y			
Range	0.3-4.8	0.8-4.8	0.7-5.8
Median	0.9†	1.7†	3.5†

*Includes 3 patients who read labels primarily because of tree nut allergy.
†$P = .01$ for trend of decreasing label reading frequency and increasing interval time of follow-up.

arm after skin contact to peanut butter. A repeat PN-IgE level was 19.8 kU_A/L, and the family declined a DBPCFC because of concerns of a possible serious reaction.

Other questionnaire results revealed that there were 8 other patients in addition to these recurrences who had suspicious allergic reactions to peanut in the period between passing their initial challenge and follow-up. These patients are described in Table III. Two of these patients, who rarely ate peanut after passing their initial challenge, were reported as possible recurrences by Fleischer et al.[5] in a previous study, and they were examined further in this study. The first patient, patient 2 in Table III, consumed and has tolerated peanut since this previous publication, whereas the other, patient 4 in Table III, was subsequently challenged in this study and passed. Of the remaining 6 patients, 1 patient continues to eat peanut products without problems, 3 patients passed challenges, and 2 patients declined challenges. Further questionnaire results regarding family characteristics of label reading, broken down by the frequency of label reading and the number of years of follow-up, are described in Table IV. As the number of years from initial challenge to follow-up increased, the frequency of label reading significantly decreased ($P = .01$ for trend).

Skin prick tests were performed in 38 of the 68 patients, and wheal diameters ranged from 0 to 12 mm (median, 3 mm; Table V). PN-IgE levels at the time of initial diagnosis were available in only 24 patients, ranging from <0.35 to 52.9 kU_A/L (median, 1.15 kU_A/L). PN-IgE levels at the time of the initial challenge for each group of patients ranged from <0.35 to 8.37 kU_A/L (median, <0.35 kU_A/L; see Fig E1 in the Journal's Online Repository at www.mosby.com/jaci). Repeat PN-IgE levels at the time of follow-up were performed in 45 of the 68 patients, and ranged from <0.35 to >100 kU_A/L (median, 0.61 kU_A/L; see Fig E2 in the Online Repository at www.mosby.com/jaci). The median PN-IgE levels at initial diagnosis, at initial challenge, and at follow-up, as well as the median SPT wheal diameter were not statistically different among patients who clearly tolerated peanut, patients whose

peanut allergy status was indeterminate, and patients who had recurrent peanut allergy (data not shown).

Three patients had a significant rise in their PN-IgE level from the time of their initial peanut challenge to the time of follow-up, yet continued to tolerate peanut. The first patient had a PN-IgE level of 1.7 kU_A/L when she passed her initial challenge 1.4 years before follow-up. She eats peanut butter regularly and also passed a DBPCFC in this study with a PN-IgE level of 7.58 kU_A/L (5.42 kU_A/L on repeat testing from the same sample). The second patient passed his initial challenge 1.7 years before follow-up with a PN-IgE level of 5.8 kU_A/L. He eats peanut butter regularly, his repeat PN-IgE was 17.1 kU_A/L (17.1 kU_A/L on repeat testing from a second sample), and he did not have a DBPCFC. The third patient had a PN-IgE level of 0.54 when he passed his initial challenge 4.3 years before follow-up. His repeat PN-IgE level was 54 kU_A/L (38.4 kU_A/L on repeat testing from a second sample), and although he ate only peanut candy infrequently, he had no symptoms of a possible recurrence. He underwent a DBPCFC and passed.

Associated atopic disorders, including the presence of other past or current food allergies, are listed in Table E1 in the Journal's Online Repository (www.mosby.com/jaci). Overall, the study population was highly atopic, with 84% of patients having a atopic disorder other than food allergy, such as asthma (47%), allergic rhinitis (59%), or atopic dermatitis (35%). Approximately 50% of patients had outgrown another food allergy, and approximately one third still had other food allergies. The number and type of atopic disorders, including food allergies past or current, did not help predict who was more likely to have recurrent peanut allergy (data not shown).

From questionnaire and challenge results, a recurrence rate of 7.9% (95% CI, 1.7% to 21.4%) was calculated. This was determined from the number of recurrences (n = 3) divided by the total number of patients whose current peanut allergy status was definitively established (n = 38); patients who had never ingested peanut and thus were diagnosed by a positive SPT or PN-IgE level were not included in the recurrence rate calculation. This denominator consisted of the sum of patients with recurrent peanut allergy (n = 3), patients who clearly tolerated peanut by eating concentrated forms of peanut frequently (n = 23 patients, 7 of whom also passed a DBPCFC), and patients who ate peanut in limited amounts but passed a DBPCFC (n = 12). In the analysis of the relationship of peanut ingestion to the risk of recurrence, 3 of 15 patients who consumed peanut infrequently had recurrences, compared with no recurrences in the 23 patients who ate peanut frequently ($P = .025$).

