

Advances in allergic skin disease, anaphylaxis, and hypersensitivity reactions to foods, drugs, and insects

Scott H. Sicherer, MD,^a and Donald Y. M. Leung, MD, PhD^b *New York, NY, and Denver, Colo*

This review highlights some of the research advances in anaphylaxis; hypersensitivity reactions to foods, drugs, and insects; and allergic skin disease that were reported primarily in the *Journal* in 2005. Although studies documented deficiencies in community management of anaphylaxis, guidelines and National Institutes of Health summary reports provide direction toward improved research and education. At least 9% of young children “outgrow” a tree nut allergy. Advances in food allergy diagnosis include reports of probability of reactions to peanut at various peanut-specific IgE concentrations and skin test response size and the utility of evaluating IgE binding to specific epitopes. Future food allergy treatments might include selection of “less allergenic” fruit cultivars, genetic silencing of major allergens, and treatment of allergic patients with Chinese herbal remedies. Osteopontin might be a useful biomarker for success of venom immunotherapy. Progress in our understanding of the immunology of atopic dermatitis and autoimmune urticaria has also been made. These observations will likely contribute toward optimizing management of these common allergic disorders. (*J Allergy Clin Immunol* ■■■■;■■■;■■■-■■■.)

Key words: *Dermatology, skin disease, urticaria, atopic dermatitis, anaphylaxis, allergy, hypersensitivity disorders, food, drug, insect venom*

This review highlights key advances in allergic skin disease, anaphylaxis, and hypersensitivity to foods, drugs, and insect venom selected from among more than 80 articles on these topics published in the *Journal of Allergy and Clinical Immunology* in 2005. Some of the key advances are summarized in [Table I](#).

From ^aThe Elliot and Roslyn Jaffe Food Allergy Institute, Division of Allergy and Immunology, Department of Pediatrics, Mount Sinai School of Medicine, New York, and ^bthe Department of Pediatrics, University of Colorado Health Sciences Center, and the Division of Pediatric Allergy/Immunology, National Jewish Medical and Research Center, Denver.

Disclosure of potential conflict of interest: D. Y. M. Leung has received grant support from Novartis. S. H. Sicherer has declared that he has no conflict of interest.

Received for publication April 3, 2006; accepted for publication April 5, 2006.

Reprint requests: Scott H. Sicherer, MD, Division of Allergy/Immunology, Mount Sinai Hospital, Box 1198, One Gustave L. Levy Place, New York, NY 10029-6574. E-mail: scott.sicherer@mssm.edu.

0091-6749/\$32.00

© 2006 American Academy of Allergy, Asthma and Immunology

doi:10.1016/j.jaci.2006.04.018

Abbreviations used

AD: Atopic dermatitis
MDM: Minor determinant mixture of penicillins
PPL: Benzylpenicilloyl poly-L-lysine
SPINK5: Serine protease inhibitor Kazal type 5 gene
TIM1: T-cell Ig domain and mucin domain gene
VIT: Venom immunotherapy

ANAPHYLAXIS

Clinical studies have identified areas of weakness in community treatment of anaphylaxis. Clark et al¹ reviewed 617 records from 15 North American emergency departments to describe treatment of insect sting allergy. Multisystem organ involvement or hypotension was observed in 31% of reactions. Treatment of systemic reactions included antihistamines (69%), systemic corticosteroids (50%), and epinephrine (12%). At discharge, there was a low rate of prescription of self-injectable epinephrine (27%) and relatively few allergy referrals (20%). If self-injectable epinephrine is prescribed, it appears to be underused in the community. A survey of parents of children with food allergy, conducted by Kim et al,² identified that factors such as a feeling of empowerment, prior self-injector use, and training were associated with increased comfort in using this medication. The lessons from these 2 studies are to increase education about the diagnosis and management of anaphylaxis. To help toward these aims, 4 reports this year are of special interest: summary reports from a National Institutes of Health panel discussion to define *anaphylaxis* and describe signs and symptoms associated with the diagnosis,^{3,4} an updated anaphylaxis practice parameter,⁵ and a review addressing difficult issues in prescribing self-injectable epinephrine and giving instructions for using it in the community setting.⁶ Additional advances pertinent to anaphylaxis are considered below in regard to specific triggers.

FOOD ALLERGY

Epidemiology

Studies continue to document a high prevalence of food allergy and food-induced allergic disease. There has been

