

The natural history of peanut allergy in young children and its association with serum peanut-specific IgE

Timothy K. Vander Leek, MD, Andrew H. Liu, MD, Kay Stefanski, RN, Betty Blacker, LPN, and S. Allan Bock, MD

Objectives: To observe the nature and frequency of adverse reactions caused by accidental peanut exposure in young children with clinical peanut hypersensitivity and to determine the value of serum peanut-specific IgE levels during follow-up.

Study design: Eighty-three children with clinical peanut hypersensitivity diagnosed before their fourth birthdays were contacted yearly to track adverse peanut reactions. Serum peanut-specific IgE levels were determined in 51 of 83 subjects.

Results: Fifty-eight percent (31/53) of subjects followed up for 5 years experienced adverse reactions from accidental peanut exposure. Regardless of the nature of their initial reaction, the majority with subsequent reactions (52%, 31/60) experienced potentially life-threatening symptoms. The group with isolated skin symptoms (11/51, 22%) had lower serum peanut-specific IgE levels than the group with respiratory and/or gastrointestinal symptoms (40/51, 78%) (median: 1.25 kU_A/L vs 11.65 kU_A/L, $P = .004$, Wilcoxon rank sums test). Despite this, there was no threshold level below which only skin symptoms appeared to occur. Four selected subjects had negative double-blind placebo-controlled food challenge responses to peanuts during follow-up.

Conclusions: The majority of children with clinical peanut hypersensitivity followed up for 5 years will have adverse reactions from accidental peanut exposure. Symptoms experienced during subsequent adverse peanut reactions may not be consistent with symptoms reported during initial reactions. Therefore proper education regarding peanut avoidance and treatment of adverse reactions is necessary in all cases of clinical peanut hypersensitivity. Young children who are allergic to peanuts can lose clinical hypersensitivity. (J Pediatr 2000;137:749-55)

Exposure and sensitization to peanuts is common and often occurs early in life.^{1,2} Adverse reactions from accidental exposure are also common once an individual has developed clinical hypersensitivity to peanuts.^{3,4} Moreover, peanut

allergy is a major cause of morbidity and death in sensitized individuals (Bock SA, Munoz-Furlong A, Sampson HA, written communication, Feb 2000).⁵⁻⁸

In general, peanut allergy appears to be lifelong, based on long-term follow-

up of children with clinical peanut hypersensitivity that was confirmed

See editorial, p 741.

by double-blind placebo-controlled food challenge.³ "Clinical hypersensitivity" indicates that an individual has

From the Departments of Pediatrics, National Jewish Medical and Research Center, and University of Colorado Health Sciences Center, Denver, Colorado.

Dr Vander Leek is supported by American Academy of Allergy, Asthma and Immunology (AAAAI) A/I Clinical Fellowship; Dr Liu is supported by AAAAI/Education Research Trust, National Institutes of Health (No. M 01 RR00051).

Submitted for publication Feb 3, 2000; revision received May 3, 2000; accepted June 9, 2000.

Reprint requests: S. Allan Bock, MD, National Jewish Medical and Research Center, 1400 Jackson St, Rm J211, Denver, CO 80206.

Copyright © 2000 by Mosby, Inc.

0022-3476/2000/\$12.00 + 0 9/21/109376

doi:10.1067/mpd.2000.109376

DBPCFC	Double-blind placebo-controlled food challenge
IgE	Immunoglobulin E
kU _A /L	Kilounits of allergen-specific antibody per liter

developed allergic symptoms after eating the implicated food rather than

having IgE sensitization alone. None of the children could tolerate peanuts by 2 to 14 years after their initial positive response to food challenge with peanuts. In contrast, the majority of young children who have clinical milk or egg hypersensitivity will stop having allergic reactions to these foods as they grow older.⁹⁻¹² It has been hypothesized that young children with a history of milder allergic reactions to peanuts may be more likely to "outgrow" clinical peanut hypersensitivity. Up to 18% of children who present with a history of mild to moderate allergic reactions to peanuts will have no reaction when undergoing a food challenge with peanuts.¹³ In another study, 68 children had negative DBPCFC responses to peanuts after positive skin prick test responses to peanuts.³ Did these children represent a group that never had clinical peanut hypersensitivity, or had some of them actually "outgrown" it by the time they were challenged?

