

# Advances in allergic skin disease, anaphylaxis, and hypersensitivity reactions to foods, drugs, and insect stings

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

This review highlights some of the research advances in allergic skin disease, anaphylaxis, and hypersensitivity reactions to foods, drugs, and insect venom that were reported primarily in the *Journal of Allergy and Clinical Immunology* from 2002 through 2003. Among the topics highlighted are new insights into the pathogenesis of atopic dermatitis and potential strategies for more effective treatment of the atopic march. Patients should remain supine with raised legs during anaphylactic shock because upper body elevation could result in sudden death from loss of venous return to the heart. A major advance in food allergy was that humanized, monoclonal anti-IgE antibody showed protection against peanut-induced anaphylaxis. In addition to studies elucidating mechanisms of drug hypersensitivity, a clinical study showed patients with a history of prior penicillin allergy with negative penicillin allergy test results are unlikely to experience reactions or resensitization on subsequent oral courses of penicillin. Lastly, there are new recommendations for patients with convincing insect sting reaction histories but negative skin test responses to venom. (*J Allergy Clin Immunol* 2004;114:-118-24.)

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

More than 100 articles concerning allergic skin disease, anaphylaxis, and hypersensitivity to foods, drugs, and insect venom were published in the *Journal of Allergy and Clinical Immunology* from October 2002 through December 2003. The current review highlights key advances in these areas reflected primarily by studies in the Journal, with additional pertinent material selected from the literature (Table I).

### Abbreviations used

AD: Atopic dermatitis

IDEC: Inflammatory dendritic epidermal cell

VIP: Vasoactive intestinal polypeptide

## ANAPHYLAXIS

Simons et al<sup>1</sup> analyzed prescription patterns for self-injectable epinephrine in Manitoba, Canada. Remarkably, they found that 0.95% of the population was prescribed this drug, with a peak prescription rate of 1.44% for children. Boys were prescribed epinephrine more frequently than girls, and adult women were prescribed epinephrine more than men, with the highest rate for boys aged 12 to 17 months (5.3%). These data cannot precisely reflect the rate of anaphylaxis or the percentage of the population at risk but clearly define anaphylaxis as a common disorder with a particular pattern of age and sex distribution that presents an important area of future research.

In addition to epinephrine, 2 additional therapies for anaphylaxis received attention in the Journal. Vadas and Perelman<sup>2</sup> performed *in vitro* studies showing that activated charcoal efficiently binds peanut protein and blocked binding by peanut to IgE, as demonstrated by a sandwich ELISA, Western blotting, and reduced skin prick test responses. They also showed efficiency in binding at low pH and when food matrices were present (eg, peanut in ice cream). Although the supposition is that activated charcoal may be a good adjunct for treatment of accidental peanut ingestion (as is commonly used for poison control) and perhaps other ingested allergens, studies are needed in a more clinically relevant system because there are physiologic (absorption of the protein before and despite charcoal therapy), practical (a large volume of offensive-tasting liquid charcoal to ingest), and medical (charcoal inactivation of oral medications, dangerous if aspirated) issues that need to be evaluated.

An astute observation by Pumphrey<sup>3</sup> may provide an immediate directive toward improved treatment of outpatient anaphylaxis. He noted in 10 cases of fatal anaphylaxis in which postural information was available that persons died while in an upright position. In fact, 4 of the deaths occurred within seconds of the victim being

From <sup>a</sup>The Elliot and Roslyn Jaffe Food Allergy Institute, Division of Allergy and Immunology, Department of Pediatrics, Mount Sinai School of Medicine, New York, and <sup>b</sup>the Department of Pediatrics, University of Colorado Health Sciences Center, Division of Pediatric Allergy/Immunology, National Jewish Medical and Research Center, Denver.

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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.

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TABLE I. Key advances

**Anaphylaxis.** Patients should remain supine with raised legs during anaphylactic shock because upper body elevation could result in sudden death from loss of venous return to the heart.

**Food hypersensitivity.** Proof of concept that humanized, monoclonal anti-IgE antibody can provide protection against peanut-induced anaphylaxis.

**Drug hypersensitivity.** Patients with a history of prior penicillin allergy with negative penicillin allergy tests are unlikely to experience reactions or re-sensitization on subsequent oral courses of penicillin.

