

Advances in allergic skin disease, anaphylaxis, and hypersensitivity reactions to foods, drugs, and insects in 2009

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This review highlights some of the research advances in anaphylaxis and hypersensitivity reactions to foods, drugs, and insects, as well as advances in allergic skin disease that were reported in the *Journal* in 2009. Among key epidemiologic observations, several westernized countries report that more than 1% of children have peanut allergy, and there is some evidence that environmental exposure to peanut is a risk factor. The role of regulatory T cells, complement, platelet-activating factor, and effector cells in the development and expression of food allergy were explored in several murine models and human studies. Delayed anaphylaxis to mammalian meats appears to be related to IgE binding to the carbohydrate moiety galactose- α -1,3-galactose, which also has implications for hypersensitivity to murine mAb therapeutics containing this oligosaccharide. Oral immunotherapy studies continue to show promise for the treatment of food allergy, but determining whether the treatment causes tolerance (cure) or temporary desensitization remains to be explored. Increased baseline serum tryptase levels might inform the risk of venom anaphylaxis and might indicate a risk for mast cell disorders in persons who have experienced such episodes. Reduced structural and immune barrier function contribute to local and systemic allergen sensitization in patients with atopic dermatitis, as well as increased propensity of skin infections in these patients. The use of increased doses of non-sedating antihistamines and potential usefulness of omalizumab for chronic urticaria was highlighted. These exciting advances reported in the *Journal* can improve patient care today and provide insights on how we can improve the diagnosis and treatment of these allergic diseases in the future. (*J Allergy Clin Immunol* 2010;125:85-97.)

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

Abbreviations used

ACU:	Acquired cold urticaria
AD:	Atopic dermatitis
ADEH:	Atopic dermatitis with history of eczema herpeticum
ADVN:	Atopic Dermatitis Vaccinia Network
AE:	Atopic eczema
α -gal:	Galactose- α -1,3-galactose
APST:	Autologous plasma skin test
APT:	Atopy patch test
ASST:	Autologous serum skin test
CsA:	Cyclosporin A
CU:	Chronic urticaria
DC:	Dendritic cell
DKO:	Double knockout
dsRNA:	Double-stranded RNA
EAC:	Experimental allergic conjunctivitis
EPL:	ϵ -Polylysine
FAHF-2:	Food Allergy Herbal Formula-2
FLG:	Filaggrin
GDM:	Gestational diabetes
HBD:	Human β -defensin
IL-10R2:	IL-10 receptor 2 chain
<i>KIT</i> :	Mast/stem cell growth factor receptor gene
KO:	Knockout
MIF:	Macrophage migration inhibitory factor
NHL:	Non-Hodgkin lymphoma
OFC:	Oral food challenge
OIT:	Oral immunotherapy
OR:	Odds ratio
OVA:	Ovalbumin
PAF:	Platelet-activating factor
PG:	Prostaglandin
SEB:	<i>Staphylococcal aureus</i> enterotoxin B
TCI:	Topical calcineurin inhibitor
TCS:	Topical corticosteroid
TLR:	Toll-like receptor
Treg:	Regulatory T
TSLP:	Thymic stromal lymphopoietin
VIT:	Venom immunotherapy
VV:	Vaccinia virus

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This review highlights key advances in allergic skin disease, anaphylaxis, and hypersensitivity to foods, drugs, and insect venom selected primarily from more than 90 articles on these topics published in the *Journal of Allergy and Clinical Immunology* in 2009.

FOOD ALLERGY

Epidemiology and risk factors

Epidemiologic studies on peanut allergy continue to document astoundingly high prevalence rates among children. Ben-Shoshan

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et al¹ followed up on a 2000-2002 cross-sectional prevalence study evaluating peanut allergy in 2005-2007 among kindergarten to grade 3 schoolchildren in Montreal, Quebec, Canada. The study applied allergy tests, including double-blind, placebo-controlled oral food challenges (OFCs) when possible. Among 5,161 families responding to the survey (64.2% response rate), after adjustment for missing data, an estimated 1.62% of the cohort (95% CI, 1.31% to 1.98%) had peanut allergy compared with 1.34% (95% CI, 1.08% to 1.64%) 5 years earlier (P = not significant). In a retrospective study of peanut allergy based on specialist referral and evaluations in the Australian Capital Territory, the estimated minimum incidence of peanut allergy in children by age 6 years born in 2004 was 1.15% compared with an estimate of 0.73% for those born in 2001.² The search for reasons behind the increase in atopy and food allergy remains an active area of study, with little evidence that maternal dietary allergen avoidance can reduce risk.³ One theory is that delayed introduction of peanut averts an opportunity for development of oral tolerance while allowing potentially sensitizing, noningestion environmental exposure to proceed.

Fox et al⁴ performed a questionnaire-based, case-control study evaluating maternal and household peanut consumption among 133 children with peanut allergy, 150 nonallergic children, and 160 children with egg but not peanut allergy. Although there was no difference in peanut consumption among the infants, household peanut consumption was significantly greater in the children with peanut allergy (18.8 g) compared with that in the children with egg allergy (1.9 g) or nonallergic control subjects (6.9 g). They found no relationship to maternal peanut ingestion but noted a dose-response risk relationship in household (environmental) exposure to peanut. The authors further postulate that early oral exposure might have been protective for those with environmental exposure. Finally, Visness et al⁵ noted from the US National Health and Nutrition Examination Survey (2005-2006) an increased risk of food allergen sensitization (milk, egg, peanut, and shrimp) among participants with obesity (odds ratio [OR], 1.59; 95% CI, 1.28-1.98). The observation raises interesting questions about the relationship of the obesity epidemic to the apparent increase in food allergy and how systemic inflammation noted in obesity might influence an allergic outcome.

Pathophysiology, allergen characterization, and diagnosis

Several insights on the pathophysiology and expression of food allergy were reported from murine models. Working on the hypothesis that exposure to *Staphylococcus aureus* enterotoxin B (SEB) is associated with atopic disease and addressing some shortcomings in murine food allergy models that rely on LPS-hyporesponsive strains, Ganeshan et al⁶ used orally administered SEB, with peanut and ovalbumin (OVA) showing T_H2-polarized responses (increased allergen-specific IgE and IgG1 levels), clinical reactions on rechallenge, and eosinophilia (circulating and intestinal). In a series of experiments using this model, it was noted that SEB impaired expression of TGF- β and regulatory T (Treg) cells, and in dose-ranging sensitization studies SEB promoted responses to peanut antigens by impairing low-dose tolerance. In murine models of oral antigen-induced diarrhea, in which initial sensitization is performed by means of intraperitoneal injection followed by repeated oral feeding of OVA, Brandt et al⁷ evaluated the relative roles of IL-4 and IL-13. They found that IL-13 supplements the ability of IL-4 to induce allergic diarrhea by contributing to the oral sensitization phase rather than the effector phase and that blockade of both IL-4 and IL-13 after establishment of allergic diarrhea was only partially effective at reducing diarrhea. Yamada et al⁸ used a similar model of allergic diarrhea and showed that antigen-inducible regulatory CD8⁺ T cells could prevent sensitized mice from having allergic diarrhea through both IL-10-dependant and IL-10-independent mechanisms. The above-cited models include sensitization-inducing allergen-specific IgE and IgG1.

Khodoun et al⁹ explored whether peanut could induce anaphylaxis without prior sensitization in mice pretreated with β -adrenergic receptor antagonists and IL-4 to increase sensitivity. They noted dose-dependent shock after intravenous injection of peanut extract and conducted a series of experiments to elucidate the mechanisms. They concluded that peanut extract contributed to shock through activation of complement with generation of C3a stimulating macrophages, mast cells, and basophils to produce platelet-activating factor (PAF) and histamine.