What is needed is a laboratory measurement that would identify individuals who are most likely to "outgrow" their clinical peanut hypersensitivity. Skin prick tests do not serve this purpose because the size of a skin test reaction to peanuts does not correlate with symptoms experienced during a food challenge with peanuts.¹⁴⁻¹⁷ Certain serum peanut-specific IgE levels are predictive of a positive food challenge response to peanuts in individuals with atopic dermatitis.¹⁸ However, it is not known whether these results can be generalized to all individuals with peanut allergy.

In this longitudinal study, a population of children who developed clinical peanut hypersensitivity before 4 years of age has been followed up longitudinally. The objectives of this study were to observe the frequency and nature of allergic reactions after accidental exposure to peanuts, to determine whether the nature of symptoms after exposure to peanuts changes over time, and to assess the value of serum peanut-spe-

cific IgE levels for ongoing follow-up within this population.

METHODS

Subjects with Clinical Hypersensitivity to Peanuts

Children (n = 102) who had adverse reactions to peanuts diagnosed before 4 years of age were identified. Subjects were included because they had: (1) a convincing history of clinical peanut hypersensitivity and/or a positive DBPCFC response to peanuts and (2) a positive skin prick test response to peanuts. After initial inclusion, subjects were contacted at least yearly to track adverse reactions caused by accidental exposure to peanuts. Nineteen subjects discontinued their participation in the study or were lost to follow-up for various reasons, leaving 83 for inclusion in the analysis.

The study was approved by the National Jewish Medical and Research Center Institutional Review Board. Informed consent was obtained from the parents or guardians of the children who served as subjects of this study.

Skin Prick Testing with Peanuts

Skin prick tests with peanuts were performed according to standard methods^{15,16} with commercially available peanut extracts. A skin test response was considered positive when the wheal measured after 15 to 20 minutes was at least 3 mm larger than the wheal of the negative control site.

Convincing History of Clinical Hypersensitivity to Peanuts

A history was considered to be convincing if allergic symptoms: (1) began within 60 minutes of an isolated exposure to peanuts and (2) involved the skin, respiratory tract, cardiovascular system, and/or gastrointestinal tract.^{4,13,19-21} All individuals were seen by a physician for confirmation of their history within 1 year of their reaction.

DBPCFCs with Peanuts

When clinically indicated, DBPCFCs with peanuts were performed as part of routine clinical care by using methods previously described.²² Patients were asked to stop medications that may interfere with challenge results: antihistamines (short-acting for 72 hours, long-acting for 5 days), β -agonists (short-acting for 12 hours, long-acting for 24 hours), theophylline (for 12 hours), and cromolyn (for 12 hours). Peanut challenges began in the morning, starting with the subject eating 0.5 g of pulverized peanuts hidden in chocolate pudding, and continuing at intervals of 20 to 30 minutes with doses of 1 g, 2 g, 4 g, and 8 g. If the subject did not have allergic symptoms after eating the 8-g dose, he or she consumed approximately double the amount of peanuts (without chocolate pudding) to be certain that no reaction occurred. If no reaction occurred, peanuts were added to the diet without restriction beginning the next day. The placebo challenges were done with the chocolate pudding alone.

Classification of Symptoms Experienced After Exposure to Peanuts

All allergic symptoms after exposure to peanuts were recorded, including reactions after accidental skin contact or ingestion and intentional (ie, DBPCFC) exposures. Symptoms were classified by organ system involvement and severity as follows:

1. Skin (non-life-threatening)
 - a. Contact reactions (no peanut ingestion)—hives/urticaria, erythematous flushing, cutaneous pruritus, cutaneous angioedema, and atopic dermatitis
 - b. Skin-limited symptoms after peanut ingestion—symptoms as above with contact reactions
2. Respiratory
 - a. Non-life-threatening—rhinitis, sneezing, an abnormal

Table. Age and number of subjects according to when they experienced their first reaction to peanuts