TABLE I. Summary of selected key advances reported in the *Journal*

Topic	Clinical or basic research concerns	Advances and observations
Anaphylaxis	Diagnosis and management	• Studies document underdiagnosis and undertreatment of anaphylaxis • National Institutes of Health summary reports and practice parameters provide guidance for definition, diagnosis, and management
Food allergy	Apparent increasing prevalence and altered natural course	• 2.3% of teenagers have food allergy
	Molecular aspects of food allergy	• Tree nut allergy resolves in 9% of young children • IgE-mediated milk allergy persists in 15% at age 8 years • <i>In vitro</i> cross-reactivity of fish parvalbumin identifies potential patterns for clinical cross-reactivity • Hevein-like domain of latex allergen likely responsible for food-related allergy • Digestion impairment (antacids) might increase the likelihood of an allergic reaction to codfish proteins • Digested peptides (Bet v 1–related fruit protein) might stimulate T-cell responses
	Diagnostic testing	• Data relating skin test wheal size/IgE antibody concentration to probability of clinical allergy to peanut improves diagnostic ability • Microarray analysis of IgE peptide binding might advance diagnostic capabilities/identify informative peptides for commercial assay
	Treatment	• A Chinese herbal remedy blocked peanut anaphylaxis in a murine model • In regard to pollen-related allergy, less reactive apple cultivars were identified
Drug allergy	Diagnosis without commercial PPL/MDM	• RNA interference techniques can silence allergenic protein (Mal d 1) • Study of 824 patients reveals lack of these reagents likely associated with missing >15% of patients with β-lactam allergy (when testing with only a battery of available β-lactam antibiotics)
Insect allergy	Treatment	• Osteopontin might be an important biomarker for success of VIT
AD	Immunology and Treatment	• FDA concerns over safety of topical calcineurin inhibitors • Single nucleotide polymorphisms involving the <i>TIM1</i>, <i>TIM3</i>, <i>NOD</i>, and <i>IL18</i> genes are associated with AD • IgE autoreactivity has been established in AD and might be stimulated by exposure to environmental microbes
Autoimmune urticaria	Diagnosis and mechanism	• 50% of these patients have basophil-activating IgG autoantibodies • Nonfollicular cholinergic urticaria shows strong positive reaction to autologous sweat

very little previous investigation of the prevalence of food allergy among teenagers, a group that might be at special risk for fatal anaphylaxis. Pereira et al⁷ reported that among 757 eleven-year-olds and 775 fifteen-year-olds in the Isle of Wight, United Kingdom, 17% were avoiding at least one food, 5% were food sensitized, and on the basis of objective assessments, 2.3% had clinical food hypersensitivity (0.9% to peanut). Eosinophilic esophagitis is typically associated with food allergy and also seems to be increasing. Straumann and Simon⁸ report diagnoses of eosinophilic esophagitis over a 16-year period in Olten County, Switzerland, and found an increasing yearly incidence and, consequently, prevalence (23 of approximately 100,000 inhabitants in 2004). In addition to the important epidemiologic observations provided by these studies, they serve as a strong reminder that primary care physicians and specialists should discuss potential food allergies with their patients and seek to confirm a diagnosis so that proper treatment can proceed and that foods are not avoided unnecessarily.

Sensitization to foods, or food allergy, might also be a marker for increased asthma severity. Wang et al⁹ evaluated a random sample of sera (n = 504) collected from children participating in the National Cooperative Inner City Asthma Study for specific IgE to 6 common food allergens. A remarkable 45% of the cohort were sensitized to at least one food, and 4% had food-specific IgE concentrations that are highly associated (>95%) with clinical food allergy. Sensitization to food allergens was highly associated ($P < .03$) with asthma hospitalization, need for steroids, and sensitization to environmental allergens. Further studies will be needed to determine whether food allergies themselves, possibly underdiagnosed, are causally related to asthma severity.

Another important clinical-epidemiologic issue is the natural course of food allergy. It is typically thought that milk allergy is short lived and that tree nut allergy is permanent; however, 2 studies have challenged and refined our understanding of these notions. In a study of 118 children with cow's milk allergy followed to age 8.5

years, Saarinen et al¹⁰ found that all of the children ($n = 32$) with non-IgE-mediated cow's milk allergy had become milk tolerant by the age of 5 years. For those with IgE-mediated cow's milk allergy, only 75% were tolerant by age 5 years, and by age 8.6 years, 15% of the original group were still allergic. The study indicates that after age 5 years, the rate of allergy loss is quite slow. In regard to tree nut allergy, Fleischer et al¹¹ showed that at least 9% of young children with tree nut allergy became tolerant of tree nuts. Many families (78/117 eligible to undergo challenge) declined oral food challenges, and therefore the estimate of resolution rates might be lower than documented. The authors additionally considered tree nut-specific IgE antibody concentrations and suggested that children older than 4 years with IgE levels of 5 kUa/L or less (Pharmacia CAP System) and without recent tree nut-induced allergic reactions might be good candidates for a physician-supervised oral food challenge.

Although it is still unclear how genetic, immunologic, and environmental factors conspire to determine the outcomes of food allergy, some headway has been reported. Specific serine protease inhibitor Karzal type 5 (*SPINK5*) gene polymorphisms were reported to be associated with an increased risk for food allergies (20/91 with the AA or AG genotype had food allergies compared with 1/26 with the GG genotype) in a group of Japanese children with atopic dermatitis (AD) reviewed retrospectively.¹² Further prospective studies in other populations will be needed to confirm and explore the association further.

Pathophysiology

Molecular characterization of food allergens is key for understanding cross-reactivity, predicting clinical allergy, improving diagnostic methodologies, and designing treatments. Van Do et al¹³ evaluated sera from 10 patients allergic to codfish for evidence of cross-reactivity between codfish parvalbumin and other common fish. Cod (Gad c 1), salmon (Sal s 1), pollack (The c 1), herring, and wolf-fish shared antigenic and allergenic determinants, as shown by means of immunoblotting and IgE ELISA, whereas halibut, flounder, tuna, and mackerel displayed the lowest cross-reactivity, and participants generally had smaller skin test reactions to these latter fish. Although the study did not pursue oral food challenges to determine the rates of clinical reactions to various fish species, the results imply that certain types are more likely to be tolerated. As a note of caution, Lim et al¹⁴ described one of the many nuances that must be appreciated for evaluation of fish allergy, namely, in regard to tuna, that the major allergen parvalbumin is absent in the red muscle and present in the white muscle, with increasing concentrations from the caudal to the rostral areas of the fish. Cross-reactivity is also an issue for nut allergy. Robotham et al¹⁵ identified a cashew major allergen, Ana o 3, that is a 2S albumin. Probing of overlapping synthetic Ana o 3 peptides with patient sera identified 4 reactive peptides with strong signals, one of which positionally overlaps linear epitopes in mustard and walnut 2S albumins that might be a basis for cross-reactivity with these foods. Another common issue in cross-reactions is the latex-fruit