**Insect venom hypersensitivity.** Patients with convincing histories but negative skin test responses may be at risk; repeated testing with skin and serum tests and warnings to avoid the insects and have epinephrine available are advised.

**Atopic dermatitis.** Microbial products influence the course of skin disease. The role of cytokines, chemokines, and FcεRI dendritic cells continue to be delineated.

placed upright after being supine. He explains that in shock there is insufficient venous return, so that moving the patient into the upright position may result in a sudden loss of filling to the heart and a cascade of events leading to circulatory collapse and cardiac ischemia. Conversely, raising the legs while leaving the individual supine may increase blood flow by means of autotransfusion. Therefore for anaphylactic shock, forget the old adage and plan for your patient to indeed “take this lying down.”

We may be nearer to understanding why there are persons who can eat wheat without incident unless they exercise, in which case they experience anaphylaxis. Palosuo et al<sup>4</sup> showed that individuals with wheat-dependent, exercise-induced anaphylaxis have IgE antibody directed to omega-5 gliadin and, in a series of *in vitro* experiments and with skin prick tests, further showed that digested wheat treated with tissue transglutaminase, compared with untreated wheat, caused large peptide complexes with enhanced IgE binding. These findings raise the interesting hypothesis that an exercise-induced activation of tissue transglutaminase may be a factor in this disorder.

## FOOD ALLERGY

The notion that food allergy has increased in prevalence has been promulgated with little direct evidence. Two studies in the Journal have now documented an increase in peanut allergy in young children. Grundy et al<sup>5</sup> compared a birth cohort of 1273 children on the Isle of Wight, United Kingdom, born in 1989 and followed to age 4 years with another cohort of 1218 born from 1994 through 1996 followed to age 3 years. Remarkably, the rate of positive skin test responses to peanut tripled from 1% to 3.3% ( $P = .001$ ), and the rate of reported reactions doubled from 0.5% to 1% (and approximately 1.5% were estimated to have peanut allergy when allergy was evaluated in children who had not knowingly eaten peanut). Sicherer et al<sup>6</sup> performed a nationwide random telephone survey in the United States in 2002 with the same methodology used in 1997 to estimate the prevalence of peanut allergy by self-report. In 2002, the rate of reported peanut allergy in children younger than 18 years of age was 0.8%, which was double the rate reported in 1997 (0.4%,  $P = .05$ ). The study did not include physician evaluations, but Kagan et al<sup>7</sup> performed a comprehensive evaluation of peanut

allergy in Montreal schoolchildren from kindergarten to third grade that included IgE antibody tests and oral food challenges to confirm diagnoses; with conservative estimates, the rate of peanut allergy in these young children was an alarming 1.34% (95% CI, 1.08% to 1.64%).

While we await epidemiologic studies regarding prevalence rates of other common food allergies, focus on peanuts continues. Why has there been an increase? What else can be done? Rational and effective prevention strategies require data on risk factors. A variety of factors have been considered, including that roasting of peanut may enhance allergenicity,<sup>8-10</sup> that our environment may promote allergic responses (eg, the hygiene hypothesis), and that early exposure (eg, through breast milk) could be an issue, but there are few data.<sup>11</sup> Lack et al<sup>12</sup> reported factors associated with peanut allergy by means of analysis of a cohort of 13,971 preschool children participating in the Avon Longitudinal Study of Parents and Children. Peanut allergy was independently associated with use of soy formula (odds ratio, 2.6), complaints that may indicate atopic dermatitis (AD; odds ratio, 2.6-5.2), and the use of skin creams that contain peanut protein (odds ratio, 6.8), although such creams are not in widespread use in the United States. Interestingly, after regression analysis, the study did not support the hypotheses that maternal ingestion of peanut during pregnancy or lactation was a significant risk factor. The observation that infant skin cream with peanut but not nipple creams with peanut protein (nor maternal ingestion) were factors associated with peanut allergy raised the interesting hypothesis that skin rather than oral sensitization may be occurring in peanut allergy, but the study results must be confirmed.

