

New insights on the natural history of peanut allergy

Over the past decade, a new appreciation has emerged concerning the allergic potential of peanut (*Arachis hypogaea*).^{1,2} Indeed, several features of peanut allergy conspire to make this legume infamous. First, peanut allergy is relatively common. Our study of the general US population indicates that 0.6%, or approximately 1.6 million Americans, are peanut allergic.³ A striking feature of peanut allergy is the young age of presentation, generally under age 2 years^{4,5,6} with approximately 75% of reactions occurring on the first known oral ingestion.^{2,6,7} The early development of clinical reactivity is probably related to the fact that peanut is introduced early,⁸ is common in the food supply, and can be passed in breast milk,^{2,9,10} thereby facilitating sensitization and recurrent exposure.

The second remarkable feature of peanut allergy is the severity of reactions. In our study, of 102 children with acute reactions to peanut, nearly half experienced symptoms in two or more organ systems and epinephrine was required for treatment in 19%.⁶ Peanut accounted for 7 of 13 published cases of fatal, food allergic reactions in the US.^{11,12} Because peanut is a hidden ingredient or potential contaminant in a number of processed foods, accidental ingestions are common.^{5,13} We found that 55% of peanut allergic children experienced a reaction to an accidental ingestion over a period of 5.4 years.⁶ The potential for accidental exposure affects the individual's approach to activities such as school,¹ dining out, parties, family activities and even commercial airline travel¹⁴ with a

significant impact on quality of life.¹⁵ Notwithstanding the high prevalence, severity and reaction rate of peanut allergy, the notion that peanut allergy is permanent makes the diagnosis all the more disheartening.

The dogma that peanut allergy does not resolve stems, in part, from observations that peanut allergy affects adults, and has a prevalence rate in adults that is similar to that in children.^{3,16} In 1989, Bock and Atkins¹⁷ reported a follow-up study on 32 peanut-allergic children (confirmed by double-blind, placebo-controlled oral food challenges) that gave specific evidence for the persistence of this allergy. Over the 2 to 14 years (mean, 7 years) of follow-up, none experienced resolution of the allergy (although 8 were never knowingly re-exposed). The authors cautioned that larger controlled studies would be needed to determine if peanut allergy was truly permanent.

In a study that could be considered a landmark in unraveling the epidemiology of peanut allergy in children, Tariq and colleagues⁵ reported a birth cohort study of peanut sensitization on the Isle of Wight, UK. Among 1,218 infants followed to age 4 years, 1.1% had a positive skin test to peanut and 0.5% had experienced a clinical reaction to peanut (6 of 13, or 46%, with a positive skin test had experienced a reaction). Two children of the six who reacted to peanut (at ages 9 months and 24 months) lost their clinical reactivity and one was documented to have converted from positive to negative on prick skin test to peanut over the 4 year period of evaluation. Thus, this epidemiologic study documented a high sensitization rate (1.1%), a modest reac-

tion rate (0.5%) and the potential for resolution of peanut allergy (33%).

Subsequent reports highlighted the potential for resolution of peanut allergy. In data presented in an abstract, Golding and colleagues¹⁸ found that 41% of 22 children with peanut allergy diagnosed by clinical histories of reaction before age 2 years, culled from a birth cohort of 14,210 in the UK, had outgrown their allergy by age 5 years. Those with persistent reactivity to peanut had a higher rate of asthma, atopic dermatitis and food allergy than those whose peanut allergy did not resolve. Hourihane and colleagues²⁰ have also shown that peanut allergy may resolve in young children when the allergy manifested first in infancy. This group performed oral challenges to peanut in 120 children with convincing histories of peanut allergy selected from 230 with peanut allergy based upon convincing history. Selection of children for oral challenges were individualized, but included criteria such as negative skin tests and possible ingestion without reaction. Twenty-two of the 120 children (18%) passed the oral challenge; this group experienced a first reaction at a mean of 11 months of age and were challenged at a median of 5 years. In a case-control comparison of 15 who experienced resolution to 15 subjects with persistent peanut allergy, the former group had smaller or negative prick skin tests (a cut-off for wheal of 6 mm had a 100% positive predictive value and 80% negative predictive value), a longer interval since their last reaction (median 40 months versus 12 months) and fewer additional food allergies. There was no difference in severity of initial reactions.