TABLE V. SPT results

Skin test result	Clearly tolerate (n = 28)	Indeterminate (n = 9)	Recurrence (n = 1)	Total (n = 38)
0	12 (43%)	4 (44%)	0	16 (42%)
1+	4 (14%)	0	0	4 (10%)
2+	5 (18%)	1 (11%)	0	6 (16%)
3+	2 (7%)	3 (33%)	0	5 (13%)
4+	3 (11%))	0	1 (100%)	4 (10%)
5+	2 (7%)	1 (11%)	0	3 (8%)
Wheal diameter, mm				
Range	0-12	0-7	9	0-12
Median	2.5	4	(actual wheal)	3

DISCUSSION

In this study, we found 3 patients with recurrent peanut allergy, yielding a 7.9% recurrence rate in our patient population in whom current peanut allergic status was determined by questionnaire and DBPCFCs. There are several limitations in calculating the recurrence rate. First, the study population used to determine this rate was small, even though more than 70% of patients who were contacted agreed to participate in the study and it is the largest study of its kind since Busse et al[3] first estimated a recurrence rate of 14% after 3 of their 21 patients had recurrences. Second, 7.9% may be an overestimate or underestimate of the true recurrence rate for several reasons. There were 18 patients whose peanut allergic status was labeled as indeterminate because they did not consume peanut frequently and they declined to undergo a DBPCFC, and 2 of these patients had had suspicious reactions after peanut ingestion. Therefore, if any of these 18 patients had decided to undergo a food challenge, the recurrence rate could have been higher or lower. We also excluded 12 patients who had never ingested peanut and thus were diagnosed by a positive SPT or PN-IgE level only. If we were to add these patients to the calculated recurrence rate, the rate of recurrence would slightly decrease to 6% (95% CI, 1.3% to 16.5%).

One could also argue that we did not prove that patient 3, who developed urticaria only after skin contact with peanut butter, has a recurrence of her allergy. However, given that her current PN-IgE level was 19.8 kU_A/L, which is highly (>95%) predictive of a clinical reaction,[6] and the fact that she developed urticaria with peanut contact, we thought it was most reasonable to include her as a recurrence even though she did not undergo a DBPCFC. Finally, one can argue that our designation of patients' peanut-eating frequencies and the relative concentrations of peanut-containing products eaten were arbitrarily designated. However, we thought that if a patient consumes concentrated forms of peanut at least once a month, then they likely eat enough peanut protein to say that they continue to tolerate peanut, whether or not they were challenged again.

The exact mechanism by which peanut allergy may recur is not known, so it is difficult to analyze risk factors. However, we found that those patients who consumed concentrated forms of peanut frequently had a significantly lower chance of having a recurrence of their allergy. In fact, although it may represent selection bias, there were no recurrences in 23 patients who consumed peanut

frequently, compared with 3 recurrences in 15 patients who consumed limited amounts of peanut ($P = .025$). Although we know from our previous study that patients who have outgrown their peanut allergy often dislike the taste of peanut or are afraid to eat it and therefore limit the amount they consume,[5] it is possible that these patients who are not ingesting large amounts of peanut could be self-avoiding it because they never truly lost their sensitivity and have ongoing symptoms. However, this is unlikely because all patients in this study passed standardized food challenges in academic settings, and no patients besides those with recurrent allergy mentioned any symptoms after peanut ingestion since outgrowing their allergy.

There have been several other reports of recurrent peanut allergy that also found a higher risk of recurrence in patients who did not consume peanut frequently after passing a peanut challenge. In the first reports, Busse et al[3,4] described in an abstract and then a letter to the editor 3 patients who consumed peanut intermittently in small amounts after passing a food challenge to peanut and then reacquired their allergy 1 to 2 years later. In a second abstract, Kerr and Pong[7] described 4 patients with recurrent peanut allergy, 3 of whom refused to eat peanut after passing their initial challenge and became resensitized 1 to 6 years later. The fourth patient tolerated peanut twice within a week of the initial challenge and then developed abdominal cramps and vomiting after 2 further ingestions. In the final report, an abstract describing 5 patients with recurrent peanut allergy, Factor et al[8] found that whereas 2 of the 5 had never been offered peanut after their initial challenge, the remaining 3 ate peanut often. However, the types of peanut product ingested and what eating peanut ''often'' referred to were not mentioned in the text, so it is difficult to determine their true peanut intake. Thus, although it may be possible that patients who eat peanut frequently could develop recurrent peanut allergy, we think that the risk of recurrence is likely to be far greater if patients eat peanut less frequently or in limited amounts. This may be because ingesting small amounts of peanut intermittently is more likely to result in sensitization, compared with continuously eating small amounts or intermittently consuming large amounts of peanut, which might better sustain tolerance.[4]

