

Progress in peanut allergy research: Are we closer to a cure?

Key words: Peanut allergy, food allergy

Thirty years ago, the allergy literature contained very few articles on peanut allergy, and textbooks of allergy gave the problem scant mention. May¹ was the first to report a significant series of children with positive blinded food challenge results to peanut. This study initiated the systematic search for better diagnostic, treatment, education, and prevention modalities. Several articles in this issue of the *Journal* address the current status of advances in these areas. Recent data indicate that the incidence and prevalence of peanut allergy are increasing, although the reasons for this change remain speculative. With more than a million Americans with peanut allergy, this subject has become an important public health issue.² This statistic is magnified by the fact that sensitization to peanut seems to be increasingly prevalent in the United Kingdom as well.³ In addition to the sheer size of the population with this one food allergy, the mortality from anaphylactic reactions to peanut is of mounting concern. The exact mortality rate is difficult to ascertain, but even anecdotal series demonstrate that peanut alone accounts for a significant number (about 50%) of deaths caused by food allergy.^{4,5} Despite an increasing public awareness of food allergy, most patients are ill prepared to deal with anaphylactic reactions.⁶ In a recent series more than 80% of patients dying from food-induced allergic reactions had not been previously provided with appropriate information or self-injectable epinephrine to avoid or manage accidental food-induced reactions.⁵

If the goal of containing the development and morbidity of peanut allergy is to be achieved, then more research in this area is urgently needed. At this time, good progress has been made in the diagnosis of peanut allergy in individual subjects. The properly performed skin test followed by the *in vitro* quantitative assay for specific IgE antibodies to peanut protein has provided a straightforward approach to the identification of subjects likely to have the problem. This in turn has decreased the need for blinded food challenges in many subjects who have a reasonable history of immediate-onset symptoms when peanut is ingested.^{7,8} However, there is the need for a test that could predict the severity of an individual's reaction. Without the means to gauge how severe a

response might be, many families are hesitant to pursue peanut challenges for their loved ones, even when the patient's peanut antibody value has decreased to levels indicating that a challenge might be tolerated. In the current issue of the *Journal*, Beyer et al⁹ found that the measurement of peanut peptide-specific IgE was a particularly useful additional tool for identifying patients with clinical reactivity to peanut but low levels of peanut-specific serum IgE. This new assay might reduce the need for peanut food challenges in patients who have a nondiagnostic serum IgE assay for peanut.

The article by Fleischer et al¹⁰ is most helpful in extending the data reporting that approximately 20% of youngsters with peanut allergy, especially when diagnosed at a young age, might lose their reactivity over time.¹¹ Now Fleischer et al¹⁰ are reporting the loss of reactivity at various levels of specific peanut antibody in serum. This lends support to recommendations that children with low levels of antibody should undergo a challenge. However, it would still be optimal if future research identified a test that predicted the likely severity of reactions both initially and on subsequent exposure. The counter concern raised both by Fleischer et al¹⁰ and another recent report¹² is the possibility of redevelopment of peanut allergy, especially if a reaction might be life-threatening. Therefore another crucial area of research will be longitudinal outcome studies in the group of subjects who pass their food challenges, either after a previous failure or a highly likely diagnosis on the basis of history and laboratory testing. Ultimately, the true natural history of peanut allergy is likely to involve different patterns in different subpopulations that might yet be found to be genetically divergent. Further studies that eventually include genotyping will finally clarify the issue.

Another important question is raised by the study of Roberts et al.¹³ Is food allergy, and in particular peanut allergy, a risk factor for life-threatening asthma? By extension, one might raise the question of whether severe asthma episodes are due to food allergens in which the diagnosis is missed, and therefore the reactions recur repeatedly. The data presented support the hypothesis that food allergy triggers life-threatening asthma in children. If food allergy triggers life-threatening asthma, how often does it trigger non-life-threatening, food-induced allergic asthma episodes? Perhaps the former is more common than is appreciated and the latter is less common, but additional research will be necessary to reach a firm conclusion. Examination of the reported mortality from peanut reactions has shown that many, if not all, of the known fatalities in which the data exist have occurred in individuals who are known to have asthma.^{4,5} A question that must be answered is whether the degree of control of the asthma at the time of a peanut reaction influences the outcome.

