

ATOPIC DERMATITIS & HENOCH-SCHÖNLEIN PURPURA

ATOPIC DERMATITIS: New findings and Novel Therapies

Mark Boguniewicz, M.D.
and Donald Leung, M.D., Ph.D

Recent advances in our understanding of the pathogenesis of atopic dermatitis (AD) and asthma have made it clear that these two diseases have many features in common.

Consideration of the similarities between these two diseases has helped underscore the role of allergens in triggering the inflammatory reaction of AD, and has given us new insights into how to manage this disorder. Physicians today should not simply treat all cases of AD with topical steroids without asking what is triggering the patient's skin inflammation. A more rational approach is to learn from the successes of asthma treatment and base AD treatment on systematically looking for the allergens that are critical in triggering an AD patient's flares.

Although topical steroids play a key role in treatment, they are limited by their incomplete efficacy and adverse effects. Our new understanding of the immunology underlying AD gives us important clues for novel approaches to treatment. The fundamental message

regarding AD management is that whenever possible triggering allergens for each patient should be identified, followed by patient education and allergen avoidance.

The Immunologic Basis of AD

A number of immunoregulatory abnormalities have been identified in AD patients, including increased IgE synthesis, increased histamine release from basophils, eosinophilia, an impaired delayed-type hypersensitivity response, elevated levels of interleukins (IL-) 4 and 5 made by T-helper type 2 cells, and decreased interferon- γ made by T-helper type 1 cells. The deficit of interferon- γ and the overproduction of IL-4 and IL-5 are believed to be critical in AD pathogenesis.

Results from various studies indicate that AD is caused by a dysfunction of bone marrow-derived cells, not by a skin defect. Allergen-specific helper type 2 T cells accumulate in the skin lesions of AD patients and in the airways of patients with allergic asthma. The key difference between these two diseases is that skin T-helper type 2 cells in patients with AD express the skin homing receptor, CLA, whereas airway T-helper type 2 cells in patients with asthma do not. Thus, AD is associated with a skin-directed T-helper type 2 cell response.

A finding of potentially great

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importance is that Langerhans cells in the skin express the high-affinity receptor for IgE. This receptor was previously believed to be present only on mast cells and basophils. IgE that is bound to these receptors can capture and focus allergens more efficiently than the classic antigen-uptake mechanism used by these cells.

Our recent findings show that the initiation of acute skin inflammation in AD patients is associated with abnormally high IL-4 production by T cells. Chronic inflammation may be maintained by repeated antigen exposure, with an excess of IL-5 production and eosinophil infiltration. These observations may explain the high level of serum IgE and the elevated eosinophil counts that are characteristic of AD. In addition, we have identified other cytokine abnormalities in AD, including elevated levels of IL-13 in acute lesions and elevated levels of IL-12 in chronic lesions.

The Role of Allergens

About 80-85% of AD patients have elevated serum levels of IgE, and also have immediate skin test reactions to food or inhaled allergens. More importantly, blinded, controlled food challenge tests have shown that food allergens can exacerbate skin rashes in a subset of AD patients. In addition, elimination of food allergens from their diet results in improvement of skin lesions and a drop in the spontaneous release of histamine by their basophils.

The majority of atopic dermatitis patients, particularly adults, do not have food allergy. This suggests that inhaled allergens may play a major role.

However, the majority of AD patients, particularly adults, do not have food allergy. This suggests that inhaled allergens may play a major role, which is supported by the presence of allergen-specific T cells and IgE in AD patients. Exposure to allergens such as house dust mites, animal dander and pollens will often worsen AD, while elimination of such allergens from a patient's environment leads to disease improvement.

Another characteristic feature of AD is the

intense pruritus that patients experience.