Age (mo) at time of first reaction	Symptoms of first reaction		Totals (%)
	No. with isolated skin symptoms (%)	No. with respiratory and/or gastrointestinal ± skin symptoms (%)	
<12	11 (13.3)	11 (13.3)	22 (26.5)
12-24	26 (31.3)	19 (22.9)	45 (54.2)
24-36	6 (7.2)	6 (7.2)	12 (14.5)
36-48	2 (2.4)	2 (2.4)	4 (4.8)
Totals (%)	45 (54.2)	38 (45.8)	83 (100)

sensation in the mouth and throat (eg, itching, a “funny” feeling), eye symptoms

b. Potentially life-threatening—throat tightness and angioedema, laryngeal angioedema, angioedema in the mouth, cough, wheeze, chest tightness, shortness of breath, noisy breathing, tachypnea, voice change

3. Gastrointestinal (non-life-threatening)—emesis, diarrhea, abdominal pain/cramping

4. Other (potentially life-threatening)—hypotension, loss of consciousness

determine statistical significance. Statistical significance was accepted when $P < .05$.

RESULTS

All subjects (57 boys and 26 girls) were enrolled at a median of 2.4 years of age (range, 0.4 to 6.8 years); all had clinical peanut hypersensitivity diagnosed before 4 years of age, and a positive skin prick test response to peanuts (Table). Subjects have been followed up prospectively for up to 22 years (median, 5.9 years; range, 1.4-22.4 years).

Adverse Reactions Caused by Accidental Exposure to Peanuts

Of the 83 subjects 60% (50) had a total of 115 documented adverse reactions caused by accidental exposure to peanuts during follow-up. They had a mean of 0.33 adverse reactions caused by accidental peanut exposure per year of follow-up (approximately 1 in every 3 years); 58% (31/53) of subjects followed up for 5 years and 75% (9/12) of subjects followed up for 10 years experienced adverse reactions caused by accidental peanut exposure. Of the 40% (33/83) of the population who did not experience adverse reactions caused by accidental peanut exposure during follow-up, none were followed up for >10 years, and the majority (76%, 25/33) were followed up for <6 years.

We have addressed the nature of adverse reactions to peanuts in two ways:

(1) grouping symptoms by severity (“non-life-threatening” and “potentially life-threatening”) and (2) grouping symptoms by organ system involvement (see Methods section). An analysis of adverse reactions by severity revealed that 73% of children (61/83) had initial non-life-threatening reactions, whereas 27% (22/83) had potentially life-threatening reactions (Fig 1). Of the children with initial non-life-threatening reactions who had additional reactions, 44% (19/43) had at least one potentially life-threatening reaction. Of those with potentially life-threatening first reactions who had additional reactions, 71% (12/17) had at least one potentially life-threatening reaction. There is a trend toward difference between the two groups with respect to the nature of their subsequent reactions ($P = .07$, χ^2 , Fig 1).

Alternatively, adverse reactions can be classified by organ system involvement (Fig 2). During their initial reactions, 12 children experienced skin symptoms alone after only skin contact with peanuts, whereas 26 others experienced only skin symptoms after eating peanuts. The remaining 45 children experienced respiratory and/or gastrointestinal symptoms (with or without skin symptoms) during their first reaction to peanuts.

Eight of the 12 children with skin contact reactions experienced a subsequent reaction caused by accidental peanut exposure. Of particular interest is that all 8 children (100%) experi-

Determination of Serum Peanut-Specific IgE Levels

Serum was obtained from 51 of 83 subjects and analyzed for peanut-specific IgE levels by using the Pharmacia CAP System (Pharmacia & Upjohn Diagnostics AB, Uppsala, Sweden). Results are reported as kilounits of allergen-specific antibody per liter (assay limits: 0.35-100 kU_A/L). For statistical analysis, measurements <0.35 kU_A/L and >100 kU_A/L were recorded as 0.34 kU_A/L and 101 kU_A/L, respectively.⁴

Statistical Methods

Data were recorded and analyzed by using the JMP statistical program, version 3.2.2 (SAS Institute Inc, Cary, NC). Analysis of variance, χ^2 test, and Wilcoxon rank sums test were used to