With regard to the importance of mediators in anaphylaxis, 2 additional murine studies^{10,11} of anaphylaxis to peanut emphasize a crucial role of PAF. Arias et al¹⁰ found that blockade of PAF prevented severe reactions, and blockage of both PAF and histamine had an even greater effect. Lopez-Exposito et al¹¹ noted that peanut-induced anaphylaxis on first exposure in offspring of peanut-sensitized mice was associated with peanut-specific IgG1 levels and was blocked by a PAF antagonist. In this group's experiments the offspring were more protected from peanut allergy if their peanut-sensitized mothers continued to be fed peanut during pregnancy and lactation rather than continuing avoidance after sensitization. Although this effect was likely associated with maternal transfer of peanut-specific IgG2a over IgG1 and is very different from that seen in human subjects, in which IgE is more relevant, it raises questions about the role of human maternal ingestion of peanut with regard to infant risk factors.

Two studies in human subjects evaluated the mechanistic associations related to the observation that about 70% of children with milk allergy can tolerate extensively heated milk in products such as cookies and cakes; children with this phenotype have milder disease and presumably a favorable prognosis. The contribution of Treg cells to this phenotype was observed by Shreffler et al,¹² who noted a higher percentage (median, 16.85%) of proliferating allergen-specific CD25⁺CD27⁺ T cells from cultures of the heated milk-tolerant subjects compared with those with milk allergy who react to heated milk (4.91%, $P < .01$) or control subjects with no history of milk allergy (2.9%). Children who had outgrown milk allergy had intermediate percentages (9.0%). Allergen-specific Treg cells were found to be forkhead box protein 3-positive, CD25^{hi}CD27⁺, cytotoxic T lymphocyte-associated antigen 4-positive, CD45RO⁺CD127⁻ and were derived from circulating CD25^{hi} T cells. In another study of this patient population focusing on basophil activation, Wanich et al¹³ found that basophils of children who could tolerate heated milk products were significantly less responsive to milk allergen stimulation than were basophils from children who reacted to these foods. Additionally, in the absence of autologous serum, the subjects who tolerated heated milk products were noted to have basophils that were significantly more reactive at low allergen concentrations. The autologous serum also inhibited IL-3- and anti-IgE-induced, but not N-formyl-methionyl-leucyl-phenylalanine-induced, responses, indicating that they were extrinsically suppressed. These studies therefore present insights into the mechanisms of a transitional state toward tolerance and a potential test to determine which patients might tolerate baked milk products.

Identifying and characterizing humoral and cellular responses to specific allergens within foods and to epitopes of those allergens has implications for diagnosis, prognosis, and therapy.¹⁴⁻¹⁷ Correlating clinical expression of allergy against IgE binding to specific food proteins comprises an approach termed "component-resolved diagnosis," which was the focus of several publications in 2009.¹⁸⁻²¹ For example, evaluation of patients with soy allergy from Switzerland, Denmark, and Italy identified that IgE binding to Gly m 5 or Gly m 6 was found in 86% (6/7) of subjects with anaphylaxis to soy and 55% (6/11) of subjects with moderate and only 33% (4/12) of subjects with mild soy-related symptoms (OR for severe vs mild symptoms, 12; $P < .05$).¹⁸ Studies have previously shown relationships of clinical outcomes to epitope-binding patterns, an observation that lends itself to methodologies such as microarray analysis for improved diagnostics.¹⁷

Albrecht et al²² questioned the clinical contribution of such epitopes *in vivo*. They constructed synthetic soluble peptides representing the identified sequences of Ara h 2 (peanut) and Pen a 1 (shrimp) to assess their capacity to inhibit IgE binding to the parent allergens by means of ELISA and in mediator release assays. The IgE-binding capacity of unfolded rAra h 2 was analyzed. A hybrid tropomyosin carrying the IgE-binding regions of Pen a 1 grafted into the structural context of the nonallergenic murine tropomyosin was applied in ELISA inhibition experiments and ImmunoCAP analysis. Although IgE-binding peptides representing sections of the allergen sequences were detected, no relevant capacity to inhibit the IgE binding to the parent allergen in ELISA or basophil activation tests was observed. Unfolded rAra h 2 showed reduced IgE-binding capacity compared with folded rAra h 2 and failed to elicit mediator release. Additionally, hybrid tropomyosin bound less IgE than rPen a 1 in ImmunoCAP analysis and revealed marginal inhibitory capacity. The authors concluded that IgE-binding peptides might be useful for diagnosis but might not act as full epitopes causing clinical reactions. Although various caveats in the approach can limit the conclusions (type of allergen and fluid-phase experiments), additional studies in this area will be important when considering development of therapeutic interventions.

Regarding diagnosis, OFCs remain the most definitive tool. Järvinen et al²³ reviewed their experience with administration of epinephrine during 1,273 physician-supervised diagnostic OFCs in which the test was performed primarily on patients with an estimated 50% or better chance of tolerating the feeding. Thirty-four percent of the challenge results were positive, and epinephrine was administered in 11% of these (eg, 3.9% of the total food challenges). Among many demographic features considered, only older age (7.9 vs 5.8 years, $P < .001$) and peanut allergen challenge ($P = .006$) were associated with use of epinephrine. Of 50 patients treated with epinephrine, 3 received 2 doses. Of 436 reactions during challenge, there was only 1 biphasic reaction. These data and those reviewed in a recent workgroup report on performing OFCs²⁴ provide insights on safety when undertaking this important diagnostic test.

Although dogma has been that IgE antibody-mediated, clinically significant food allergy is related primarily to recognition of proteins, Commins et al²⁵ presented a new paradigm regarding galactose- α -1,3-galactose (α -gal), which is a carbohydrate moiety expressed on nonprimate mammalian proteins. They describe 24 patients with IgE antibodies to α -gal presenting to the University of Virginia Allergy Clinic who described a history of anaphylaxis or urticaria 3 to 6 hours after the ingestion of beef, pork, or lamb. Skin prick tests to mammalian meat produced wheals of usually less than 4 mm, whereas intradermal or fresh-food skin tests provided larger and more consistent wheal responses. Serum IgE tests identified specific IgE antibodies to beef, pork, lamb, cow's milk, cat, and dog but not poultry or fish, and additional studies identified binding to α -gal. These novel observations therefore include (1) serious reactions caused by a carbohydrate determinant, (2) an unusual delay in classical anaphylactic symptoms after ingestion of a food trigger, (3) weak responses to skin prick tests, and (4) thus far an apparent geographic distribution to α -gal sensitization matching reports of cetuximab hypersensitivity (which also contains the α -gal moiety and was recently proposed for use as a diagnostic skin test reagent for α -gal sensitization).²⁶ Key questions include the pathophysiologic explanation for the delayed reaction and the initial sensitizing exposure among the adult patients described.

Treatment

Current management of food allergy requires avoidance and ready access to medications. Important pitfalls and challenges include ambiguities in labeling of manufactured foods,²⁷ avoidance of unintentional exposures at school and other settings,²⁸⁻³⁰ prevention of risk-taking behaviors,³¹ increased education about epinephrine use,³² and management of the stress of living with food allergy.³³ Thankfully, numerous studies are evaluating more definitive measures to treat or reduce the risks of food allergy. The area of most intensive investigation continues to be oral immunotherapy (OIT). Jones et al³⁴ describe their experience with peanut OIT in an open study with an intention to treat 39 children. The regimen included an initial day of escalation toward 50 mg of peanut protein, buildup to 300 mg and eventually to 1,800 mg for some after food challenges, and maintenance phases. Of 29 subjects who completed the protocol, 27 ingested 3.9 g of peanut protein during an OFC. Most symptoms noted during OIT resolved spontaneously or with antihistamines. By 6 months, titrated skin prick tests and activation of basophils significantly decreased. Peanut-specific IgE levels decreased by 12 to 18 months, whereas IgG4 levels increased significantly. Secretion of IL-10, IL-5, IFN- γ , and TNF- α from peanut-stimulated PBMCs increased over a period of 6 to 12 months. Peanut-specific forkhead box protein 3 T cell numbers increased until 12 months and then decreased, and T-cell microarrays showed downregulation of genes in apoptotic pathways. Analysis of safety data³⁵ revealed that allergic reactions to treatment were more common on the escalation days, although the risk of a reaction during home doses was 3.5%, and treatment was given for 0.7% of home doses (2/28 patients received epinephrine). Continued evaluation³⁶ of home dosing revealed circumstances related to reactions during maintenance: (1) concurrent illness, (2) suboptimally controlled asthma, (3) dose not given with other foods, (4) physical exertion after dosing, and (5) dosing during menses.