syndrome, typically involving banana, kiwi, avocado, and papaya (although a case study¹⁶ further implicated a high-molecular-weight allergen in latex to be cross-reactive with fruits in the Prunoideae family, such as plum, peach, and cherry). Hevein and its homologues are thought to be the major allergens involved in the typical latex-associated food cross-reactions, and 31-kd endochitinases with a conserved N-terminal hevein-like domain are the typical targets used in studies concerning cross-reactivity. Karisola et al¹⁷ provided further insight on identifying the responsible allergenic protein by using 31-kd endochitinases and corresponding hevein-like domains that were purified or produced from avocado, banana, latex, and wheat germ for skin prick testing and inhibition ELISA. They found that 73% of 15 subjects with latex allergy had skin prick test reactions to isolated hevein-like domains but rarely (7%) to the corresponding 31-kd endochitinases, with corresponding results in inhibition ELISA. The results indicate that the isolated hevein-like domain molecules alone, although not when linked to endochitinases, are likely to be responsible for IgE-mediated clinical reactions in latex-fruit syndrome.

The various mysteries of cross-reactivity, why certain homologous proteins do or do not account for clinical cross-reactivity among various foods, might eventually be solved partly through a bioinformatics approach. Jenkins et al¹⁸ used a bioinformatics approach to assess conserved surface features important for IgE cross-reactivity and found that most plant food allergens belong to only 4 structural families. The results underscore the importance of considering the 3-dimensional structure in assessment or prediction of cross-reactivity.

Digestion is an important variable that can influence the induction and expression of food allergy by altering the features of food proteins-peptides before processing by the immune system. For example, the symptoms of oral allergy syndrome, or pollen-food allergy syndrome, are presumably isolated to the mouth because the causal proteins are labile and easily digested after being swallowed. Conversely, fish, more commonly than fruits and vegetables, causes severe allergic reactions, presumably because major allergens are resistant to digestion. However, a study by Untersmayr et al¹⁹ has modified the latter notion. They evaluated codfish proteins by means of IgE immunoblotting, RAST inhibition, basophil histamine release, and SDS-PAGE after exposure to simulated gastric fluid with a range of pH values. They found that codfish proteins were degraded within 1 minute under physiologic gastric conditions and that a small pH shift from 2.5 to 2.75 completely abrogated the digestion. The peptic fragments of digested proteins showed a 10,000 times reduced allergenic potency in the *in vitro* tests. Although the researchers previously demonstrated that neutralization of stomach acid might increase the risk for allergen sensitization, they here showed a potential for impaired digestion to lower the threshold for a clinical reaction to ingested allergen. In a different model Schimek et al²⁰ showed that digested allergen, in this case birch pollen (Bet v 1)-related allergens in fruits, might lose IgE-binding activity after exposure to digestive enzymes *in vitro*, while maintaining the

ability to stimulate a T-cell response, interestingly both in patients with pollen allergy and in nonallergic control subjects. This study lays the groundwork for more investigation of the role of these digestion products on non-IgE-mediated allergy and mechanisms of tolerance.

In regard to tolerance induction, Omata et al²¹ used a murine model of IgE-mediated food allergy (double-transgenic mice with ovalbumin-specific T-cell receptor and expression of ovalbumin-specific IgE compared with ovalbumin-specific T-cell receptor-transgenic mice) to explore the responses to oral administration of allergen. Mice were fed with high doses of ovalbumin or saline every other day, and T-cell responses were evaluated after 14 days. Without OVA administration, the splenocytes from the double-transgenic mice showed a higher proliferative response and produced more IL-4 and IL-10 and less IFN- γ than those from mice without ovalbumin-specific IgE. However, the proliferative responses of the splenocytes from either type of transgenic mouse fed ovalbumin were significantly reduced compared with those from saline-fed mice, and irrespective of the presence of ovalbumin-specific IgE, repetitive oral administration of ovalbumin induced tolerance associated with clonal deletion-anergy and TGF- β 1-mediated active suppression. The studies provide insights on the mechanisms of tolerance that might occur from oral exposure that are relevant for the context of treating a food allergy through oral immunotherapy.

Diagnosis

The clinical utility of evaluating a food-specific IgE test, either a serum test or skin prick test, with regard to the degree of positivity and not simply as a dichotomous positive or negative result is being increasingly appreciated. Roberts and Lack²² report the results of 161 food challenges to peanut in children up to the age of 16 years. The results confirm prior studies showing that skin tests with a wheal diameter of 8 mm or more and peanut-specific serum IgE concentrations of 15 kUa/L or higher are associated with predictive values of 95% and 92%, respectively. The large number of challenges allowed the authors to construct graphic relationships and to calculate likelihood ratios. The larger the skin test responses or higher the concentration of peanut-specific IgE antibodies, the more likely there was a clinical reaction on oral food challenge. However, the study also documented the previously reported observation that test results might, on occasion, be negative, despite a clinical allergy documented by oral challenge. Hauswirth and Burks²³ also reported an important example of this predicament. A woman with anaphylaxis to banana had a negative skin prick test response to commercial extract but a positive skin prick test response to fresh banana. Therefore it is vital to consider the medical history in evaluation of food allergy (assessment of prior probability) and to recognize test limitations and utility.