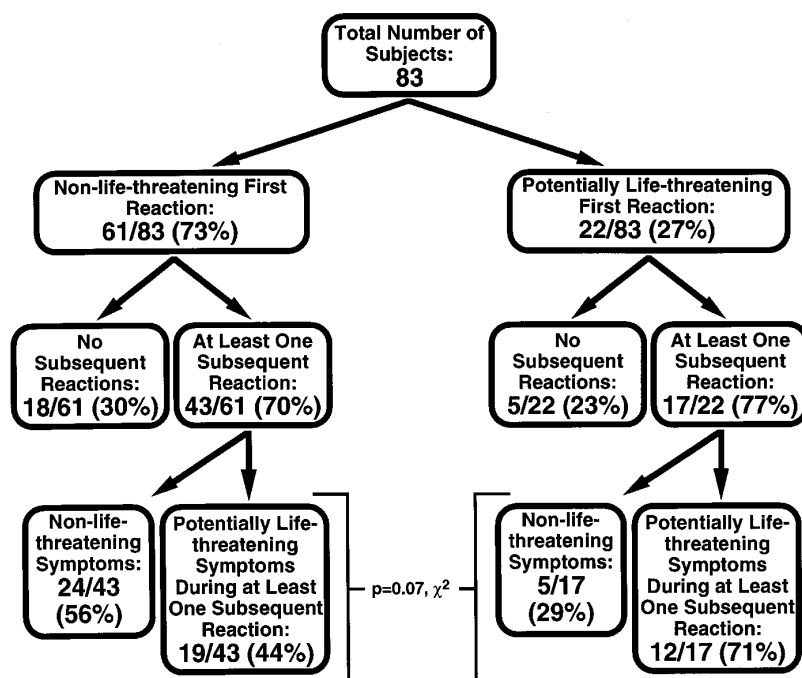


Fig 1. Clinical nature of adverse reactions from accidental peanut exposure based on classification by severity. Of those with potentially life-threatening first reactions who had a subsequent reaction, 71% had another potentially life-threatening reaction. Of note, even if their first reaction was non-life-threatening, 44% had potentially life-threatening subsequent reactions. Note that numbers in this figure refer only to reactions that occurred because of accidental peanut exposures and do not include reactions to peanut challenges.

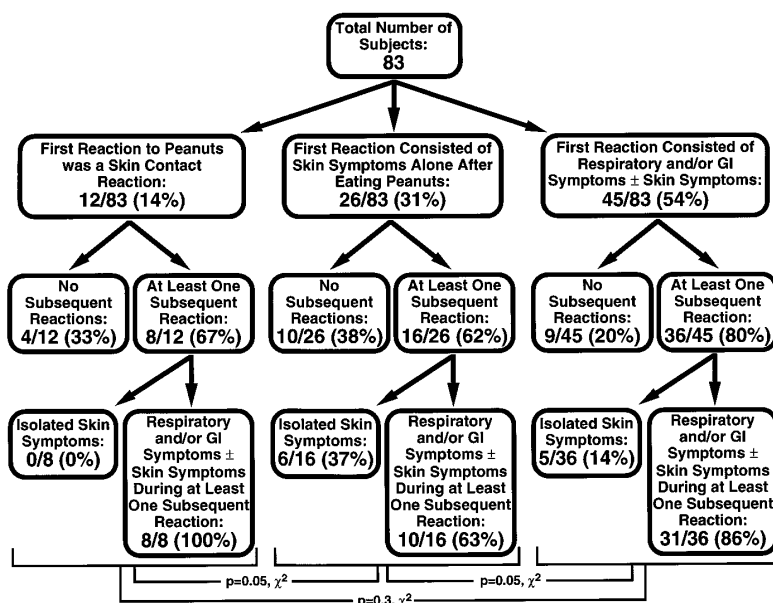


Fig 2. Clinical nature of adverse reactions from accidental peanut exposure based on classification by organ system involvement. Most children experienced respiratory and/or gastrointestinal symptoms during subsequent reactions, regardless of the nature of their initial reaction. Note that numbers in this figure include only reactions caused by accidental peanut exposures that occurred after their initial evaluation. *P* values indicate comparisons between groups with respect to symptoms experienced during subsequent reactions. *GI*, Gastrointestinal.

enced respiratory and/or gastrointestinal symptoms (with or without skin symptoms) during at least one subsequent reaction. Of the 26 children who initially had only skin symptoms after eating peanuts, 16 developed reactions caused by subsequent accidental peanut exposure; 10 of these children (63%) experienced respiratory and/or gastrointestinal symptoms (with or without skin symptoms) during at least one subsequent reaction.