In a follow-up open study of milk OIT performed initially in a blinded, randomized controlled trial,³⁷ continued dose advancement revealed general continued success (although not uniformly) but various pitfalls as well, including unpredictable allergic reactions to doses, recurrence of allergy after brief cessation of dosing, and development of eosinophilic esophagitis. Clearly, these studies show promise, but more needs to be determined with regard to safety, acceptable dosing regimens, efficacy, prediction of patients likely to respond, and, most importantly, whether these regimens can induce permanent tolerance or only desensitization during dosing.

Additional reports on therapy include murine studies of Food Allergy Herbal Formula-2 (FAHF-2), which is also in clinical trials. In a murine study to determine long-term effects,³⁸ mice with peanut allergy received FAHF-2 daily orally by means of gavage for 7 weeks and then underwent 7 oral peanut challenges at intervals of 4 to 10 weeks over a period of 36 weeks. FAHF-2 treatment protected mice from anaphylaxis for more than 36 weeks after discontinuing treatment. Peanut-specific IgE levels were reduced as much as 50%, whereas IgG2a levels were increased as much as 60%, and these effects persisted over time. T_H2 cytokine production by CD4⁺ T cells from FAHF-2-treated mice was reduced as much as 75%, whereas CD8⁺ T-cell IFN- γ production was markedly increased by as much as 85% at the final challenge. Neutralization of IFN- γ and depletion of CD8⁺ T cells markedly attenuated FAHF-2 efficacy,

indicating these mechanisms for a central role in the treatment effect.

Another strategy for treatment involves vaccination with food allergen genes, but targeting these vaccines is problematic. A study from Behnecke et al³⁹ describes a genetically engineered human ϵ -polylysine (EPL) fusion protein that binds allergen gene expression systems and targets the gene-vaccine complex to antigen-presenting cells through the interaction of EPL and the high-affinity IgE receptor. The EPL-DNA complexes were shown not to trigger mast cell degranulation and might allow for improved allergen vaccine strategies in the future.

ANAPHYLAXIS AND HYPERSENSITIVITY TO STINGING INSECTS AND DRUGS

Liew et al⁴⁰ reviewed national databases to evaluate anaphylaxis fatalities and hospital admissions in Australia from 1997-2005. Fatality rates were approximately 0.64 per million inhabitants per year, and drug or probable drug reactions were the leading cause (58%). Although food-induced anaphylaxis admissions increased 350% over this period, food-induced anaphylaxis fatalities did not appear to increase (although drug-related anaphylaxis death rates did increase). Seven food-induced fatalities were noted, and none of these subjects appeared to have self-injected epinephrine; there was 1 child (<10 years of age), although food anaphylaxis hospital admissions were primarily among children younger than age 5 years. With regard to food-induced fatalities, the conclusion is that lack of prompt administration of epinephrine is a risk factor, but management strategies were likely successful in reducing fatalities despite an increasing prevalence of episodes.

Simons et al^{41,42} point out important anaphylaxis management risk reduction and treatment strategies. In an e-mail questionnaire study of persons having experienced anaphylaxis for themselves or having treated another with anaphylaxis who were recruited while visiting a commercial Web site about anaphylaxis, Simons et al⁴² noted that only 27% of the 1,885 participants had used epinephrine despite similar systemic reactions compared with nonusers (although users more often had shock or respiratory symptoms). Nonusers reported excuses, such as having used antihistamine (38%), not having a prescription for epinephrine (28%), or having a mild past reaction (13%). Epinephrine users described confusion regarding when to use, when to repeat doses, and when to seek emergency care. These observations are a reminder to providers to carefully review these issues with patients at risk for anaphylaxis in the community.

Determining who with insect venom hypersensitivity is at greater risk for severe reactions is an important goal, which has primarily been based on epidemiologic considerations. A working group from the European Academy of Allergology and Clinical Immunology⁴³ conducted a multicenter observational study enrolling 962 patients with Hymenoptera venom allergy (21.4% had a severe anaphylactic reaction to a field sting) to determine risk factors for severe reactions. Serum baseline tryptase was identified as a risk factor (as were vespid allergy, male sex, older age, and use of angiotensin-converting enzyme inhibitors). Bonadonna et al⁴⁴ evaluated 379 persons (266 male subjects; age range, 6-79 years; median age, 43 years) with a systemic reaction to Hymenoptera stings for serum baseline tryptase levels and found 11.6% to have levels of greater than 11.4 ng/mL, and 31

(70.5%) of these subjects had experienced anaphylaxis. Thirty-four of the 44 subjects with increased baseline serum tryptase levels (all adults) underwent a bone marrow analysis, and ultimately, 61.7% were given a diagnosis of indolent systemic mastocytosis or a monoclonal mast cell activation syndrome (26.5%); all of the subjects who had experienced anaphylaxis had one of these disorders. These studies and others indicate the need for additional diagnostic considerations in venom hypersensitivity.

Several studies on venom immunotherapy (VIT) have also added insights into pathophysiology and treatment.⁴⁵⁻⁴⁷ For example, Saverino et al⁴⁶ measured levels of soluble cytotoxic T lymphocyte-associated antigen 4, which is a potential negative regulator of T cells, in persons undergoing VIT and in healthy control subjects and subjects with respiratory allergy. They noted higher pre-VIT treatment levels of soluble cytotoxic T lymphocyte-associated antigen 4 in subjects with hymenoptera allergy compared with levels seen in control subjects, which decreased after therapy (and IL-10 levels increased). The authors propose this as a possible disease and treatment response marker, although more studies are needed. Maintz et al⁴⁸ noted that during the build-up phase of rush VIT, there were changes in histamine levels but also in expression of histamine synthesis and degradation metabolic enzymes that might influence efficacy and side effects of immunotherapy and deserve additional study.

Golden et al⁴⁵ present a pilot study on using VIT to treat large local reactions. They noted recurrence of large local reactions after sting challenge in 34 of 41 subjects, and 29 were treated with VIT for 7 to 11 weeks. Subsequent stings resulted in reactions 42% smaller in treated subjects versus 18% smaller in control subjects ($P < .01$). The response improved further with continued therapy (ie, 70% reduction at 4 years).

With regard to drug hypersensitivity, Atanaskovic-Markovic et al⁴⁹ evaluated 124 children with a history of β -lactam allergy and a positive skin test response to at least 1 β -lactam for hypersensitivity to imipenem. A total of 123 had negative test responses to imipenem and tolerated challenge, indicating a low risk of cross-reactivity in this study group.

Hesterberg et al⁵⁰ evaluated women with carboplatin hypersensitivity and noted that positive skin test responses were more likely in those with a recent reaction history; test responses became negative in as little as 9 months, but these women were at risk for conversion to positive test responses and having subsequent reactions, indicating caution for proceeding with desensitization. Additional studies on desensitization procedures for aspirin⁵¹ and mAbs^{52,53} were described.