Several studies gave a peek into the window of the future of testing for food hypersensitivity. On the basis of prior studies showing a distinct IgE-binding pattern to informative epitopes that might reflect current allergy and predict allergy persistence or eventual resolution, relevant

informative peptides were coupled to a commercial matrix and tested, with promising results.²⁴ Microarray analysis of IgE binding to food peptides might eventually allow for broad and informative testing with very small samples.²⁵ Tests for food-specific IgE antibodies are not relevant for non-IgE-mediated food allergies, but alternative markers of inflammation²⁶ and studies showing the potential utility of patch tests with foods are emerging, and it might eventually be possible to use commercial reagents for food patch testing.²⁷

Treatment

Many clinicians have observed patients with pollen-food allergy syndrome who report more symptoms with certain types of apples and fewer or no symptoms with other types. Bolhaar et al²⁸ used prick-prick tests and oral food challenges to assess the allergic potential of 21 apple cultivars. Both skin test response size and oral challenge outcomes identified a ranking of these cultivars in regard to allergenicity. Storage conditions were also assessed and showed differences in allergenicity testing. The prick-prick results correlated with challenge outcomes. Less reactive cultivars included Santana and Fuji, midrange were Granny Smith and Fiesta, and higher were Golden Delicious and Gala. Five patients underwent oral food challenges, showing that they could have tolerated 30 times more of the Santana compared with the Golden Delicious before experiencing symptoms. Although this study might provide practical advice for advising patients with oral food allergy to apple, genetic engineering might eventually provide more options. Gilissen et al²⁹ presented data showing that by using an RNA interference approach (a method of postranscriptional gene silencing), the expression of apple Mal d 1 (the birch-related protein) could be reduced in transformed apple plantlets.

Additional studies showed promise for future treatment of food allergies. Srivastava et al³⁰ showed that a Chinese herbal remedy was effective in completely blocking anaphylaxis in a murine model of peanut allergy and had effects lasting at least 5 weeks after therapy ended. Mechanistic studies showed reduced IgE levels and an increased T_H1 to T_H2 cytokine profile of splenocytes stimulated *in vitro* with peanut in the treated group. In human subjects a double-blind randomized study showed the efficacy of sublingual immunotherapy with hazelnut³¹; 5 subjects in the treatment group had a history of anaphylaxis, and 3 of them tolerated 10 g or more of hazelnut after treatment. Treatment of eosinophilic esophagitis is challenging and often dietary, and medical therapy is required. Swallowing inhaled steroid from a metered-dose inhaler has been one approach to apply topical steroids, and successful use of a viscous mixture of budesonide was also effective, as reported for 2 children.³²

DRUG ALLERGY

With the current absence of commercial Pre-Pen (benzylpenicilloyl poly-L-Lysine [PPL]), and with the

lack in many countries of a commercial minor determinant mixture of penicillins (MDM), the allergist must appreciate the potential limitations of testing for β -lactam allergy. Bousquet et al³³ present their 8-year experience with 824 patients evaluated for histories consistent with IgE-mediated allergic reactions to β -lactam antibiotics. Testing was performed with PPL, MDM, penicillin G, amoxicillin, ampicillin, and any other β -lactam implicated in the history that was available in injectable form. Of the 824 evaluations, 688 resulted in negative test responses (but 53 [7.7%] resulted in reactions on oral testing, including anaphylactic shock in 11). Those with positive test responses were not challenged. There were 136 with positive test responses, and 20 of them had positive responses solely to the now unavailable agents (6 to PPL, 5 to PPL and MDM, and 9 to MDM). Among 116 who had positive test responses to other β -lactams, about 30% also had positive test responses to MDM, PPL, or both. With the authors' approach, 20 additional persons would have undergone challenge because of the absence of the reagents. Without MDM and with PPL (the prior US experience), 9 persons with only positive MDM responses would have been challenged. Without the additional determinants tested and without MDM and PPL, 46.7% would not have received a proper diagnosis. Hopefully, these agents will become available to improve the accuracy of testing.

Of additional note for the clinician is a report by Win et al³⁴ on their experience with rapid (2 hours and 15 minutes) intravenous desensitization to cephalosporins. Reactions to specific COX-2 inhibitors were the focus of case reports: anaphylaxis to celecoxib without reaction to rofecoxib³⁵ and a severe skin reaction to valdecoxib.³⁶ Insights on the immunologic mechanisms of delayed reactions to iodinated contrast media identified the role of T cell-mediated responses because there was a large number of positive patch test responses and delayed skin responses to intradermal skin tests among subjects who had experienced primarily delayed skin rash from these agents.³⁷

INSECT ALLERGY

It is a relative contraindication to use β -blockers in persons with insect venom hypersensitivity undergoing venom immunotherapy (VIT). However, there are limited data on the potential risk. Muller and Haeberli³⁸ observed a death in a patient who had switched from a β -blocker to a thiazide diuretic before starting VIT who succumbed to a cardiac event attributed to this switch in medication. They therefore evaluated their experiences with 1389 patients for whom VIT was recommended: 156 (11.2%) had cardiovascular disease, and 44 were receiving β -blockers before starting VIT. On the basis of cardiovascular disease, 4 were continued on β -blockers during VIT, and an additional 9 were started on the drug once maintenance VIT was reached. Twelve others began β -blockers while receiving VIT. No differences were seen between those who continued treatment compared with those who did not in regard to outcomes of stings or side effects of

VIT, although the number of subjects was small. The authors acknowledge the relative contraindication of β -blocker therapy but suggest careful risk-benefit assessments and involvement of the cardiologist and primary care physician and patient to assess risks.