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In this month's *Annals*, Spergel and colleagues¹⁹ document several previously noted observations pertaining to the natural history of peanut allergy in young children: (1) the allergy may resolve in a subset of young children within 2 years of their last reaction (14 of 33, or 42%, of those challenged), (2) skin tests may revert to negative, and (3) resolvers have smaller skin tests than children with persistent allergy. In contrast to several of the previous reports, this study shows evidence that children with severe reactions may be less likely to have resolution of the allergy, and that resolution was not related to the number of other food allergies or atopic diseases. In addition, this report documents a child with a positive physician-supervised challenge reverting to a negative challenge. Lastly, the study includes information on 13 children who had positive skin tests to peanut and "refused to eat" the food; in these, 5 (40%) had a positive oral challenge.

How can we resolve the discrepancies among these various studies? Bock's study that showed persistence of peanut allergy was different from these recent studies in two respects: in Bock's study the allergy was initially documented by blinded oral food challenges and the age at initial documentation was 7 years. In contrast, the recent studies relied on possibly erroneous initial diagnosis based upon history, evaluated much younger children, and may have selected for children with milder phenotypes to undergo challenges (eg, Hourihane's selection of 52% and Spergel's selection of 16% of the total group to undergo challenges). Taken together, these studies indicate that infants may become tolerant of peanut, but once the allergy is established in early childhood, resolution is rare. Furthermore, Spergel's study¹⁹ and others^{5,21} show roughly half of children with positive skin tests who have avoided peanut for a number of reasons without a history of reactions are tolerant of peanut.

Further studies are needed to more accurately estimate the percentage of children who become tolerant of peanut, and to get a better understanding of factors that may indicate the development

of tolerance. Several studies have indicated that small or negative skin tests bode well for resolved allergy. In children with atopic dermatitis, a peanut-specific IgE concentration value greater than 15 kU/L (CAP-System FEIA, Pharmacia & UpJohn Diagnostics, Uppsala, Sweden) was highly predictive of clinical reactivity.²² Skolnick and colleagues²³ recently reported that 71% of a selected subset of children diagnosed peanut allergic when under age 2 years with peanut-specific IgE concentration below 2 kU/L when over age 4 years, tolerated an oral challenge to peanut.

The key to improved diagnosis, management, and treatment of peanut allergy is linked to unraveling the immunopathogenesis of tolerance. Alteration in gut permeability is not a likely explanation since peanut protein is fully capable of entering the circulation in immunologically intact form following ingestion, even in normal adults.²⁴ True immunologic tolerance is a more likely explanation. The tools are in place to evaluate the evolution of tolerance in peanut allergy. The major allergenic proteins of peanut have been identified and cloned, and B cell and T cell epitopes have been mapped. The stage is now set for more detailed basic, clinical and translational studies of the natural history of peanut allergy.

For the unfortunate majority with persistent peanut allergy, avoidance and emergency medications are a way of life as research into a variety of novel therapies (eg, anti-IgE antibodies, immunotherapy with engineered peptides, immunostimulatory sequences, etc) offer future hope. Our lesson from the recent studies is that physician-supervised oral food challenges are warranted in a "lower risk" subset of young children with peanut allergy so that we can allow these children and their families to lead more unrestricted lives.