ATOPIC DERMATITIS

Risk factors

Identification of risk factors leading to atopic dermatitis (AD) is of great importance in optimizing management of this common skin disease and early intervention in the atopic march to respiratory allergy, including eczema-associated asthma. The increased prevalence of AD and its marked geographic variation suggest that environmental factors trigger a genetically predisposed host to develop the clinical phenotype of this common skin disease. Filaggrin (*FLG*)-null mutations are the most replicated gene associations found in patients with AD and highlight the importance of barrier dysfunction in the pathogenesis of AD.^{54,55}

A recent meta-analysis of 24 studies on *FLG* mutations and eczema involving 5,791 cases, 26,454 control subjects, and 1,951 families, as well as 17 studies on asthma involving 3,138 cases, 17,164 control subjects, and 1,511 offspring, was carried out to provide an estimate of *FLG* effect sizes and to better refine *FLG* risk profiles within the broad and inclusive eczema diagnosis.⁵⁶ Both case-control and family studies showed strong associations with eczema. Combined analysis showed that *FLG* haploinsufficiency strongly increases the eczema risk and is associated with more severe skin disease. *FLG* mutations are also significantly associated with asthma. However, although strong effects for the compound phenotype asthma plus eczema were observed, there appears to be no association with asthma in the absence of eczema. This meta-analysis established the strong evidence for a high eczema risk conferred by *FLG* mutations and refines their risk profiles, suggesting an association with more severe disease. *FLG* mutations are also a robust risk factor for asthma and might help define the asthma endophenotype linked with eczema.

Because *FLG* mutations only affect a minority of patients with AD, it is likely that genetic and acquired defects in other epidermal proteins and lipids contribute to barrier dysfunction in AD.⁵⁷ De Bendetto et al⁵⁸ recently reported abnormalities in tight junctions, such as claudin, in patients with AD prone to eczema herpeticum. Using genomic analysis, Guttman-Yassky et al⁵⁹ reported that patients with AD had broad defects in epidermal cornification. In this study genomic profiling of mRNA in chronic psoriasis ($n = 15$) and AD ($n = 18$) skin lesions was compared with that in normal human skin ($n = 15$). The most striking differences were identified in epidermal differentiation programs that could be used for precise disease classifications. Although both psoriasis and AD skin lesions displayed regenerative epidermal hyperplasia, which is a general alteration in epidermal growth, keratinocyte terminal differentiation was differentially polarized. In patients with AD, they found selective defects in expression of multiple genes encoding the cornified envelope, with the largest alteration in loricrin (expressed at 2% the level of normal skin). At the ultrastructural level, the cornified envelope in patients with AD was broadly defective, with highly decreased compaction of corneocytes and reduced intercellular lipid levels. Hence the entire keratinocyte terminal differentiation program (cytoplasmic compaction, cornification, and lipid release) is defective in patients with AD. Their study shows that epidermal differentiation is differentially polarized in patients with AD and psoriasis.

Bisgaard et al⁶⁰ analyzed the effect of environmental exposures in early life and genetic predisposition on the development of eczema before age 3 years. The Copenhagen Study on Asthma in Childhood is a prospective clinical study of a birth cohort of 411 children born of mothers with asthma. Eczema was diagnosed, treated, and monitored at the clinical research unit, and complete follow-up for the first 3 years of life was available for 356 children. Their study found that eczema developed in 43.5% of the infants. *FLG* mutation, mother's eczema, and father's allergic rhinitis were directly associated with the risk of eczema. This study concluded that dog exposure reduced the risk of eczema, whereas *FLG* mutation and parental atopy increased the risk of eczema.

Kumar et al⁶¹ reported on the relationship between the prenatal environment, maternal-fetal interaction, and allergic disease in the offspring, including AD and allergen sensitization. This study included 680 children from the Boston Birth Cohort.

Mother-child dyads were recruited at birth and followed prospectively. Of the 680 children, 488 were term, and 192 were preterm (<37 weeks' gestation). Overall, 4.9% of the mothers had gestational diabetes (GDM). Among the 680 children, 34.4% had AD, and 51% had allergen sensitization. In term births GDM was significantly associated with AD and allergen sensitization. Adjusting for fetal growth had little effect. The association with allergen sensitization was driven primarily by food sensitization. The above associations were not observed in preterm births. This study indicates that in term births GDM increases the risk of AD and early childhood allergen sensitization independently of maternal prepregnancy body mass index and fetal growth.

Factors contributing to infection in patients with AD

As part of the National Institutes of Health/National Institute of Allergy and Infectious Diseases-funded Atopic Dermatitis Vaccinia Network (ADVNI), Beck et al⁶² in the ADVNI established a registry of clinical information and biologic samples of patients with AD with a history of eczema herpeticum (ADEH⁺), patients with AD without a history of eczema herpeticum (ADEH⁻), and healthy subjects. They analyzed the data from 901 subjects (ADEH⁺ subjects, n = 134; ADEH⁻ subjects, n = 419; and healthy control subjects, n = 348) at 7 US medical centers. They found that ADEH⁺ subjects had more severe skin disease and biomarkers (circulating eosinophil counts and serum IgE, thymus and activation-regulated chemokine, and cutaneous T cell-attracting chemokine) than ADEH⁻ subjects. ADEH⁺ subjects were also more likely to have a history of food allergy or asthma and were more commonly sensitized to many common allergens. Cutaneous infections with *Staphylococcus aureus* or molluscum contagiosum virus were more common in ADEH⁺ subjects than in ADEH⁻ subjects. Overall, this report indicates that subjects with AD in whom eczema herpeticum develops have more severe T_H2-polarized disease with greater allergen sensitization and more commonly have a history of food allergy, asthma, or both. They were also much more likely to experience cutaneous infections with *S aureus* or molluscum contagiosum.

The increased propensity of patients with AD to have bacterial and viral skin infections, as well as chronic skin inflammation, likely results from cross-talk between the innate and adaptive immune response. T_H2 cytokines, such as IL-4 and IL-13, have been found to inhibit the expression and secretion of keratinocyte-derived antimicrobial peptides required for killing of bacteria and viruses.^{63,64} Leung et al⁶⁵ have also found that patients with ADEH have reduced production of IFN- γ by their circulating T cells.

Recent studies have demonstrated that T_H2 cytokines might inhibit keratinocyte-derived production of antimicrobial peptides by downregulating the *S100A11* gene, a calcium-binding member of the epidermal differentiation complex located on chromosome 1q21, where other epidermal barrier proteins, including filaggrin, are encoded. Bin et al⁶⁶ investigated the mechanism by which *S100A11* affects the innate immune response of keratinocytes. Small interfering RNA duplexes were used to reduce gene expression of *S100A11* in keratinocytes. Keratinocytes with deficient *S100A11* expression supported increased vaccinia virus (VV) replication and manifested augmented VV cytopathic effects. Gene microarray analysis revealed downregulation of the keratinocyte IL-10 receptor 2 chain (IL-10R2), which binds type 3 interferons

(including IL-29) known to have potent antiviral actions. IL-10R2 expression was also found to be decreased in skin biopsy specimens from patients with acute infection compared with skin from healthy subjects. Furthermore, deficient *S100A11* gene expression significantly impaired IL-29 responsiveness and its anti-VV effects in keratinocytes. These data suggest that inhibition of *S100A11* gene expression impairs the ability of keratinocytes to control VV replication through downregulation of IL-10R2.

The adaptive immune response

Studies on the role of IL-17 in skin immune responses has been an active area of investigation. Eyerich et al⁶⁷ evaluated the effect of IL-17 on antimicrobial immune responses in skin from patients with atopic eczema (AE). T cells infiltrating atopy patch test (APT) reactions were characterized for IL-17 secretion to varying stimuli. IL-17-dependent induction of the antimicrobial peptide human β -defensin (HBD) 2 in keratinocytes was examined. Approximately 10% of APT-infiltrating T cells secreted IL-17 after phorbol 12-myristate 13-acetate/ionomycin stimulation. Among these, 33% belonged to the newly characterized subtype T_H2/IL-17 cells. Despite the capacity to secrete IL-17, specific T-cell clones released only low amounts of IL-17 on cognate allergen stimulation, whereas IL-4, IFN- γ , or both were efficiently induced. IL-17 secretion was not enhanced by IL-23, IL-1 β , or IL-6 but was enhanced by the *S aureus*-derived superantigen staphylococcal enterotoxin B. Both healthy and AD keratinocytes upregulated HBD-2 in response to IL-17, but coexpressed IL-4/IL-13 partially inhibited this effect. Additional application of staphylococcal enterotoxin B induced IL-17 in APT reactions, whereas IL-4, IFN- γ , and IL-10 were marginally regulated. Induced IL-17 upregulated HBD-2 in human keratinocytes *in vivo*. These studies indicate that IL-17-expressing T cells, in particular T_H2/IL-17 cells, infiltrate acute AE reactions. Although IL-17 secretion by specific T cells is tightly regulated, it can be triggered by bacteria-derived superantigens. The ineffective IL-17-dependent upregulation of HBD-2 in patients with AE is due to a partial inhibition by the T_H2 microenvironment, which could partially explain why patients with AE do not clear *S aureus*.