Treatment of Hymenoptera allergy with VIT is effective and life saving, but biomarkers, such as venom IgE or IgG levels, have not been uniformly informative in regard to predicting successful response to treatment. Konno et al^{39,40} used Gene chip expression arrays and serum studies that found that osteopontin, which regulates bone metabolism but has also been postulated to be a T_H1 cytokine, might be a good biomarker for success of VIT. Diagnosis and treatment of insect sting or bite allergy requires characterization of the causal allergens, and several reports were published on these topics. Pigeon ticks can bite people and can induce anaphylaxis, and the responsible allergen, a lipocalin, has been identified and cloned.⁴¹ Sol I 1, a phospholipase allergen of fire ants, has also been characterized, and its relationship to other venoms has been elucidated.⁴²

CHRONIC URTICARIA

Considerable research has focused on the autoimmune aspects of chronic urticaria. The autoimmune nature of chronic urticaria is supported by its association with other autoimmune diseases, such as type I diabetes and Graves disease.⁴³ In a study by De Swert et al,⁴⁴ 50% of patients with chronic idiopathic urticaria were found to have basophil-activating autoantibodies by using CD62 as a marker of basophil activation. Soundararajan et al⁴⁵ functionally assessed IgG subclasses from patients with chronic autoimmune urticaria for their ability to induce histamine release from basophils. They reported functional antibody in IgG1 and IgG3 and occasionally IgG4. However, nonfunctional antibody was found in the IgG2 subclass plus nonfunctional antibody mixed with functional antibody within the other IgG subclasses, thus accounting for a lack of correlation of histamine release with binding assays for the α subunit of the high-affinity IgE receptor.

Cholinergic urticaria also appears to be an autoimmune disease. Fukunaga et al⁴⁶ found that 11 of 17 patients with cholinergic urticaria had positive skin test reactions with their own diluted sweat, and basophils from 10 of 17 patients released histamine on exposure to sweat. Eight of 15 patients with cholinergic urticaria had positive immediate skin test reactions to their autologous serum. Classification of these patients according to clinical subtypes suggested that the nonfollicular subtype shows strong positive reactions to autologous sweat and negative reactions to autologous serum. In contrast, the follicular subtype shows weak reactions to autologous sweat and positive reactions to autologous serum.

AD

Understanding the pathogenesis and treatment of AD are important areas of investigation. Several studies have

revealed novel genetic polymorphisms associated with AD. These include *IL4*, *IL13*, T-cell Ig domain and mucin domain (*TIM1*), *IL18*, *NOD1*, and *SPINK5* genes.⁴⁷ The involvement of *IL4*, *IL13*, *IL18*, and *TIM1* genes supports the importance of CD4⁺ T cells and dysregulation of T_H1 and T_H2 genes in the pathophysiology of AD.^{48,49} *SPINK5* is expressed in the uppermost epidermis, where its product, LEKT1, inhibits 2 serine proteases involved in desquamation and inflammation (SCTE and SCCE).⁵⁰ Involvement of the *NOD1* gene, which encodes cytosolic pathogen recognition receptors⁵¹ and Toll-like receptors,⁵² suggests an important role for microbes in the pathogenesis of at least a subset of patients with AD.⁵³

Clinical expression of AD depends on gene-environment interactions. However, the classification of various subtypes of AD and risk factors for development of AD are still evolving. Most (but not all) investigators agree that there are at least 2 types of AD, atopic and nonatopic, based on increase of serum IgE levels. However, there is some uncertainty in making a diagnosis of nonatopic eczema because at least half of these patients have been found to make IgE against microbial antigens, such as staphylococcal superantigens or autoantigens, that are usually not tested for by most allergists.⁵⁴⁻⁵⁷ The role of IgE in AD remains controversial, and some believe it relates more to severity of illness rather than defining a subtype of AD.⁵⁸ The early-life risk factors for the development of AD remain poorly defined, although its prevalence is reproducibly higher in urban compared with rural areas and has a higher prevalence among children of more educated parents. A recent study in a developing country found the prevalence of AD tended to be increased in children with intestinal parasite infection but was unrelated to breast-feeding, family size, or crowding in the home.⁵⁹

The immunologic basis of atopic skin disease remains an active area of study. Recent reports include the observation that AD is associated with increased levels of brain-derived neutrophilic factor and that this molecule reduces eosinophil apoptosis and enhances eosinophil chemotaxis.⁶⁰ IL-17 was found to suppress TNF- α -induced CCL27 production by inhibiting nuclear factor κ B and might thereby reduce the infiltration of T cells into the skin.⁶¹ Keratinocyte-derived costimulation mediated by B7-1, but not B7-2, resulted in the emergence of T_H2 lymphocyte immune responses and might thereby contribute to atopic skin inflammation.⁶²

The most significant therapeutic-related event in the past year involved the recommendation that a black-box warning be issued against topical calcineurin inhibitors because of concerns about potential long-term risks of malignancy. A task force report by the American Academy of Allergy, Asthma and Immunology and the American College of Allergy, Asthma and Immunology did not find any causal evidence supporting an association between use of topical calcineurin inhibitors and malignancy.⁶³ Indeed, immunologic studies suggest that topical pimecrolimus cream is more selective in its anti-T-cell effects than topical corticosteroids, which depleted both T cells and Langerhans cells.⁶⁴ The immunomodulatory

effects of probiotic therapy in AD also continue to attract interest.⁶⁵

CONCLUSIONS AND SUMMARY

As reported in the *Journal* in 2005, clinical studies have documented a great need for more public and physician education about management of anaphylaxis and food allergy, underscored the need for commercial diagnostic agents for drug allergy evaluations, and revealed new insight into the natural course of food allergy and the utility of currently available diagnostic tests. Translational and basic research has revealed important insights for creating better food and venom diagnostic tests and treatments, provided insight on the immunopathology and genetic cause of AD, and identified novel autoimmune features of chronic urticaria. These advances present information that is immediately helpful to improve patient care and set the stage for further discoveries likely to improve diagnosis and management.