Another interesting hypothesis regarding the development of food allergy is that inefficient digestion, as may be the case in neonates, may expose the immune system to a higher load of allergenic components of foods, particularly novel ones. Untersmayr et al<sup>13</sup> noted that a nonatopic adult reacted to caviar after ingesting this food while using sucralfate and designed a study to test the influence of antacids on food sensitization. Attempts to sensitize BALB/c mice to caviar and recombinant parvalbumin were undertaken with and without ranitidine, omeprazole, or sucralfate; acid blockade facilitated generation of caviar-specific IgE and resulted in increased numbers of gastrointestinal eosinophils and mast cells. The effect of antacid therapies on food allergy in human

subjects, in particular the use of these medications in young children with reflux symptoms, remains to be explored.

Although advances are being made in stemming the rising tide of food allergy, important advances have also been made that have practical management implications, some immediate and some emerging. With respect to peanut allergy, Fleischer et al<sup>14</sup> re-evaluated their approach to young patients with the possibility of resolved peanut allergy. Eighty children at a median age of 6 years with peanut IgE concentrations of 5 kIU/L or less were evaluated, and 55% overall and 63% of those with levels of 2 kIU/L or less passed challenges, confirming that young children with peanut allergy deserve evaluations for possible resolution. The study also found 2 children who may have subsequently reacquired their allergy, and therefore caution is advised, particularly if the children do not regularly consume peanut.

Families with children with peanut allergy often harbor anxiety regarding reactions from casual exposure. Simonte et al<sup>15</sup> exposed children highly allergic to peanut to inhalation of peanut butter for 10 minutes and to skin contact with a small amount of peanut butter for 1 minute and found no reactions aside from local ones from contact. They concluded with 96% confidence that 90% of children highly allergic to peanut would not have a reaction from similar contact with peanut butter. Although the result does not indicate a change in approach to the management of peanut allergy, the study may alleviate some of the anxiety. The issue of ingestion of peanut is, of course, a more serious issue. Wensing et al<sup>16</sup> studied 26 adults with peanut allergy and found that reactions could be elicited by as little as 100 µg, and 50% of the adults had reacted by the time they ingested 3 mg. Patients with more severe reaction histories were sensitive to lower doses. These findings have strong implications for industry and food safety and the need for sensitive assays to detect peanut protein in foods.<sup>17</sup>

Another common clinical condition is oral allergy syndrome. Ma et al<sup>18</sup> surveyed allergists and found a wide range of practice responses regarding the care of patients with this syndrome. For example, about 50% recommended complete avoidance of fruits causing this reaction, whereas 9% never did, and 3% always prescribed self-injectable epinephrine, whereas 30% never did. The authors suggested that the term *pollen food allergy syndrome* be used to express the scenario of mild oral symptoms to fruits caused by homologous but labile proteins to which sensitization developed initially after respiratory exposure to pollen. However, a uniform practice approach will not be easily forthcoming until we are better able to differentiate persons with or without a risk for severe reactions. Major headway toward this type of diagnostic ability is being reported through the study of specific triggering proteins and epitopes.<sup>19-22</sup>

Perhaps one of the greatest leaps in treatment of food allergy was reported in the *New England Journal of Medicine*.<sup>23</sup> A double-blind, randomized, dose-ranging trial of a humanized monoclonal anti-IgE antibody (TNX-

901) was conducted in adults with peanut allergy. At the highest dose of anti-IgE tested, the threshold of peanut sensitivity increased from about one half to almost 9 peanuts. The study proved the concept that this treatment could provide a potential safety net for persons undertaking peanut avoidance. However, practical use of this treatment has not reached fruition because about 20% of the subjects experienced no protection at the highest dose, a significant problem that must be addressed, and the antibody tested has become commercially unavailable (a commercially available anti-IgE product may have different properties than the one studied). However, anti-IgE remains a tenable approach to peanut and other food allergies, albeit not curative. In one of several current research approaches to more definitive therapy, Li et al<sup>24</sup> reported the results of immunotherapy with heat-killed *Escherichia coli* producing recombinant peanut proteins (altered to reduce IgE binding) injected per rectum in a murine model of peanut allergy. At maximal doses, this therapy suppressed peanut-induced anaphylaxis nearly completely out to 22 weeks, with significant reduction in peanut IgE levels, and altered T<sub>H</sub>2 to T<sub>H</sub>1 cytokine profiles were observed. While various therapies must move from animals to human subjects, an additional important advance is the use of additional animal models, such as the atopic dog, to evaluate food allergy.<sup>25</sup>