Nogales et al⁶⁸ examined differences in IL-23/T_H17 expression between psoriatic and AD lesions. In peripheral blood no significant difference was found in percentages of different T-cell subsets between these diseases. In contrast, psoriatic skin had significantly increased frequencies of T_H1 and T_H17 T cells compared with AD skin, whereas T_H2 T-cell numbers were significantly increased in patients with AD. Distinct IL-22-producing CD4⁺ and CD8⁺ T-cell populations were significantly increased in AD skin compared with those seen in psoriatic skin. IL-22⁺CD8⁺ T-cell frequency correlated with AD disease severity. Their data established that T cells could independently express IL-22, even with low expression levels of IL-17. This argues for a functional specialization of T cells, such that T_H17 and T_H22 T cells might drive different features of epidermal pathology in inflammatory skin diseases, including induction of antimicrobial peptides for T_H17 T cells and epidermal hyperplasia for T_H22 T cells. Given the clinical correlation with disease severity, further characterization of T_H22 T cells is needed because they might have future therapeutic implications.

Thymic stromal lymphopoietin (TSLP) is highly expressed by keratinocytes in skin lesions of patients with AD, but environmental triggers for its release from keratinocytes with

endogenous factors are not well understood. Patients with AD in whom allergic sensitization is already established are susceptible to viral dissemination. Kinoshita et al⁶⁹ investigated TSLP release from primary human keratinocytes stimulated with a Toll-like receptor (TLR) 3 ligand, polyinosinic-polycytidylic acid, which mimics viral double-stranded RNA (dsRNA), and its modulation by cytokines. They found that stimulation of keratinocytes with dsRNA induced release of TSLP and upregulated gene expression of TSLP and other cytokines and chemokines. The release of TSLP was enhanced by the addition of IL-4, IL-13, and/or TNF- α . With or without the T_H2/TNF cytokines, the dsRNA-induced release of TSLP was upregulated by IFN- α and IFN- β and suppressed by IFN- γ , TGF- β , or IL-17. The effect of the TLR3 ligand on keratinocytes suggests contribution of viral dsRNA to skin inflammation under the influence of a cytokine milieu. These results suggest that viral dsRNA and a T_H2 cytokine milieu might promote T_H2-type inflammation through an induction of TSLP expression and a possible blockade of this cycle by other cytokine milieus provided by cells, such as T_H1 cells. Of interest, Gao et al⁷⁰ in the ADVN found that *TSLP* polymorphisms are associated with patients with ADEH.

Trafficking of dendritic cell (DC) subtypes to and from the skin plays a pivotal role in AD. To further assess the function of DCs in patients with AD, Gros et al⁷¹ determined the chemokine receptor pattern of epidermal DC subtypes and their chemokine expression in relation to the state of AD. The total number of CD1a⁺ epidermal DCs increased and the proportion of Langerin-positive CD1a⁺ DCs decreased, whereas the percentage of Langerin-negative CD1a⁺ DCs increased after allergen application. Expression of CCR5 and CCR6 of Langerin-negative CD1a⁺ DCs was characteristic for acute AD. Expression of CCL1, CCL3, CCL4, and CCL11 mRNA was greater in patients with acute AD versus that seen in patients with chronic AD. Only a strong increase of chemokines, in particular CCL1, CCL17, and CCL18, went along with eczema development, and increased CCL1, CCL13, CCL17, and CCL18 expression was specific for patients with chronic AD compared with those with psoriasis. These data indicate that the recruitment and differentiation of DCs from their dermal and blood precursors occurs in the acute phase of AD. A boost in the amplitude of chemokines after allergen application goes along with eczema development.

IL-27 is produced by antigen-presenting cells early during immune responses. IL-27 has been described to support T-cell polarization along the T_H1 lineage but also to exert important anti-inflammatory responses in later phases of inflammation in murine models. Wittmann et al⁷² analyzed the potential role of IL-27 in epidermal inflammatory skin responses in human subjects. Surface receptor expression and apoptosis of human primary keratinocytes were analyzed by means of flow cytometry. They found that both subunits of IL-27 were expressed in chronic AD skin, whereas the IL-27 subunit EBV-induced gene 3 was not detectable in the acute phase of eczema. Stimulation of keratinocytes with IL-27 resulted in activation of the signal transducer and activator of transcription 1 and 3 pathways. Major effects found for IL-27 included CXCL10 production and MHC class I upregulation. Importantly, they could demonstrate that IL-27 acts as a priming signal on keratinocytes able to amplify chemokine production and surface molecule expression when used before a second signal, such as TNF- α . These results support the notion that IL-27 might act in an inflammatory, disease-maintaining manner in the epidermal compartment of patients with eczema.

Zeller et al⁷³ assessed the repertoire of IgE-binding self-antigens in patients with AD. In this study phage surface-displayed human cDNA libraries were enriched for clones binding to serum IgE from patients with AD and screened by using high-throughput technology. One hundred forty-one sequences encoding potential IgE-binding self-antigens associated with AD were identified. Sixteen sequences encoded previously described self-antigens. Three new sequences showed homology with environmental allergens, 86 encoded known human proteins, 7 predicted proteins, and 28 showed sequence identity with genomic contigs. Immunoblotting and ELISA experiments demonstrated the presence of IgE antibodies in sera from patients with AD to 5 selected recombinant self-antigens and their ability to induce mediator release from basophils of patients with AD who have self-antigen-specific IgE antibodies. These data demonstrate a broad spectrum of at least 140 IgE-binding self-antigens associated with AD. By binding IgE antibodies or activating specific T cells, they can promote or perpetuate existing skin inflammation.

Broccardo et al⁷⁴ used large-scale proteomic profiling to use high-throughput screening to provide potential new hypotheses regarding AD pathogenesis. In this study AD skin lesions and nonlesional sites were tape stripped. Proteins were then extracted and analyzed by means of mass spectrometry. Two proteins were uniquely identified in AD skin (but not normal skin): epidermal fatty acid-binding protein and α -enolase. α -Enolase has been reported to be autoantigenic in patients with psoriasis. Epidermal fatty acid-binding protein binds and stabilizes leukotriene A₄ and might modify the production of bioactive eicosanoids, which has been found to be increased in patients with AD. Further studies will be needed to determine the role of these proteins in AD pathogenesis and their potential use as biomarkers for the development of AD.

Animals models of skin inflammation

The interplay of filaggrin defects and the resultant skin immune response has been studied in filaggrin-deficient mice. As noted above, mutations in human *FLG* are associated with AD and are presumed to provoke a barrier abnormality. Yet additional acquired stressors might be necessary because the same mutations can also result in a noninflammatory disorder, ichthyosis vulgaris. Scharschmidt et al⁷⁵ used filaggrin-deficient mice to determine whether filaggrin deficiency alone suffices to produce a barrier abnormality. In their study filaggrin-deficient mice exhibited low-grade inflammation with increased bidirectional, paracellular permeability of water-soluble xenobiotics caused by impaired lamellar body secretion and altered stratum corneum extracellular membranes. This barrier abnormality correlated with reduced inflammatory thresholds to both topical irritants and haptens. Moreover, when exposed repeatedly to topical haptens at doses that produce no inflammation in wild-type mice, these mice experience a severe AD-like dermatosis with a further deterioration in barrier function and features of a T_H2 immunophenotype, increased serum IgE levels, and reduced antimicrobial peptide expression. These data indicate that filaggrin deficiency alone provokes a paracellular barrier abnormality in mice that reduces inflammatory thresholds to topical irritants/haptens, likely accounting for enhanced antigen penetration in patients with AD with *FLG*-null mutations.