REFERENCES

- Clark S, Long AA, Gaeta TJ, Camargo CA Jr. Multicenter study of emergency department visits for insect sting allergies. *J Allergy Clin Immunol* 2005;116:643-9.
- Kim JS, Sinacore JM, Pongracic JA. Parental use of EpiPen for children with food allergies. *J Allergy Clin Immunol* 2005;116:164-8.
- Sampson HA, Muñoz-Furlong A, Bock SA, Schmitt C, Bass R, Chowdhury BA, et al. Symposium on the definition and management of anaphylaxis: summary report. *J Allergy Clin Immunol* 2005;115:584-91.
- Sampson HA, Muñoz-Furlong A, Campbell RL, Adkinson NF Jr, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report-Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol* 2006;117:391-7.
- The diagnosis and management of anaphylaxis: an updated practice parameter. *J Allergy Clin Immunol* 2005;115(suppl):S483-523.
- Sicherer SH, Simons FE. Quandaries in prescribing an emergency action plan and self-injectable epinephrine for first-aid management of anaphylaxis in the community. *J Allergy Clin Immunol* 2005;115:575-83.
- Pereira B, Venter C, Grundy J, Clayton CB, Arshad SH, Dean T. Prevalence of sensitization to food allergens, reported adverse reaction to foods, food avoidance, and food hypersensitivity among teenagers. *J Allergy Clin Immunol* 2005;116:884-92.
- Straumann A, Simon HU. Eosinophilic esophagitis: escalating epidemiology? *J Allergy Clin Immunol* 2005;115:418-9.
- Wang J, Visness CM, Sampson HA. Food allergen sensitization in inner-city children with asthma. *J Allergy Clin Immunol* 2005;115:1076-80.
- Saarienen KM, Pelkonen AS, Makela MJ, Savilahti E. Clinical course and prognosis of cow's milk allergy are dependent on milk-specific IgE status. *J Allergy Clin Immunol* 2005;116:869-75.
- Fleischer DM, Conover-Walker MK, Matsui EC, Wood RA. The natural history of tree nut allergy. *J Allergy Clin Immunol* 2005;116:1087-93.
- Kusunoki T, Okafuji I, Yoshioka T, Saito M, Nishikomori R, Heike T, et al. *SPINK5* polymorphism is associated with disease severity and food allergy in children with atopic dermatitis. *J Allergy Clin Immunol* 2005;115:636-8.
- Van Do T, Elsayed S, Florvaag E, Hordvik I, Endresen C. Allergy to fish parvalbumins: studies on the cross-reactivity of allergens from 9 commonly consumed fish. *J Allergy Clin Immunol* 2005;116:1314-20.
- Lim DL, Neo KH, Goh DL, Shek LP, Lee BW. Missing parvalbumin: implications in diagnostic testing for tuna allergy. *J Allergy Clin Immunol* 2005;115:874-5.
- Robotham JM, Wang F, Seamon V, Teuber SS, Sathe SK, Sampson HA, et al. Ana o 3, an important cashew nut (*Anacardium occidentale* L.) allergen of the 2S albumin family. *J Allergy Clin Immunol* 2005;115:1284-90.