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Clinicians struggle each day with the practical management and education of both children and adults with peanut allergy and their families. Families have many questions and concerns that must be addressed. The study by Simonte et al¹⁴ is most helpful in allaying 2 of the most common fears that families experience and that often lead to significant alterations in lifestyle for individuals with peanut allergy. Parents of young children are usually very concerned about the potential for a life-threatening reaction to occur from incidental contact or exposure to peanut. This study has shown that an exposure to peanut protein when it is in peanut butter vastly reduces the potential for a reaction to occur. It is important to be able to explain to families that they might distinguish between the potential dangers of peanut butter versus peanut fragments that are released into the air from packaged products. In other words casual skin contact or inhalation of peanut butter fumes will not usually cause a severe allergic reaction. However, these results cannot be generalized to larger exposures or to contact with peanut in other forms, such as roasted peanuts. Practical studies of this type dramatically enhance our ability to educate and reassure families.

Prevention of the development of peanut allergy is also a crucial subject for study. A recent article by Lack et al¹⁵ has raised the issue of whether exposures to peanut by multiple routes in very young children are responsible for sensitization leading to clinical peanut allergy in susceptible infants. They propose that topical exposure to peanut or ingestion of cross-reacting epitopes might lead to early sensitization, and by extension, the avoidance of these might lead to prevention. Confirmation of this study and especially examination of the genetic predisposition of a portion of the population is urgently needed.

Why is peanut such an allergenic food in the United States? Some studies suggest that cooking practices might be part of the explanation.¹⁶ Now an article by Maleki et al¹⁷ in this month's issue reports that the major peanut allergen, Ara h 2, functions as a trypsin inhibitor and that roasting increases this trypsin inhibitory activity by 3.6-fold. Interestingly, another major peanut allergen, Ara h 1, was protected from digestion with trypsin in the presence of roasted Ara h 2. These observations might account for the reason that roasting enhances the allergenic properties of peanuts and explain why peanut is such a potent allergen. The possibility that functional properties of allergens influence their allergenicity has important implications for studies of other allergens, in which research has previously focused primarily on structural characteristics.

The number of severe and fatal food-induced allergic reactions indicates that the current management strategies (ie, allergen avoidance and early use of epinephrine) are not adequate for dealing with this disorder. Interestingly, one fundamental aspect of poison management has not been commonly applied to the management of food-induced anaphylaxis. This relates to the prevention of ongoing absorption of food allergens from the gastrointestinal tract into the systemic circulation. Activated charcoal, when administered as an oral suspension, has been

shown to prevent the absorption and increase the elimination of a variety of poisons and drugs from the gut. This month, Vadas and Perelman¹⁸ report that activated charcoal adsorbs to peanut proteins, forming insoluble complexes that no longer allow the peanut proteins to bind IgE. These data suggest that administration of activated charcoal soon after accidental ingestion of peanut might be a useful adjunct in the management of peanut-induced anaphylaxis. This approach is likely to be applicable to the prevention of more severe and prolonged anaphylactic reactions to other foods as well.

Unlike traditional immunotherapy for inhalant and bee sting allergy, the risk/benefit ratio for injection of peanut extracts is unacceptable because of the high prevalence of intolerable side effects.^{19,20} Given this unfavorable risk/benefit ratio of traditional immunotherapy, novel immunotherapeutic strategies are needed for treatment of food allergy. Recently, several potentially effective therapeutic approaches have been identified that might be effective in the long-term management of peanut allergy.