Oyoshi et al⁷⁶ also examined whether filaggrin deficiency predisposes to skin inflammation and epicutaneous sensitization with

protein antigen. In their studies filaggrin-deficient mice had eczematous skin lesions after age 28 weeks and a progressive increase in serum IgE and IgG1 levels. Normal-appearing skin from 8-week-old filaggrin-deficient mice had epidermal thickening and increased dermal infiltration with CD4⁺ cells and expression of mRNA for IL-17, IL-6, and IL-23 but not IL-4, IL-13, or IFN- γ . Lesional skin of 32-week-old ft/ft mice exhibited qualitatively similar but more pronounced changes and increased IL-4 mRNA levels. Epicutaneous application of OVA to shaved skin of 8-week-old filaggrin-deficient mice, but not wild-type mice, resulted in increased epidermal thickening, dermal infiltration by CD4⁺ cells but not eosinophils, and expression of IL-17, IL-6, IL-23, IL-4, and IFN- γ but not IL-5 or IL-13 mRNA. Splenocytes from epicutaneously sensitized filaggrin-deficient mice, but not control animals, secreted cytokines in response to OVA stimulation, and their sera, but not those of control animals, contained OVA-specific IgE antibodies. These data indicate that filaggrin-deficient mice exhibit T_H17-dominated skin inflammation and eczematous changes with age and are permissive to epicutaneous sensitization with protein antigen.

He et al⁷⁷ examined the effect of the absence of IL-4 and IL-13 on the T_H17 response to epicutaneous sensitization in a murine model of allergic skin inflammation with features of AD. Wild-type, *IL4* knockout (KO), *IL13* KO, and *IL4/IL13* double-knockout (DKO) mice were subjected to epicutaneous sensitization with OVA or saline and airways challenged with OVA. OVA-sensitized DKO mice exhibited impaired T_H2-driven responses with undetectable OVA-specific IgE levels and severely diminished eosinophil infiltration at sensitized skin sites but intact dermal infiltration with CD4⁺ cells. DKO mice mounted exaggerated IL-17A but normal IFN- γ and IL-5 systemic responses. Airway challenge of these mice with OVA caused marked upregulation of IL-17 mRNA expression in the lungs, increased neutrophilia in bronchoalveolar lavage fluid, airway inflammation characterized by mononuclear cell infiltration with no detectable eosinophils, and bronchial hyperresponsiveness to methacholine that were reversed by IL-17 blockade. IL-4, but not IL-13, was identified as the major T_H2 cytokine that downregulates the IL-17 response in epicutaneously sensitized mice. These data indicate that epicutaneous sensitization in the absence of IL-4/IL-13 induces an exaggerated T_H17 response both systemically and in the lungs after antigen challenge that results in airway inflammation and airway hyperresponsiveness.

Jin et al⁷⁸ examined the role of TLR2 in murine models of AD and allergic contact dermatitis. In response to OVA sensitization, *TLR2* KO mice experienced skin infiltration with eosinophils and CD4⁺ cells, as well as upregulation of T_H2 cytokines that was comparable with that seen in wild-type littermates. In contrast, epidermal thickening, IFN- γ expression in the skin, IFN- γ production by splenocytes, and IgG2a anti-OVA antibody levels were impaired in *TLR2* KO mice. After oxazolone ear challenge, contact-sensitized *TLR2* KO mice exhibited defective ear swelling with impaired cellular infiltration, decreased epidermal thickening and local IFN- γ expression, and impaired oxazolone-specific IgG2a responses. DCs from *TLR2* KO mice induced significantly lower production of IFN- γ but normal IL-4 and IL-13 production in naive T cells. These results indicate that TLR2 promotes the IFN- γ response to cutaneously introduced antigens.

Prostaglandin (PG) E₂ exerts a variety of actions through 4 G protein-coupled receptors designated as EP1, EP2, EP3, and

EP4. PGE₂ acts on EP3 in airway epithelial cells and exerts anti-inflammatory actions in OVA-induced murine allergic asthma. Although EP3 is also expressed in skin and PGE₂ is produced abundantly during skin allergic inflammation, the role of PGE₂-EP3 signaling in skin allergic inflammation remains unknown.

Honda et al⁷⁹ investigated whether PGE₂-EP3 signaling exerts anti-inflammatory actions in skin allergic inflammation. They used a murine contact hypersensitivity (CHS) model and examined the role of EP3 by using an EP3-selective agonist, ONO-AE-248 (AE248), and EP3-deficient mice. Administration of AE248 during the elicitation phase significantly suppressed CHS compared with that seen in vehicle-treated mice. Microarray analysis revealed that administration of AE248 inhibited the gene expression of neutrophil-recruiting chemokines, including CXCL1, at the elicitation site. X-gal staining in EP3-deficient mice revealed EP3 expression in keratinocytes, which was further confirmed by anti-EP3 antibody in wild-type mice. In cultured keratinocytes AE248 suppressed CXCL1 production induced by TNF- α . These data indicate that PGE₂-EP3 signaling inhibits keratinocyte activation and exerts anti-inflammatory actions in murine CHS.

Macrophage migration inhibitory factor (MIF) is a proinflammatory cytokine that has been implicated in the pathogenesis of AD. Hamasaka et al⁸⁰ developed a novel DNA vaccine that generates neutralizing endogenous anti-MIF antibodies. They recently explored the preventive and therapeutic effects of this MIF-DNA vaccine. In murine models of AD, MIF-DNA vaccination prevented occurrence of the AD skin phenotype. Furthermore, administration of MIF-DNA vaccine to mice that had already had AD produced a rapid improvement in AD skin manifestations. There were reduced histologic signs of inflammation and lower serum IgE levels in treated mice compared with those seen in control animals. Finally, passive transfer of IgG from MIF-DNA-vaccinated mice to AD mice also produced a significant therapeutic effect. These results demonstrate that MIF-DNA vaccination not only prevents the development of AD but also improves the symptoms of pre-existing AD. Further studies are needed to determine the relevance of these observations to human AD.

Insights into drugs used in AD management

Therapeutic advances in AD treatment are being driven by new insights into the pathophysiology of AD. In addition, an understanding of the mechanisms by which established therapies for skin inflammation act might identify new pathways of intervention and more effective management plans.⁸¹ TNF inhibitors have revolutionized the treatment of psoriasis vulgaris, as well as other autoimmune inflammatory diseases. Despite our understanding that these agents block TNF, their complex mechanism of action in disease resolution is still unclear.

Zaba et al⁸² have analyzed globally the genomic effects of TNF inhibition in patients with psoriasis and compared genomic profiles of patients who responded or did not respond to treatment. In a clinical trial with etanercept, a TNF inhibitor used for treatment of psoriasis vulgaris, Affymetrix gene arrays were used to analyze gene profiles in lesional skin at multiple time points during drug treatment compared with nonlesional skin. Patients were stratified as responders or nonresponders on the basis of histologic disease resolution. Cluster analysis was used to define gene sets

that were modulated with similar magnitude and velocity over time. In responders 4 clusters of downregulated genes and 3 clusters of upregulated genes were identified. Genes downmodulated most rapidly reflected direct inhibition of myeloid lineage immune genes. Upregulated genes included the stable DC population genes *CD1c* and *CD207* (langerin). Comparison of responders and nonresponders revealed rapid downmodulation of innate IL-1b and IL-8 sepsis cascade cytokines in both groups, but only responders downregulated IL-17 pathway genes to baseline levels. These data indicate that although both responders and nonresponders to etanercept inactivated sepsis cascade cytokines, response to etanercept is dependent on inactivation of myeloid DC genes and inactivation of the T_H17 immune response, a cytokine that has drawn increased interest in AD-induced skin inflammation.