## DRUG ALLERGY

Several studies have addressed common clinical concerns in the area of drug hypersensitivity. Gyllfors et al<sup>26</sup> evaluated the potential for reactions to COX-2—selective nonsteroidal anti-inflammatory agents in 33 adults with challenge-proved, aspirin-intolerant asthma. None reacted to blinded challenges and open treatment with celecoxib. As reviewed in last year's *Advances*<sup>27</sup> and cautioned by the authors of this study, persons with aspirin-induced urticaria and anaphylactoid reactions appear to have a risk of reaction to COX-2—selective agents, and more long-term studies in aspirin-induced asthma are needed before routine use of COX-2 inhibitors for persons with aspirin-induced asthma can be recommended. Another issue regarding cross-reactivity is the conundrum of using sulfonamide nonantibiotics (eg, furosemide) in persons with allergy to sulfonamide antibiotics. Strom et al<sup>28</sup> conducted a retrospective cohort study aimed toward persons with a reaction to sulfonamide nonantibiotics culled from the General Practice Research Database in the United Kingdom with information on more than 8 million patients. Although they documented an increased risk for a person with a reported sulfonamide antibiotic allergy to react to nonantibiotic sulfonamides (odds ratio, 2.8), the risk that such persons would react to penicillin was even greater (odds ratio, 3.9). The study was faulted by loose definitions of allergy and the retrospective design, but it appears to support the notion that there is not relevant allergic cross-reactivity between sulfonamide antibiotics and nonantibiotics,

although persons with a reported reaction to a drug may have a general increased risk to react to others.

Another common clinical question has been addressed by Macy et al<sup>29</sup> regarding the clinical course of patients with a history of allergy to penicillin administered orally who have negative test responses in advance of their need for treatment. The authors reviewed medical records of 568 such individuals who received at least one course of oral penicillin after their negative test response (from a total of 1246 persons with negative skin test responses evaluated initially over about 6.5 years). These patients had received from 1 to 22 courses of penicillin (mean, 4), and 65 (11.4%) reported reactions (6 subjects had 2 reactions each), with 27 (4.8%) reporting the reaction on their first oral re-exposure. There were no serious reactions; 66.2% of reactions included rash. Repeated testing was done in 33 subjects older than 18 years, and only 1 result was positive. The authors concluded that penicillin use after a negative penicillin skin test result done in advance of need is safe and resensitization is rare, a conclusion supporting previous reports in children<sup>30</sup> and a study of a smaller group of adults.<sup>31</sup> An additional practical skin test–related study was performed by Empedrad et al,<sup>32</sup> who determined the maximal non-irritating intradermal concentration of 15 common antibiotics on 25 healthy subjects. Although the sensitivity and specificity of testing with most agents is not known, the published table of concentrations provides a practical guide in which a positive test result may indicate IgE-mediated sensitization and a negative test result may indicate a starting point for desensitization.

Several insights into the role of the T cell in drug hypersensitivity were reported this year in the Journal. Naisbitt et al<sup>33</sup> evaluated T-cell responses in 4 subjects with significant reactions (skin rashes, including Stevens-Johnson syndrome, toxic epidermal necrolysis, and fever) to lamotrigine, an anticonvulsant. Lymphocytes from 3 of the 4 patients proliferated when stimulated with lamotrigine, and 44 drug-specific T-cell clones were generated from one patient. All expressed the skin-homing receptor cutaneous lymphocyte antigen and most were CD4<sup>+</sup>, with occasional CD8<sup>+</sup> cells. The clones were cytotoxic and secreted perforin, IFN- $\gamma$ , IL-5, macrophage inflammatory protein 1 $\alpha$ , macrophage inflammatory protein 1 $\beta$ , RANTES, and I-309. Lamotrigine was present on HLA-DR and HLA-DQ caused by antigen-presenting cells in the absence of drug metabolism and processing, and no cross-reactivity was seen with other anticonvulsants. The authors concluded that at least some lamotrigine hypersensitivity reactions are mediated by T cells whose activation characteristics are consistent with the clinical symptoms and that metabolism of the drug is not required to stimulate the response. Teraki and Shiohara<sup>34</sup> characterized T cells by means of flow cytometry with material obtained by means of biopsy of fixed drug eruptions caused by a variety of medications at a time of activity (challenge) and rest (pigmented lesions). In resting lesions most of the intraepidermal T cells were of the CD8 phenotype, most of which expressed cutaneous