16. Asero R, Mistrello G, Roncarolo D, Amato S, Falagiani P. Detection of novel latex allergens associated with clinically relevant allergy to plant-derived foods. *J Allergy Clin Immunol* 2005;115:1312-4.
17. Karisola P, Kotovuori A, Poikonen S, Niskanen E, Kalkkinen N, Turjanmaa K, et al. Isolated hevein-like domains, but not 31-kd endochitinases, are responsible for IgE-mediated in vitro and in vivo reactions in latex-fruit syndrome. *J Allergy Clin Immunol* 2005;115:598-605.
18. Jenkins JA, Griffiths-Jones S, Shewry PR, Breiteneder H, Mills EN. Structural relatedness of plant food allergens with specific reference to cross-reactive allergens: an in silico analysis. *J Allergy Clin Immunol* 2005;115:163-70.
19. Untersmayr E, Poulsen LK, Platzer MH, Pedersen MH, Boltz-Nitulescu G, Skov PS, et al. The effects of gastric digestion on codfish allergenicity. *J Allergy Clin Immunol* 2005;115:377-82.
20. Schimek EM, Zwolfer B, Briza P, Jahn-Schmid B, Vogel L, Vieths S, et al. Gastrointestinal digestion of Bet v 1-homologous food allergens destroys their mediator-releasing, but not T cell-activating, capacity. *J Allergy Clin Immunol* 2005;116:1327-33.
21. Omata N, Ohshima Y, Yasutomi M, Yamada A, Karasuyama H, Mayumi M. Ovalbumin-specific IgE modulates ovalbumin-specific T-cell response after repetitive oral antigen administration. *J Allergy Clin Immunol* 2005;115:822-7.
22. Roberts G, Lack G. Diagnosing peanut allergy with skin prick and specific IgE testing. *J Allergy Clin Immunol* 2005;115:1291-6.
23. Hauswirth DW, Burks AW. Banana anaphylaxis with a negative commercial skin test. *J Allergy Clin Immunol* 2005;115:632-3.
24. Beyer K, Jarvinen KM, Bardina L, Mishoe M, Turjanmaa K, Niggemann B, et al. IgE-binding peptides coupled to a commercial matrix as a diagnostic instrument for persistent cow's milk allergy. *J Allergy Clin Immunol* 2005;116:704-5.
25. Shreffler WG, Lencer DA, Bardina L, Sampson HA. IgE and IgG4 epitope mapping by microarray immunoassay reveals the diversity of immune response to the peanut allergen, Ara h 2. *J Allergy Clin Immunol* 2005;116:893-9.
26. Augustin MT, Kokkonen J, Karttunen R, Karttunen TJ. Serum granzymes and CD30 are increased in children's milk protein sensitive enteropathy and celiac disease. *J Allergy Clin Immunol* 2005;115:157-62.
27. Kalach N, Soulaïnes P, De Boissieu D, Dupont C. A pilot study of the usefulness and safety of a ready-to-use atopy patch test (Diallertest) versus a comparator (Finn Chamber) during cow's milk allergy in children. *J Allergy Clin Immunol* 2005;116:1321-6.
28. Bolhaar ST, van de Weg WE, van Ree R, Gonzalez-Mancebo E, Zuidmeer L, Bruijnzeel-Koomen CA, et al. In vivo assessment with prick-to-prick testing and double-blind, placebo-controlled food challenge of allergenicity of apple cultivars. *J Allergy Clin Immunol* 2005;116:1080-6.
29. Gilissen LJ, Bolhaar ST, Matos CI, Rouwendal GJ, Boone MJ, Krens FA, et al. Silencing the major apple allergen Mal d 1 by using the RNA interference approach. *J Allergy Clin Immunol* 2005;115:364-9.
30. Srivastava KD, Kattan JD, Zou ZM, Li JH, Zhang L, Wallenstein S, et al. The Chinese herbal medicine formula FAHF-2 completely blocks anaphylactic reactions in a murine model of peanut allergy. *J Allergy Clin Immunol* 2005;115:171-8.
31. Enrique E, Pineda F, Malek T, Bartra J, Basagana M, Tella R, et al. Sublingual immunotherapy for hazelnut food allergy: a randomized, double-blind, placebo-controlled study with a standardized hazelnut extract. *J Allergy Clin Immunol* 2005;116:1073-9.
32. Aceves SS, Dohil R, Newbury RO, Bastian JF. Topical viscous budesonide suspension for treatment of eosinophilic esophagitis. *J Allergy Clin Immunol* 2005;116:705-6.
33. Bousquet PJ, Co-Minh HB, Arnoux B, Daures JP, Demoly P. Importance of mixture of minor determinants and benzylpenicilloyl poly-L-lysine skin testing in the diagnosis of beta-lactam allergy. *J Allergy Clin Immunol* 2005;115:1314-6.
34. Win PH, Brown H, Zankar A, Ballas ZK, Hussain I. Rapid intravenous cephalosporin desensitization. *J Allergy Clin Immunol* 2005;116:225-8.
35. Fontaine C, Bousquet PJ, Demoly P. Anaphylactic shock caused by a selective allergy to celecoxib, with no allergy to rofecoxib or sulfamethoxazole. *J Allergy Clin Immunol* 2005;115:633-4.
36. Talhari C, Lauceviciute I, Enderlein E, Ruzicka T, Homey B. COX-2-selective inhibitor valdecoxib induces severe allergic skin reactions. *J Allergy Clin Immunol* 2005;115:1089-90.
37. Kanny G, Pichler W, Morisset M, Franck P, Marie B, Kohler C, et al. T cell-mediated reactions to iodinated contrast media: evaluation by skin and lymphocyte activation tests. *J Allergy Clin Immunol* 2005;115:179-85.
38. Muller UR, Haeberli G. Use of beta-blockers during immunotherapy for Hymenoptera venom allergy. *J Allergy Clin Immunol* 2005;115:606-10.
39. Konno S, Golden DB, Schroeder J, Hamilton RG, Lichtenstein LM, Huang SK. Level of osteopontin is increased after bee venom immunotherapy. *J Allergy Clin Immunol* 2005;115:1317-8.
40. Konno S, Golden DB, Schroeder J, Hamilton RG, Lichtenstein LM, Huang SK. Increased expression of osteopontin is associated with long-term bee venom immunotherapy. *J Allergy Clin Immunol* 2005;115:1063-7.
41. Hilger C, Bessot JC, Hutt N, Grigioni F, De Blay F, Pauli G, et al. IgE-mediated anaphylaxis caused by bites of the pigeon tick *Argas reflexus*: cloning and expression of the major allergen Arg r 1. *J Allergy Clin Immunol* 2005;115:617-22.
42. Hoffman DR, Sakell RH, Schmidt M. Sol i 1, the phospholipase allergen of imported fire ant venom. *J Allergy Clin Immunol* 2005;115:611-6.
43. Asero R, Orsatti A, Tedeschi A, Lorini M. Autoimmune chronic urticaria associated with type 1 diabetes and Graves' disease. *J Allergy Clin Immunol* 2005;115:1088-9.
44. De Swertdt A, Van Den KC, Kasran A, Cadot P, Neyens K, Coorevits L, et al. Detection of basophil-activating IgG autoantibodies in chronic idiopathic urticaria by induction of CD 63. *J Allergy Clin Immunol* 2005;116:662-7.
45. Soundararajan S, Kikuchi Y, Joseph K, Kaplan AP. Functional assessment of pathogenic IgG subclasses in chronic autoimmune urticaria. *J Allergy Clin Immunol* 2005;115:815-21.
46. Fukunaga A, Bito T, Tsuru K, Oohashi A, Yu X, Ichihashi M, et al. Responsiveness to autologous sweat and serum in cholinergic urticaria classifies its clinical subtypes. *J Allergy Clin Immunol* 2005;116:397-402.
47. Morar N, Willis-Owen SAG, Moffatt MF, Cookson WOC. The genetics of atopic dermatitis. *J Allergy Clin Immunol* 2006. In press.
48. Graves PE, Siroux V, Guerra S, Klimecki WT, Martinez FD. Association of atopy and eczema with polymorphisms in T-cell immunoglobulin domain and mucin domain-IL-2-inducible T-cell kinase gene cluster in chromosome 5 q 33. *J Allergy Clin Immunol* 2005;116:650-6.
49. Novak N, Kruse S, Potreck J, Maintz L, Jenneck C, Weidinger S, et al. Single nucleotide polymorphisms of the IL18 gene are associated with atopic eczema. *J Allergy Clin Immunol* 2005;115:828-33.
50. Cork MJ, Robinson DA, Vasilopoulos Y, Ferguson A, Moustafa M, MacGowen A, et al. New perspectives on epidermal barrier dysfunction in atopic dermatitis: gene-environment interactions. *J Allergy Clin Immunol* 2006. In press.
51. Weidinger S, Klopp N, Rummeler L, Wagenpfeil S, Novak N, Baurecht HJ, et al. Association of NOD1 polymorphisms with atopic eczema and related phenotypes. *J Allergy Clin Immunol* 2005;116:177-84.
52. Ahmad-Nejad P, Mrabet-Dahbi S, Breuer K, Klotz M, Werfel T, Herz U, et al. The toll-like receptor 2 R753Q polymorphism defines a subgroup of patients with atopic dermatitis having severe phenotype. *J Allergy Clin Immunol* 2004;113:565-7.
53. Tosi MF. Innate immune responses to infection. *J Allergy Clin Immunol* 2005;116:241-9.
54. Williams HC, Johansson SG. Two types of eczema—or are there? *J Allergy Clin Immunol* 2005;116:1064-6.
55. Kusel MM, Holt PG, de Klerk N, Sly PD. Support for 2 variants of eczema. *J Allergy Clin Immunol* 2005;116:1067-72.
56. Schmid-Grendelmeier P, Fluckiger S, Disch R, Trautmann A, Wuthrich B, Blaser K, et al. IgE-mediated and T cell-mediated autoimmunity against manganese superoxide dismutase in atopic dermatitis. *J Allergy Clin Immunol* 2005;115:1068-75.
57. Mothes N, Niggemann B, Jenneck C, Hagemann T, Weidinger S, Bieber T, et al. The cradle of IgE autoreactivity in atopic eczema lies in early infancy. *J Allergy Clin Immunol* 2005;116:706-9.
58. Flohr C, Johansson SG, Wahlgren CF, Williams H. How atopic is atopic dermatitis? *J Allergy Clin Immunol* 2004;114:150-8.
59. Haileamlak A, Dagoye D, Williams H, Venn AJ, Hubbard R, Britton J, et al. Early life risk factors for atopic dermatitis in Ethiopian children. *J Allergy Clin Immunol* 2005;115:370-6.
60. Raap U, Goltz C, Deneka N, Bruder M, Renz H, Kapp A, et al. Brain-derived neurotrophic factor is increased in atopic dermatitis and modulates eosinophil functions compared with that seen in nonatopic subjects. *J Allergy Clin Immunol* 2005;115:1268-75.