Thirty-six children who experienced respiratory and/or gastrointestinal symptoms during their first reaction had subsequent adverse reactions caused by accidental peanut exposure (36/45). The majority (86%) experienced respiratory and/or gastrointestinal symptoms during at least one subsequent reaction (Fig 2).

There was no significant difference among the 3 groups with respect to the number of children experiencing subsequent adverse reactions ($P = .2$, χ^2), or with respect to the nature of subsequent reactions when the group of children with skin contact reactions and the group with respiratory and/or gastrointestinal symptoms were compared ($P = .3$, χ^2). However, the group of children with initial skin symptoms after ingestion had fewer subsequent respiratory and/or gastrointestinal symptoms than the group with initial skin contact reactions ($P = .05$, χ^2) and the group with initial respiratory and/or gastrointestinal symptoms ($P = .05$, χ^2) (Fig 2).

It is important to clarify that these numbers do not include any reactions that occurred as a result of food challenges with peanuts.

Serum Peanut-Specific IgE

Fifty-one children (51/83) had serum peanut-specific IgE determinations between 1.5 and 24.8 years of age (median age, 7.9 years), with values ranging from <0.35 kU_A/L to >100 kU_A/L (median, 9.33 kU_A/L). Eleven of the 51 (22%) children experienced only skin symptoms after skin contact with or ingestion of peanuts during their first reaction and

any subsequent reactions (including both accidental and food challenge exposures). These children had significantly lower serum peanut-specific IgE levels (median, 1.25 kU_A/L; range, <0.35-38.9 kU_A/L) than another 25% (13) who had isolated skin symptoms during their first reaction but had subsequent reactions that involved the respiratory and/or gastrointestinal tract (median, 24.1 kU_A/L; range, 2.46->100 kU_A/L, $P = .003$) (Fig 3). The 11 children who experienced only skin symptoms also had significantly lower serum peanut-specific IgE levels than the remaining 53% (27) who experienced respiratory and/or gastrointestinal symptoms during their first reactions (median, 10.4 kU_A/L; range, <0.35->100 kU_A/L, $P = .02$). Despite the significant difference in peanut-specific IgE levels between the groups, there was no identifiable threshold level below which only skin symptoms appeared to occur. There were no significant differences among these 3 groups with respect to age and years of follow-up.

Eighteen children each had two separate serum peanut-specific IgE determinations at least 10 months apart (mean, 1 year). No significant difference was found between the two values (data not shown).

DBPCFCs with Peanuts

Seventeen children underwent DBPCFCs with peanuts during the study period, and 4 had negative challenge responses. These latter 4 were selected for DBPCFC because of low serum peanut-specific IgE levels and a history suggesting that they had lost clinical hypersensitivity to peanuts. One child with a negative DBPCFC response to peanuts at 10 years of age had an undetectable serum peanut-specific IgE level (<0.35 kU_A/L) at the time of the challenge, after having a level of 0.473 kU_A/L obtained 14 months before. His only reaction to peanuts occurred 5 years before his food challenge and consisted of facial erythema and possible urticaria after

an isolated peanut ingestion. Another child had two reactions to peanuts when she was 3 years old, an undetectable serum peanut-specific IgE level at 7 years of age, and a negative DBPCFC response to peanuts when she was 8 years old. Her initial reaction involved the gastrointestinal tract, whereas her second involved only the skin.

The third child with a negative DBPCFC response to peanuts at 4 years of age had a serum peanut-specific IgE level of 1.05 kU_A/L at 7 years of age. He had experienced two reactions to peanuts at 8 and 12 months of age. The first reaction involved the skin and gastrointestinal tract, where-

as the second only involved the skin. A third known exposure at 3 years of age did not result in any symptoms. He subsequently tolerated 9 g of peanuts during a DBPCFC with peanuts and has been eating peanuts without any problem since that time.