The most direct approach is based on the concept that allergic reactions are mediated by means of antigen-specific IgE bound to high-affinity Fcε receptors (FcεRI) on mast cells and basophils.²¹ TNX-901 is a humanized IgG₁ anti-IgE mAb that binds with high affinity to an epitope in the CH3 domain of IgE, masking a region responsible for binding to both FcεRI and low-affinity Fcε receptors (FcεRII [CD23]).²² Recently, a double-blinded, placebo-controlled, randomized, dose escalation trial of TNX-901 (anti-IgE) was conducted in 84 patients with a history of peanut allergy.²³ Patients were randomized to receive either TNX-901 (150, 300, and 450 mg) or placebo subcutaneously every 4 weeks for 4 doses. From mean baseline values of 178 to 436 mg of peanut in the various treatment groups, the mean increases in the peanut challenge threshold were 710, 913, 1650, and 2627 mg for the placebo and 150, 300, and 450 mg for the TNX-901 dose groups, respectively ($P = .0008$ for trend with dose). No significant adverse effects were associated with TNX-901 treatment. TNX-901 at a dose of 450 mg significantly increased the threshold of sensitivity to peanut from a level of approximately one half that of peanut (178 mg) to almost 9 peanuts (2805 mg). Of note, 24% of patients receiving 450 mg of TNX-901 were able to tolerate 8 g of peanut. Because accidental ingestions of peanut usually only involve exposure to less than 2 peanuts, these studies suggest that treatment of patients with anti-IgE therapy might represent an effective long-term approach for management of food-induced anaphylaxis. This same approach is likely to be useful in blocking anaphylaxis to other foods, such as tree nuts and shellfish. It is important to note that although Xolair (E25),²⁴ another humanized anti-IgE, which might be approved soon for treatment of severe asthma, could be useful for prevention of food-induced anaphylaxis, the optimal dose for prevention of food-related allergic reactions might differ from the dose required for asthma therapy. Thus formal clinical trials should be carried out for Xolair before they are used in treating patients with food allergy.

Using a mouse model of peanut-induced anaphylaxis, Li et al²⁵⁻²⁷ have reported the efficacy of engineered recombinant proteins, as well as traditional Chinese herbal medicines in reducing peanut-induced allergic reactions. The development of genetically engineered major allergenic peanut proteins (mAra h 1-3) that no longer bind IgE but retain T-cell proliferation is a particularly elegant approach to overcoming frequent adverse events previously encountered in conventional immuno-therapy with native peanut proteins.²⁸ These proteins could therefore be used as a peanut vaccine that would safely elicit a protective immune response to peanut without concerns over eliciting an allergic response to peanut during desensitization.

In the current issue of the *Journal*, an important milestone is reported in the development of a peanut vaccine for long-lasting protection against peanut-induced anaphylaxis. Li et al²⁵⁻²⁷ examined the efficacy of mAra h 1-3 recombinant proteins in the prevention of peanut-induced anaphylaxis in a mouse model. Because these engineered recombinant proteins are generated in *Escherichia coli* and because *E coli* possess LPSs that favor T_H1 responses,²⁹ administration of heat-killed *E coli* containing engineered mAra h 1-3 proteins (amino acid substitutions within IgE-binding epitopes to abrogate IgE binding, such as illustrated for Ara h 1 on this month's *Journal* cover)²⁸ should be highly efficacious in the prevention of peanut-induced anaphylaxis. Indeed, the rectal administration of 9 or 90 µg/mL HKE-mAra h 1-3 led to protection of peanut-sensitized mice, with an absence of anaphylactic symptoms or an increase in plasma histamine levels after the peanut challenge. Peanut allergy is associated with increased production of IgE and T_H2 cytokines in response to peanut.³⁰ Importantly, peanut-specific serum IgE levels, as well as peanut-induced T_H2 cytokine production, were significantly reduced at the time of challenge in the HKE-mAra h 1-3-treated mice compared with the sham-treated group and remained lower after additional peanut challenges, indicating that the protective effect of HKE-mAra h 1-3 was persistent.

Although studies in human subjects are needed to extend these promising results, the future looks bright as new paradigms for treatment of peanut allergy are emerging. The current issue of the *Journal* reports major advances in our approach to the diagnosis and understanding of the natural history and mechanisms underlying peanut allergy.^{9,10,13,14,16,17} Anti-IgE therapy, when available, is likely to provide immediate benefit for the prevention of anaphylactic reactions to unintended ingestions of peanut. Long-term protection, although still in the early experimental stages, might be on the horizon with the development of a new generation of peanut vaccines.²⁷

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