lymphocyte–associated antigen,  $\alpha$ 4 $\beta$ 1, CD11a,  $\alpha$ E $\beta$ 7, and CD45RA but not CD27, CD62L, CCR4, or CCR7. This population selectively expressed CD122 but not CD25. Intracellular staining demonstrated that most intraepidermal CD8<sup>+</sup> T cells were capable of producing IFN- $\gamma$  and TNF- $\alpha$  but produced little IL-2 and IL-4. In contrast, after drug challenge, a significant number of CD4<sup>+</sup> T cells capable of producing IL-10 migrated into the lesional epidermis, and nearly 70% expressed CD25. The authors concluded that IFN- $\gamma$ –producing CD8<sup>+</sup> T cells and regulatory IL-10–producing CD4<sup>+</sup> T cells might be responsible for the progression and resolution of fixed drug eruption, respectively.

## INSECT HYPERSENSITIVITY

Golden et al,<sup>35</sup> writing for the Insect Committee of the American Academy of Allergy, Asthma and Immunology, presented a rostrum regarding the approach to patients with negative venom skin test responses who have a history of a systemic reaction to an insect sting. Recognizing reports that *in vitro* test results are positive in 10% or more of persons with an insect reaction history but negative venom skin test responses, that some series report negative skin test responses in nearly 30% of persons with convincing histories of systemic sting reactions, and that deaths and severe systemic reactions have been reported from re-stings in these patients, the Committee made several new recommendations. They advise that in some circumstances *in vitro* testing for venom-specific IgE antibody and skin tests may be complementary and may need to be repeated for confirmation, particularly in patients with a history of severe reactions who have negative venom skin test responses. Also, they indicate that repeated negative test responses may not guarantee safety and suspected high-risk patients should be counseled on avoidance and treatment strategies and prescribed self-injectable epinephrine.

## ATOPIC DERMATITIS

AD continues to attract increasing attention because of its increasing prevalence and the compromised quality of life of patients with this disease.<sup>36</sup> Using wrist actigraphy as an objective and unobtrusive measure of sleep at home, Bender et al<sup>37</sup> reported that sleep is significantly disturbed in patients with AD. Interestingly, patients' perceptions of their sleep provided less detail and accuracy than actigraphy. Thus actigraphy may provide more objective outcomes of sleep disturbance than questionnaires in clinical trials. As the first step in the atopic march, effective treatment of AD is also being examined as one strategy for reducing the onset or severity of respiratory allergy.<sup>38</sup>

## Immune mechanisms

Advances continue to be made in our understanding of the cytokines, chemokines, and cells involved in shaping the immunologic picture of AD (reviewed by Novak et al<sup>39</sup>). Chronic AD is associated with features of tissue

remodeling and fibrosis. Toda et al<sup>40</sup> evaluated the potential role of several remodeling cytokines in the pathogenesis of chronic AD. TGF- $\beta$ 1 expression was markedly enhanced in both acute and, in particular, chronic skin lesions. IL-11 expression was significantly increased only in chronic lesions, and IL-17 was preferentially associated with acute lesions. Although collagen type III deposition was not significantly different among the groups, type I collagen deposition was significantly increased in chronic AD lesions. There was a significant correlation between IL-11 and type I collagen deposition, as well as the number of eosinophils in skin specimens from patients with AD. These results suggest that TGF- $\beta$ 1, IL-11, and IL-17 are involved in the tissue remodeling of skin lesions in patients with AD. However, these cytokines are preferentially expressed at different stages of the disease.

Because it has been suggested that the interaction between mast cells and nerves in patients with AD may be mediated by neuropeptides, such as vasoactive intestinal polypeptide (VIP), Groneberg et al<sup>41</sup> assessed the role of the inducible VIP receptor VPAC2 in AD. In situ hybridization and immunohistochemistry studies of human skin sections demonstrated VPAC2 mRNA and protein expression in mast cells surrounded by VIP-positive nerve fibers. Stimulation of mast cell lines resulted in downregulation of VPAC2. Interestingly, quantitative immunohistochemistry for VPAC2 in acute AD skin lesions showed a significantly decreased VPAC2 immunoreactivity in mast cells. These studies suggest a role for this G protein-coupled receptor in the pathophysiology of AD.