The fourth child had a level of 0.397 kU_A/L 4 years after his only reaction to peanuts, which occurred at 17 months of age and was limited to the skin. He initially had a DBPCFC to peanuts at 3 years of age, during which he did not experience any symptoms; however, he refused to complete the open portion of the challenge at that time, and so could not truly be considered to have had a negative challenge

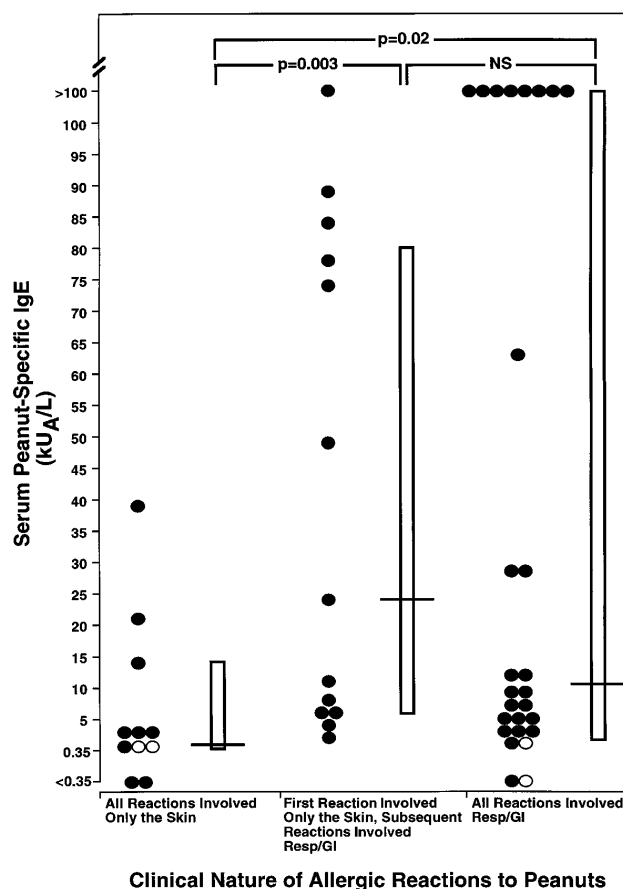


Fig 3. Clinical nature of adverse reactions to peanuts by peanut-specific IgE level. There is no threshold level below which only skin symptoms appeared to occur, despite lower serum peanut-specific IgE levels in the group with only skin symptoms than in the groups with respiratory and/or gastrointestinal symptoms. Open circles indicate individuals who had negative DBPCFC responses to peanuts subsequent to their adverse reactions to peanuts. Lines represent group medians; boxes represent 25% to 75% interquartile ranges. Note that the nature of the reactions described refers to those experienced after both accidental and peanut challenge exposures. kU_A/L, Kilounits of allergen-specific antibody per liter; Resp/GI, respiratory and/or gastrointestinal tract(s).

response. His response to a subsequent DBPCFC with peanuts at 6 years of age was negative; during that challenge he tolerated up to 17 g of peanuts.

DISCUSSION

This longitudinal study illustrates that young children with clinical hypersensitivity to peanuts frequently have subsequent reactions caused by accidental peanut exposure. The majority (58%) of subjects followed up for 5 years and 75% of subjects followed up for 10 years had reactions caused by accidental peanut exposure. This has previously been reported in older children and adults: 75% of 32 subjects with peanut allergy had adverse reactions caused by accidental peanut exposure at up to 14 years of follow-up in one study.³ In another study, 55% had accidental exposures to peanuts at a median of 5.4 years.⁴