Unfortunately, many patients who have outgrown their peanut allergy may be very reluctant to consume peanut products frequently because of both an ongoing dislike of peanut and an ongoing fear of a reaction, which may now in fact be worse given the risk of a recurrence of their allergy. In a previous study, we found that more than two thirds of patients who had outgrown peanut allergy ate peanut infrequently or in limited amounts.[5] This same trend can be seen in the results from this study, albeit to a lesser degree in that only 50% of patients in this study ate peanut in limited amounts. Also, as seen in the previous study, ongoing label reading is common in families after children outgrow their allergy,[5] although ongoing label reading does appear to decrease significantly over time, as seen by the fact that approximately one third of families always read labels approximately 1 year out from the challenge, approximately one third sometimes read labels approximately 1.5 years after the challenge, and approximately one third never read labels 3.5 years after the challenge ($P = .01$ for trend).

If patients are at risk for recurrence if they consume peanut infrequently or in limited amounts and a high percentage of patients continue largely to avoid peanut, then what is the best way to monitor patients for recurrence? Following SPTs are not likely to be helpful because many patients in this study still had significantly positive SPTs despite tolerating peanut in their diet. As for PN-IgE levels, 3 of our patients who continue to tolerate peanut had significant rises in their PN-IgE levels from the time of initial challenge to the time of follow-up, 2 of which were greater than the 95% predictive value (15 kU_A/L) of a clinical reaction.[6] On the other hand, 2 of our patients with recurrences also had significant rises in their PN-IgE level, and this knowledge could have served to warn us about their recurrences. On the basis of these findings, we recommend that patients with resolved peanut allergy who do not eat peanut frequently be evaluated by obtaining a PN-IgE level on an annual basis or if they have a suspicious allergic reaction to peanuts. On the basis of the results, allergists can then determine whether a repeat food challenge is warranted.

We conclude that patients who have outgrown peanut allergy have an approximately 8% chance of having a recurrence of their allergy, and the risk of recurrence is significantly higher in patients who essentially continue to avoid peanut after resolution of the allergy. Physicians who perform peanut challenges and take care of children with resolved peanut allergy need to inform patients and their families about the possibility of recurrent peanut allergy. Although we realize this is a small study to make global recommendations, we now recommend that our patients eat concentrated forms of peanut at least once a month after outgrowing their peanut allergy in an attempt to maintain peanut tolerance. We also recommend that patients and families who eat peanut frequently continue to carry injectable epinephrine for at least 1 year after passing their challenge. If they eat peanut only infrequently or in limited amounts, then patients should have epinephrine available indefinitely at all times because of their increased risk of recurrent allergy. Perhaps with further research, we will be better able to identify patients who have outgrown their peanut allergy who are truly at risk for recurrent allergy, and therefore be able to recommend that these patients continue to avoid peanut for life rather than risk the chance of having a serious or fatal allergic reaction in the future when their allergy may recur.

REFERENCES

1. Sicherer SH, Munoz-Furlong A, Sampson HA. Prevalence of peanut and tree nut allergy in the United States determined by means of a random digit dial telephone survey: a 5-year follow-up study. J Allergy Clin Immunol 2003;112:1203-7.
2. Skolnick HS, Conover-Walker MK, Koerner CB, Sampson HA, Burks AW, Wood RA. The natural history of peanut allergy. J Allergy Clin Immunol 2001;107:367-74.

3. Busse PJ, Noone SA, Nowak-Wegrzyn AH, Sampson HA, Sicherer SH. Recurrence of peanut allergy [abstract]. J Allergy Clin Immunol 2002; 109:s92.
4. Busse PJ, Nowak-Wegrzyn AH, Noone SA, Sampson HA, Sicherer SH. Recurrent peanut allergy [letter]. N Engl J Med 2002;347:1535-6.
5. Fleischer DM, Conover-Walker MK, Christie L, Burks AW, Wood RA. The natural progression of peanut allergy: resolution and the risk of recurrence. J Allergy Clin Immunol 2003;112:183-9.
6. Sampson HA, Ho DG. Relationship between food-specific IgE concentrations and the risk of positive food challenges in children and adolescents. J Allergy Clin Immunol 1997;100:444-51.
7. Kerr PE, Pong AH. Peanut resensitization after negative skins tests and negative oral challenge [abstract]. J Allergy Clin Immunol 2004;113:s151.
8. Factor JM, Mendelson LM, Rosen JP. Recurrence of peanut allergy cannot be predicted by continued avoidance or serum specific IgE [abstract]. J Allergy Clin Immunol 2003;111:s275.