Jensen et al⁸³ examined the effects of topical pimecrolimus versus betamethasone on the skin barrier in patients with AD. In a randomized study 15 patients with AD were treated on one upper limb with pimecrolimus and on the other with betamethasone twice daily for 3 weeks. Stratum corneum hydration and transepidermal water loss improved in both groups. Electron microscopic evaluation of barrier structure displayed prevalently ordered stratum corneum lipid layers and regular lamellar body extrusion in pimecrolimus-treated skin but inconsistent extracellular lipid bilayers and only partially filled lamellar bodies after betamethasone treatment. Both drugs normalized epidermal differentiation and reduced epidermal hyperproliferation. Betamethasone was superior in reducing clinical symptoms and epidermal proliferation; however, it led to epidermal thinning. The present study demonstrates that both betamethasone and pimecrolimus improve clinical and biophysical parameters and epidermal differentiation. Because pimecrolimus improved the epidermal barrier and did not cause atrophy, it might be more suitable for long-term treatment of AD, whereas betamethasone would be better suited for treatment of acute exacerbations of AD.

A major concern with the use of topical calcineurin inhibitors (TCIs) or topical corticosteroids (TCSs) has been whether they increase the risk of lymphoma. Alternatively, AD itself could increase the prevalence of lymphoma. Arellano et al⁸⁴ assessed the risk of lymphoma associated with AD and use of TCSs or TCIs in a database allowing medical record validation. They conducted a nested-case control study using the United Kingdom-based Health Improvement Network database. In the study population of 3,500,194 subjects, they identified 2,738 cases of lymphoma (1,722 non-Hodgkin lymphoma [NHL], 466 Hodgkin disease, and 550 indeterminate cases; overall, 188 had cutaneous involvement) and 10,949 matched control subjects. AD was associated with an increased lymphoma risk (OR, 1.83; 95% CI, 1.41-2.36). In patients with AD referred to a dermatologist, the OR further increased (OR, 3.72; 95% CI, 1.40-9.87). They did not find any cases of lymphoma in TCI users; however, the number of patients exposed to TCIs was insufficient to study any possible association between lymphoma and these drugs. TCS use was associated with an increased lymphoma risk (OR, 1.46; 95% CI, 1.33-1.61). The risk increase was dependent on TCS potency. The increased risk involved both Hodgkin disease and NHL, especially NHL with skin involvement (OR for high-potency TCSs, 26.24; 95% CI, 13.49-51.07). Their results show an association between lymphoma, especially skin lymphoma,

and use of TCSs. The risk increased with duration of exposure and potency of TCSs.

The immunosuppressant drug cyclosporin A (CsA) is being increasingly used in treating severe AD. Although it is highly efficacious, recent data have suggested that CsA might suppress naturally occurring CD4⁺CD25⁺ Treg cell function. These studies prompted Hijnen et al⁸⁵ to investigate the effects of CsA treatment on Treg cells in patients with AD. At baseline, the mean percentage of Treg cells were significantly higher in patients with AD compared with those seen in healthy control subjects. CsA treatment resulted in a rapid improvement of disease severity (after 3 and 6 weeks of treatment) in all patients with AD. After 3 and 6 weeks of CsA treatment, they found a significant decrease in the numbers of Treg cells. The clinical relevance of this effect in patients with AD treated with CsA remains to be determined.

Phototherapy is an effective anti-inflammatory therapy for skin inflammation. Despite its immunosuppressive effects on the adaptive immune response, bacterial infections are not a problem. To understand the basis for this phenomenon, Gläser et al⁸⁶ asked whether UV radiation induces antimicrobial peptides *in vitro* and *in vivo*. Real-time PCR of normal human keratinocytes revealed a dose-dependent increase in HBD-2, HBD-3, ribonuclease 7, and psoriasin (S100A7) levels after UV radiation. This was confirmed at the protein level by means of intracellular fluorescence activated cell sorting and *in vitro* immunofluorescence analysis. Immunohistochemistry of biopsy specimens taken from healthy volunteers exposed to different UV radiation doses revealed enhanced epidermal expression of antimicrobial peptides after UV exposure. This was also confirmed by exposing human skin explants to UV radiation. Thus although UV radiation suppresses the adaptive immune response, it induces the innate immune response and might thereby protect against bacterial invasion.

URTICARIA AND ANGIOEDEMA

Although it is known that thyroid autoantibodies are present at a relatively high frequency in patients with chronic urticaria (CU), there has been considerable controversy about whether there is a causative link and whether treatment with thyroxine might benefit the patient. Therefore Sheikh et al⁸⁷ carried out a survey of American Academy of Allergy, Asthma & Immunology members to determine their opinion of the association of thyroid autoimmunity in the treatment of CU. Only a minority of allergists (11%) believed strongly that there is a pathogenic link. Despite the lack of consensus on pathogenesis, 65% of responders order thyroid autoantibodies in the work-up of the majority of their patients with CU, but relatively few treat euthyroid patients with thyroid hormone. The data presented show that clinicians are prescribing thyroid hormone in some cases when increases of antithyroid antibody levels are found during diagnostic work-up. However, there are minimal data on what dose of thyroid hormone to use in these patients (who are often clinically euthyroid) and no consensus as to what the target thyroid-stimulating hormone level should be. These findings underscore a significant need for further large-scale research in this area.

Little is known about the course of aspirin-induced urticaria. A regulatory role for cysteinyl leukotrienes and PGD₂ has been

postulated. Setkowicz et al⁸⁸ performed a long-term observation on the clinical course, aspirin sensitivity, and urinary eicosanoids in patients with aspirin-induced urticaria. During a 4-year follow-up period, the severity of urticaria decreased. In 14 of 22 patients, the results of aspirin challenge remained positive. In 2002, these 14 patients responded to aspirin with a significant increase in urinary LTE₄ and 9 α , 11 β PGF₂ levels. When studied 4 years later, they showed a similar response of 9 α , 11 β PGF₂ and a tendency toward an increase in LTE₄ levels. There was a correlation observed between the urinary LTE₄ concentration after aspirin challenge and the intensity of skin eruptions. Aspirin hypersensitivity manifesting as urticaria/angioedema remained present after 4 years in about two thirds of patients. These data indicate that aspirin-precipitated skin reactions are associated with increased excretion of LTE₄ and PGD₂.

In a subpopulation of patients with CU, a circulating endogenous factor or factors are present that can induce a wheal and flare-type reaction, defining the subgroup as autoreactive urticaria. The commonly used *in vivo* test for autoreactivity is the autologous serum skin test (ASST), which in most studies has been shown to elicit positive results in about 35% to 45% of patients with CU. However, the overall percentage of patients with CU with positive ASST results reported ranges from 4% to 76%, possibly reflecting patient selection and differences in methodology. Recently, it has been reported that the percentage of patients with CU exhibiting skin autoreactivity is much higher if intradermal testing is performed with autologous plasma (autologous plasma skin test [APST]) instead of autologous serum. Metz et al⁸⁹ aimed to characterize the skin autoreactivity in response to intradermal injection of autologous serum versus autologous plasma in 200 patients throughout Europe. Skin reactivity to autologous serum (positive ASST result) was found in 37.5% of patients with CU tested, and only slightly higher numbers of patients exhibited skin reactivity to autologous plasma (positive APST result, 43.0%). Interestingly, patients with positive ASST results were found to have increased disease activity and a significantly impaired quality of life compared with patients with CU with negative ASST results. In contrast, patients with positive and negative APST results exhibited no significant differences in disease activity and quality of life.

Kaplan,⁹⁰ who has been a leading investigator in CU, recently reviewed his extensive experience in the treatment of this disease. Some of his key points in the management of CU included the use of increased doses of nonsedating antihistamines first. If this fails, one should consider increased doses of hydroxyzine in combination with H₂ blockers, low-dose corticosteroids, or cyclosporine. He also questioned the use of thyroid therapy as a treatment for CU. The possible role of omalizumab was considered as well.