It is generally believed that allergic reactions to peanuts remain consistent over time. However, when initial and subsequent reactions were compared in this population, the majority of children who first had only skin symptoms after eating peanuts experienced respiratory and/or gastrointestinal symptoms during a subsequent peanut exposure. All of those who initially had skin contact reactions (without eating peanuts) experienced respiratory and/or gastrointestinal symptoms during a subsequent peanut exposure. When symptoms are arbitrarily classified according to severity ("non-life-threatening" vs "potentially life-threatening"), even if the initial reaction was considered non-life-threatening, 44% had subsequent reactions that were potentially life-threatening. Similarly, in a study by Hourihane et al,¹⁹ 59% of 107 individuals with peanut allergy who were polled by questionnaire experienced mild symptoms (defined as urticaria and pruritus) during their first reaction but had more severe symp-

toms after a subsequent exposure to peanuts.¹⁹ Although the difference between groups classified by severity of reactions approaches significance, we believe that one should not predict a different prognosis for future reaction severity on the basis of the nature of a child's first reaction to peanuts. Furthermore, the group with first reactions consisting of skin symptoms after ingestion had fewer subsequent respiratory and/or gastrointestinal symptoms than either of the other two groups. Despite this, it is important to note that the majority of all subjects with subsequent reactions experienced respiratory and/or gastrointestinal symptoms, regardless of their initial reaction.

A number of explanations could account for a change in the nature of symptoms experienced in this population. Skin contact reactions could indicate individuals who were extremely sensitive to peanuts and therefore likely to experience more worrisome symptoms when peanuts were actually ingested. Others could have become more sensitive to peanuts since their first reactions. Individuals who experienced wheezing during a subsequent reaction could also have developed asthma during the interim period. Additionally, children could have experienced a change in the nature of their symptoms because they ingested a greater amount of peanuts. Experience with graded food challenges has shown that the degree of symptoms experienced as a result of food allergy may be related to the amount of allergen ingested.²³ This third explanation is less likely, however, because many accidental peanut exposures are the result of ingesting minute quantities of peanut "hidden" in other foods. Because many children were very young at the time of their initial reaction, it is conceivable that subjective respiratory or gastrointestinal tract symptoms (eg, oral pruritus and abdominal pain) could have been missed. If these symptoms were then reported during subsequent reac-

tions because the child was older, it could lead to a false impression that the symptoms had changed. Nevertheless, a need to properly educate children and their caregivers about peanut avoidance and treatment of adverse reactions still exists, regardless of the symptoms experienced (or reported) during an initial reaction to peanuts.

The group of children with only skin symptoms during their first and any subsequent reactions had significantly lower levels of serum peanut-specific IgE than those who experienced respiratory and/or gastrointestinal symptoms after peanut exposure. It would be tempting to suggest that serum peanut-specific IgE levels could predict future symptoms during adverse reactions to peanuts. However, because the overlap of individual values between groups is so great, we cannot suggest that these values have any prognostic value. Further study with food challenges at the time of peanut-specific IgE determinations is needed to substantiate these findings.

Finally, 4 selected individuals lost clinical hypersensitivity to peanuts during the follow-up period. All 4 had low serum peanut-specific IgE levels despite differing initial presentations. This suggests that a low serum peanut-specific IgE level in a child who has not had a reaction to peanuts for at least 1 to 2 years may help guide the clinician in deciding whether to proceed with a DBPCFC with peanuts.

In conclusion, the following observations and recommendations are made based on the findings of this longitudinal study of young children with peanut allergy. First, the majority of children with clinical peanut hypersensitivity followed up for 5 years will have adverse reactions caused by accidental peanut exposure. Second, the nature of symptoms experienced during subsequent adverse peanut reactions may not be consistent with symptoms experienced (or reported) during initial adverse reactions to peanuts. Therefore proper education regarding

peanut avoidance and treatment of adverse reactions is necessary in all cases of clinical peanut hypersensitivity. Finally, young children who are allergic to peanuts can lose clinical hypersensitivity to peanuts.

We thank F. M. Atkins, MD, Allen Adinoff, MD, and Leon Greos, MD, for referring subjects to this study.