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REFERENCES

1. Furlong TJ, Sicherer SH, Muñoz-Furlong A, Burks AW, Sampson HA. Establishment of a Registry for aller-

- gic reactions to peanut [abstract]. *J Allergy Clin Immunol* 1998;101:S104-S104.
2. Hourihane JO, 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. *Br Med J* 1996;313:518-521.
3. Sicherer SH, Muñoz-Furlong A, Burks AW, Sampson HA. Prevalence of peanut and tree nut allergy in the United States of America determined by a random digit dial telephone survey. *J Allergy Clin Immunol* 1999;103:559-562.
4. Ewan PW. Clinical study of peanut and nut allergy in 62 consecutive patients: new features and associations. *BMJ* 1996;312:1074-1078.
5. 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. *Br Med J* 1996;313:514-517.
6. Sicherer SH, Burks AW, Sampson HA. Clinical features of acute allergic reactions to peanut and tree nuts in children. *Pediatrics* 1998;102:E6.
7. Hourihane JO, Kilburn SA, Dean P, Warner JO. Clinical characteristics of peanut allergy. *Clin Exp Allergy* 1997;27:634-639.
8. Zeiger R, Heller S, Mellon M, Forsythe A, O'Connor R, Hamburger R. Effect of combined maternal and infant food-allergen avoidance on development of atopy in early infancy: A randomized study. *J Allergy Clin Immunol* 1989;84:72-89.
9. Gerrard JW. Peanut protein in breast milk. *Annals Allergy* 1979;42:69-72.
10. Keating MU, Jones RT, Worley NJ, Shively CA, Yunginger JW. Immunoassay of peanut allergens in food-processing materials and finished foods. *J Allergy Clin Immunol* 1990;86:41-44.
11. Sampson HA, Mendelson LM, Rosen JP. Fatal and near-fatal anaphylactic reactions to food in children and adolescents. *N Engl J Med* 1992;327:380-384.
12. Yunginger JW, Sweeney KG, Sturmer WQ, Giannandra LA, Teigland JD, Bray M, Benson PA, York JA, Biedrzycki L, Squillace DL. Fatal food-induced anaphylaxis. *JAMA* 1988;260:1450-1452.
13. Bock SA. The natural history of food sensitivity. *J Allergy Clin Immunol*

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- 1982;69:173–177.
14. Sicherer SH, Furlong TJ, DeSimone J, Sampson HA. Self-reported allergic reactions to peanut on commercial airliners. *J Allergy Clin Immunol* 1999; 103:186–189.
15. Muñoz-Furlong A, Noone SA, Sicherer SH. Impact of food allergy on quality of life (abstract). *J Allergy Clin Immunol* 2000;105:S129.
16. Emmett SE, Angus FJ, Fry JS, Lee PN. Perceived prevalence of peanut allergy in Great Britain and its association with other atopic conditions and with peanut allergy in other household members. *Allergy* 1999;54:380–385.
17. Bock SA, Atkins FM. The natural history of peanut allergy. *J Allergy Clin Immunol* 1989;83:900–904.
18. Golding J, Fox D, Lack G. Prevalence and natural history of peanut allergy in children in the UK (Abstract). *J Allergy Clin Immunol* 1998;101:S103.
19. Spergel JM, Beausoleil JL, Pawlowski NA. Resolution of childhood peanut allergy. *Ann Allergy Asthma Immunol* 2000;85:473–476.
20. Hourihane JO, Roberts SA, Warner JO. Resolution of peanut allergy: case-control study. *BMJ* 1998;316:1271–1275.
21. Hayami D, Kagan R. The positive predictive value of prick skin tests to peanut in children who have never previously eaten peanuts (Abstract). *J Allergy Clin Immunol* 2000;105:S189.
22. 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: 444–451.
23. Skolnick H, Barnes Koerner C, Conover Walker MK, Sampson HA, Wood RA. The natural history of peanut allergy (Abstract). *J Allergy Clin Immunol* 2000;105:S189.
24. Gray I, Walzer M. Studies in absorption of undigested protein in human beings. VIII. Absorption from the rectum and a comparative study of absorption following oral, duodenal, and rectal administrations. *J Allergy* 1940; 11:245–250.
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