There has been considerable interest in the molecules controlling infiltration of inflammatory cells into atopic skin. In a DNA microarray study, Nomura et al<sup>42</sup> found that 18 genes, including the CC chemokines *CCL13/MCP4*, *CCL18/PARC*, and *CCL27/CTACK*, showed a statistically significant greater than 2-fold increase in gene expression compared with that seen in patients with psoriasis. In the skin of patients with psoriasis, a total of 62 genes, including *CCL4/MIP1*, *CCL20/MIP3*, *CXCL2/GROB*, *CXCL8/IL8*, and *CXCR2/IL8R*, showed a greater than 2-fold increase of gene expression compared with that seen in the skin of patients with AD. These results show a very distinctive gene expression pattern in AD compared with that in psoriasis that may explain several features of these conditions, including the specific inflammatory cell infiltrates observed in these disorders (ie, T<sub>H</sub>2 cells, eosinophils, and mast cells in AD and T<sub>H</sub>1 cells and neutrophils in psoriasis). Consistent with these findings, Kakinuma et al<sup>43</sup> found increased serum levels of cutaneous T cell-attracting chemokine (CCL27) levels in patients with AD. These and other observations point to certain candidate genes that may function to enhance infiltration of immune effector cells into the skin.

Interestingly, Reich et al<sup>44</sup> found an association of allergic contact dermatitis, but not AD, with a promoter polymorphism in the *IL16* gene, which is involved in the chemotactic response of CD4<sup>+</sup> T cells.

Patients with AD frequently have increased IgE levels. Although it is widely accepted that IgE mediates immediate-type allergic responses, such as urticaria, the role of IgE in chronic allergic inflammation is not well established. To study this further, Sato et al<sup>45</sup> investigated the role of IgE in chronic cutaneous allergic reactions by using 2 newly developed lines of antigen-specific IgE transgenic mice. A single subcutaneous injection of the relevant antigen into the ear of these IgE transgenic mice resulted not only in the usual immediate and late ear swelling but also in a third phase of ear swelling 2 to 3 days after the antigen challenge that was associated with intense skin inflammation lasting more than 1 month. These results support the role of IgE in chronic allergic inflammation.

The skin of patients with AD contains an increased number of IgE-bearing Langerhans cells and inflammatory dendritic epidermal cells (IDECs) expressing Fc $\epsilon$ RI. These antigen-presenting cells play an important role in allergen presentation and development of naive T cells into T<sub>H</sub>2 cells. The highest Fc $\epsilon$ RI expression is observed in the lesional skin of patients with active AD. However, Semper et al<sup>46</sup> have recently reported that the uninvolved skin of patients with active asthma or allergic rhinitis also has increased expression of Fc $\epsilon$ RI-bearing Langerhans cells. These data support the concept of a systemic regulatory mechanism associated with active allergic disease, which is further aggravated by local inflammation in AD. It is also consistent with other studies that suggest the skin of patients with respiratory allergy is more easily irritated than that of nonatopic individuals. There has also been interest in the role of IDECs in inflammatory skin disease. Interestingly, Kerschenlohr et al<sup>47</sup> have found that IDECs infiltrate into the skin of patients with intrinsic and extrinsic AD-, contact dermatitis-, and psoriasis-induced chronic skin lesions. In atopy patch test reactions, these cells rapidly infiltrate within 72 hours. However, the specific upregulation of Fc $\epsilon$ RI occurs later during formation of extrinsic but not intrinsic AD lesions. Thus dendritic cell alteration during skin lesion formation can be subdivided into early and late events, with the influx of IDECs as an early event and the alteration of the dendritic cell phenotype as a late event.