REFERENCES

1. Ewan PW. Clinical study of peanut and nut allergy in 62 consecutive patients: new features and associations. *BMJ* 1996;312:1074-8.
2. Tariq SM, Stevens M, Matthews S, Ridout S, Twiselton R, Hide DW. Cohort study of peanut and tree nut sensitization by age of 4 years. *BMJ* 1996;313:514-7.
3. Bock SA, Atkins FM. The natural history of peanut allergy. *J Allergy Clin Immunol* 1989;83:900-4.
4. Sicherer SH, Burks AW, Sampson HA. Clinical features of acute allergic reactions to peanut and tree nuts in children [serial online]. *Pediatrics* 1998;102:e6.
5. Sampson HA, Mendelson L, Rosen JP. Fatal and near-fatal anaphylactic reactions to food in children and adolescents. *N Engl J Med* 1992;327:380-4.
6. Yunginger JW, Sweeney KG, Sturmer WQ, Giannandrea LA, Teigland JD, Bray M, et al. Fatal food-induced anaphylaxis. *JAMA* 1988;260:1450-2.
7. Kemp SF, Lockey RG, Wolf BL, Lieberman P. Anaphylaxis: a review of 266 cases. *Arch Intern Med* 1995;155:1749-54.
8. Pumphrey RSH, Stanworth SJ. The clinical spectrum of anaphylaxis in north-west England. *Clin Exp Allergy* 1996;26:1364-70.
9. Host A, Halken S. A prospective study of cow milk allergy in Danish infants during the first 3 years of life. Clinical course in relation to clinical and immunological type of hypersensitivity reaction. *Allergy* 1990;45:587-96.
10. Sampson HA, McCaskill CC. Food hypersensitivity and atopic dermatitis: evaluation of 113 patients. *J Pediatr* 1985;107:669-75.
11. Dannaeus A, Inganas M. A follow-up study of children with food allergy. Clinical course in relation to serum IgE- and IgG-antibody levels to milk, egg and fish. *Clin Allergy* 1981;11:533-9.
12. Bishop JM, Hill DJ, Hosking CS. Natural history of cow milk allergy: clinical outcome. *J Pediatr* 1990;116:862-7.
13. Hourihane JOB, Roberts SA, Warner JO. Resolution of peanut allergy: case-control study. *BMJ* 1998;316:1271-5.
14. Bock SA, Lee WY, Remigio L, Holst A, May CD. Appraisal of skin tests with food extracts for diagnosis of food hypersensitivity. *Clin Allergy* 1978;8:559-64.
15. Bock SA, Lee WY, Remigio LK, May CD. Studies of hypersensitivity reactions to foods in infants and children. *J Allergy Clin Immunol* 1978;62:327-34.
16. Sampson HA, Albergo R. Comparison of results of skin tests, RAST, and double-blind, placebo-controlled food challenges in children with atopic dermatitis. *J Allergy Clin Immunol* 1984;74:26-33.
17. Eigenmann PA, Sampson HA. Interpreting skin prick tests in the evaluation of food allergy in children. *Pediatr Allergy Immunol* 1998;9:186-91.
18. Sampson HA, Ho DG. Clinical aspects of allergic disease. Relationship between food-specific IgE concentration and risk of positive food challenges in children and adolescents. *J Allergy Clin Immunol* 1997;100:444-51.
19. Hourihane JOB, Kilburn SA, Dean P, Warner JO. Clinical characteristics of peanut allergy. *Clin Exp Allergy* 1997;27:634-9.
20. Hourihane JOB, Dean TP, Warner JO. Peanut allergy in relation to heredity, maternal diet, and other atopic diseases: results of a questionnaire survey, skin prick testing, and food challenges. *BMJ* 1996;313:518-21.
21. Sicherer SH, Munoz-Furlong BA, Burks AW, Sampson HA. Prevalence of peanut and tree nut allergy in the US determined by a random digit dial telephone survey. *J Allergy Clin Immunol* 1999;103:559-62.
22. Bock SA, Sampson HA, Atkins FM, Zeiger RS, Lehrer S, Sachs M, et al. Double-blind, placebo-controlled food challenge (DBPCFC) as an office procedure: a manual. *J Allergy Clin Immunol* 1988;82:986-97.
23. Bock SA, Atkins FM. Patterns of food hypersensitivity during sixteen years of double-blind, placebo-controlled food challenges. *J Pediatr* 1990;117:561-7.