Increased dosing of nonsedating antihistamines has been recommended for patients with acquired cold urticaria (ACU) who do not respond satisfactorily to the standard dose. Prospective data supporting this recommendation are scant. In a prospective, randomized, double-blind, 3-way crossover trial, Siebenhaar et al⁹¹ treated patients with ACU (n = 30) with placebo, 5 mg of desloratadine, and 20 mg of desloratadine every day each for 7 days separated by 14-day washout periods. At the end of each treatment, patients underwent cold provocation, and urticarial reactions were assessed. Desloratadine at standard and high doses compared with placebo significantly improved objective signs of ACU provoked by cold exposure. Desloratadine at 4 times the standard dose (20 mg) significantly reduced ACU lesion

severity versus 5 mg of desloratadine without an increase in adverse events. This study supports current guidelines that increased desloratadine dosing might benefit patients with urticaria who do not respond to standard doses.

Alprazolam has shown competitive antagonism on muscarinic and histamine H₁ receptors and noncompetitive antagonism on histamine H₂ receptors. Pretreatment with kadsurenone or alprazolam improved survival in hypersensitivity reactions to OVA in guinea pig lung parenchymal strips and in guinea pigs *in vivo*. This antihistaminic effect has not been tested in allergic patients.

Duenas-Laita et al⁹² recently carried out a preliminary study to investigate whether alprazolam could be useful in patients with severe refractory CU. Eight patients were randomized to 2 mg of alprazolam 3 times daily or 10 mg of rupatadine, a new antihistamine PAF inhibitor, 3 times daily. After 2 days, the urticaria disappeared in the 6 patients treated with alprazolam and persisted in the 2 patients treated with rupatadine. Urticaria reappeared 36 hours after withdrawal of alprazolam and improved 8 hours after readministration. Although both alprazolam and rupatadine are PAF receptor antagonists, the poor response to rupatadine suggests that the main mechanism of alprazolam in patients with CU might be blockade of histamine H₁ receptors and not PAF inhibition. This preliminary experience suggests a controlled trial with alprazolam in a large group of patients with drug-resistant CU is necessary.

ALLERGIC CONJUNCTIVITIS

Allergic conjunctivitis is characterized by allergen-specific IgE in the serum and infiltration of eosinophils into the conjunctiva. The role of IgE and mast cells in allergic conjunctivitis, however, has not been fully delineated. Fukuda et al⁹³ investigated the importance of conjunctival mast cells in a murine model of IgE-mediated allergic conjunctivitis. IgE-mediated allergic conjunctivitis was initiated in C57BL/6-Kit(+/+) wild-type mice, mast cell-deficient Kit(W-sh/W-sh) mice, and Kit(W-sh/W-sh) mice that had been subconjunctivally or systemically engrafted with bone marrow-derived, cultured mast cells from Kit(+/+) wild-type mice, and clinical symptoms and infiltration of eosinophil of the eyes were evaluated. No mast cells were detected in the conjunctiva or eyelid dermis of adult Kit(W-sh/W-sh) mice. Subconjunctival injection of bone marrow-derived, cultured mast cells resulted in local mast cell reconstitution, with the numbers of reconstituted mast cells in the conjunctiva and eyelid dermis comparable with those observed in wild-type Kit(+/+) littermates. Reconstituted and naive conjunctival mast cells expressed proteases ascribed to connective tissue-type mast cells but not mucosal mast cells. Passive transfer of ragweed-specific IgE followed by antigen challenge resulted in both early-phase clinical symptoms and late-phase eosinophilic inflammation in Kit(+/+) mice. These responses, which were significantly decreased in Kit(W-sh/W-sh) mice, were restored on reconstitution of the conjunctival mast cell population. These results suggest a direct contribution of IgE-activated mast cells to both the early-phase reaction and late-phase inflammation during ocular allergy.

Although a relationship between viral infection and allergic inflammation has been reported, the function of TLR3 in allergic inflammation remains to be defined. Allergic conjunctivitis is an ocular surface inflammation associated with type I

hypersensitivity reactions; the degree of eosinophil infiltration in the conjunctiva reflects the degree of its late-phase reaction. Using their model of murine experimental allergic conjunctivitis (EAC) and TLR3 KO and TLR3 transgenic mice, Ueta et al⁹⁴ assessed the role of TLR3 in conjunctival eosinophil infiltration. They demonstrated that TLR3 positively regulates the late-phase reaction of EAC, which was associated with reduced eosinophilic conjunctival inflammation in TLR3 KO mice and more pronounced in TLR3 transgenic mice. They postulated that TLR3 positively regulates the late-phase reaction of EAC through the induction of TSLP.

MASTOCYTOSIS

Indolent systemic mastocytosis is a group of rare diseases for which reliable predictors of progression and outcome are still lacking. Escribano et al⁹⁵ investigated the prognostic effect of the clinical, biologic, phenotypic, histopathologic, and molecular disease characteristics in adults with indolent systemic mastocytosis who were followed with conservative therapy. A total of 145 consecutive patients were prospectively followed between January 1983 and July 2008. In addition, from 1967 to 1983, 20 patients were retrospectively studied. Multivariate analysis showed that serum β_2 -microglobulin ($P = .003$), together with the presence of mast/stem cell growth factor receptor gene (*KIT*) mutation, in mast cells plus myeloid and lymphoid hematopoietic lineages ($P = .02$) was the best combination of independent parameters for predicting disease progression (cumulative probability of disease progression of $1.7\% \pm 1.2\%$ at 5-10 years and $8.4\% \pm 5.0\%$ at 20-25 years). Regarding overall survival, the best predictive model included age greater than 60 years ($P = .005$) and development of an associated clonal hematologic non-mast cell disorder ($P = .03$) with a cumulative probability of death of $2.2\% \pm 1.3\%$ at 5 years and $11\% \pm 5.9\%$ at 25 years. These data indicate that indolent systemic mastocytosis in adults has a low disease progression rate, and the great majority of patients have a normal life expectancy, with the presence of *KIT* mutation in all hematopoietic lineages and increased serum β_2 -microglobulin the most powerful independent parameters for predicting transformation into a more aggressive form of the disease.

CONCLUSIONS AND SUMMARY

In the year since our last review,⁹⁶ numerous exciting advances have been reported in the *Journal*. In particular, novel observations about food allergy pathogenesis, including cellular and humoral mechanisms, are informing improved prevention, diagnosis, and treatment strategies. We are learning more about the opportunities and limitations of food OIT, but more work needs to be done to characterize risks and efficacy. A key unanswered question is whether the treatments promote persistent tolerance or only transient desensitization. The importance of evaluating baseline tryptase levels in persons with significant reactions to Hymenoptera insect stings appears prudent. Research in AD has revealed the importance of mechanical and immune barrier dysfunction in driving local and systemic allergen sensitization. These advances present information that can improve patient care today and provide insights on how we will be improving diagnosis and treatment in the future.

Key advances, 2009

Food allergy

- Several studies in westernized countries indicate that more than 1% of children have peanut allergy.
- There is some evidence that environmental exposure to food allergens might be sensitizing.
- IgE antibody to α -gal is responsible for delayed anaphylaxis to mammalian meats.
- There is a possible role of complement activation in peanut anaphylaxis.
- Regulatory T cells can discriminate food allergy phenotypes.
- Several studies of OIT show promise.
- A murine model testing a Chinese herbal remedy shows prolonged treatment effects.

Insect venom hypersensitivity

- Increased baseline serum tryptase levels might inform anaphylaxis risk and also risk of mast cell disorders.

Atopic dermatitis

- Defects in skin barrier are caused by null mutations in the epidermal differentiation complex, including *FLG*, as well as T_H2 immune responses.
- Filaggrin-deficient skin leads to enhanced allergen absorption and systemic allergen sensitization.
- IL-17 expression is increased in AD skin lesions, but its effects are reduced by T_H2 cytokines.
- T_H2 -polarized disease is associated with increased propensity to eczema herpeticum.

Urticaria and angioedema

- Increased doses of nonsedating antihistamines can be used for poorly controlled CU.
- There is a potential use of omalizumab for refractory CU.

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