Eosinophil granule proteins, including eosinophil cationic protein, and major basic protein, are prominently deposited in AD skin and likely contribute to disease pathology. Davis et al<sup>48</sup> investigated the persistence and induction of vasopermeabilization by eosinophil granule proteins in skin. After intradermal injection, granule proteins persisted in guinea pig skin *in vivo* for 1 week (eosinophil peroxidase), 2 weeks (eosinophil cationic protein), 2.5 weeks (eosinophil-derived neurotoxin), and 6 weeks (major basic protein). Each of the eosinophil granule proteins increased cutaneous vasopermeability in a concentration-dependent manner. The potency of vasopermeabilization induced by each granule protein was comparable with that of histamine. These data suggest that after infiltration and degranulation of eosinophils in the skin, cutaneous function may be altered for days to weeks.

## Role of microbes in AD

There are considerable data suggesting that microbes can alter the course of atopic disease. The hygiene hypothesis is frequently cited to explain the rapid increase in the prevalence of atopic diseases.<sup>49</sup> According to this hypothesis, early infections or exposure to microbially derived material, such as LPS, prevents the development of T<sub>H</sub>2-driven allergic disease. If true, polymorphisms of genes involved in the recognition of microbial material might be expected to change susceptibility for the development of allergic diseases. Indeed, polymorphisms of a number of innate immunity genes, such as the genes encoding CD14 and Toll-like receptors, have been associated with the development of allergy. Kabesch et al<sup>50</sup> reported that a polymorphism (G2722C) that results in functional impairment of caspase recruitment domain-containing protein 15, an intracellular receptor for LPS involved in nuclear factor  $\kappa$ B activation, is associated with a 2-fold increased risk of AD. Thus not only reduced microbial exposure in the environment but also impaired molecular recognition of microbial molecules may give rise to AD and allergies.

It is noteworthy, however, that the nature of the microbe is likely to be important in determining the development and course of AD. Indeed, a report by Watanabe et al<sup>51</sup> found that fecal microflora of infants with AD had low counts of bifidobacteria but had a higher frequency of *Staphylococcus aureus* than healthy infants. In an animal model of AD, Laouini et al<sup>52</sup> found that epicutaneous exposure to staphylococcal superantigens elicited a local and cutaneous inflammatory response characterized by eosinophils and T cells secreting T<sub>H</sub>2 cytokines, as well as increased serum IgE levels. Thus exposure to superantigens skews the immune response toward the induction of allergic skin inflammation.

## Management of AD

The management of AD was reviewed by Boguniewicz et al.<sup>38</sup> AD is frequently the first step in the atopic march toward respiratory allergy. Because there are no cures for asthma, the development of strategies to prevent respiratory allergy is important. One such strategy that has been proposed is to more aggressively treat and control AD with topical calcineurin inhibitors at the first signs of itching and before the development of a skin rash. This would be more similar to our approach in patients with persistent asthma to whom chronic anti-inflammatory medications are administered. Because animal models suggest that epicutaneous sensitization with allergen augments airway hyperreactivity, clinical trials are in progress to determine whether better control of AD will prevent asthma or reduce its severity.

There continue to be investigations into the potential clinical and anti-inflammatory effects of oral bacteriotherapy with probiotics in children with AD. In a double-blind, placebo-controlled, crossover study 2 probiotic *Lactobacillus* strains were given in combination for 6 weeks to 1- to 13-year-old children with AD. After

active treatment, 56% of the patients experienced improvement of the eczema, whereas only 15% believed their symptoms had improved after placebo.<sup>53</sup> The extent of the eczema significantly decreased during active treatment. The treatment response was more pronounced in allergic patients (at least one positive skin prick test response and increased IgE levels). During active treatment, serum eosinophil cationic protein levels significantly decreased. These data suggest that probiotics were beneficial in the management of AD. Further controlled studies are warranted to evaluate their efficacy and safety in larger groups of children.

## CONCLUSIONS

During the year in review, significant advances have been made in our understanding of the mechanisms underlying allergic skin diseases. Evidence mounts for a role of microbes in shaping the allergic immune response. The local expression of chemokines and cytokines, as well as IgE and Fc $\epsilon$ RI-bearing dendritic cells, plays a key role in the evolution of skin inflammatory responses. Research reported in this Journal in the past year has also expanded our understanding of the mechanisms of food and drug hypersensitivity, with a clear potential for improved diagnostic and therapeutic modalities. Importantly, research reports with imminent clinical practice implications have emerged for improved treatment of patients with anaphylaxis; hypersensitivity to foods, drugs, and insect venom; and allergic skin disease.

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