61. Kanda N, Koike S, Watanabe S. IL-17 suppresses TNF-alpha-induced CCL27 production through induction of COX-2 in human keratinocytes. *J Allergy Clin Immunol* 2005;116:1144-50.
62. Burns R, Luzina I, Nasir A, Haidaris CG, Barth RK, Gaspari AA. Keratinocyte-derived, CD80-mediated costimulation is associated with hapten-specific IgE production during contact hypersensitivity to TH1 haptens. *J Allergy Clin Immunol* 2005;115:383-90.
63. Fonacier L, Spergel J, Charlesworth EN, Weldon D, Beltrani V, Bernhisel-Broadbent J, et al. Report of the topical calcineurin inhibitor Task Force of the American College of Allergy, Asthma and Immunology and the American Academy of Allergy, Asthma and Immunology. *J Allergy Clin Immunol* 2005;115:1249-53.
64. Hoetzenecker W, Ecker R, Kopp T, Stuetz A, Stingl G, Elbe-Burger A. Pimecrolimus leads to an apoptosis-induced depletion of T cells but not Langerhans cells in patients with atopic dermatitis. *J Allergy Clin Immunol* 2005;115:1276-83.
65. Viljanen M, Pohjavuori E, Haahtela T, Korpela R, Kuitunen M, Sarnesto A, et al. Induction of inflammation as a possible mechanism of probiotic effect in atopic eczema-dermatitis syndrome. *J Allergy Clin Immunol* 2005;115:1254-9.