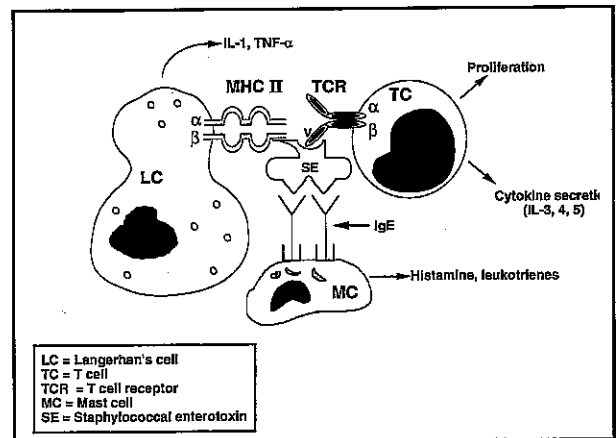
Allergens may first trigger an acute pruritus, leading to scratching that causes mechanical skin trauma including keratinocyte injury. This causes the release of a variety of cytokines including IL-1 and tumor necrosis factor- γ . These cytokines attract additional inflammatory cells that contribute to the inflammatory cycle.

The Role of Bacteria

Patients with AD have an increased susceptibility to skin colonization or infection by bacteria, fungi, and viruses that are generally not part of the normal skin flora. The exact reason for this is not known, but we speculate that it may be related

More than 90% of AD patients have *Staphylococcus aureus* on their skin, compared with only 5% of normal subjects.

to skin inflammation, which may induce production of an increased number of microbial attachment sites on the skin. This hypothesis comes from the observation that when topical steroids are used to reduce skin inflammation, the number of microbes decline.



Our attention has focused on the role of *Staphylococcus aureus* in AD because more than 90% of AD patients have *S. aureus* on their skin, compared with only 5% of normal subjects. Recent evidence suggests that *S. aureus* secretes a group of toxins that can act as superantigens, proteins that cause massive activation of the immune system. The superantigens can trigger T cells as well as

epidermal macrophages or Langerhans cells to release proinflammatory cytokines. Our research has shown that almost half of AD patients who have toxin-secreting *S. aureus* on their skin produce a specific IgE antibody that binds to that specific toxin. The local production of these bacterial toxins can lead to IgE-mediated histamine release, thereby triggering the itch-scratch cycle that plays a critical role in AD flares. In short, it seems that bacterial colonization or infection can contribute to the chronic inflammation of AD through both allergic and nonallergic mechanisms.

Finding the Triggers

Failure to identify specific triggers may lead to suboptimal control of AD and overuse of medication. The challenge is to determine the relevant allergens. The value of a good history cannot be overstated; it can clarify links between environmental factors and flares.

Selective allergy testing and controlled challenges are very helpful when sorting out a food allergy. Extensive elimination diets are almost never indicated. An avoidance test is a good way to

identify culprit allergens in the environment. To further hone the diagnosis of allergy to inhalants, patch testing may be useful. When the complete investigation is done by experienced clinicians, several allergens generally emerge as the critical triggers for the typical AD patient.

Evolving Aspects of Treatment

Once specific triggers are identified, allergen avoidance is of paramount importance. Of course, many patients also require additional steps to control their disease. These include careful attention to skin hydration and antimicrobial therapy. Although topical steroids can be very effective at reducing AD flares, chronic use of potent steroids may be associated with a number of adverse effects. This is especially true with use in younger patients and on the

face. Systemic steroids must be used with extreme caution in this chronic disease.

Two new immune-based therapies appear promising, although both remain at the clinical trial stage.

One of these is tacrolimus ointment, a topical form of FK506. A systemic formulation of drug, which acts on T cells and mast cells by inhibiting the production of cytokines, has already been found to be a useful and safe immunosuppressant for organ transplant recipients. Studies of the topical formulation for AD patients are in progress. The results from a phase II study have been reported at recent allergy and dermatology meetings, and suggest that tacrolimus is highly effective at reducing skin inflammation. Manuscripts on the work have been submitted for publication.

A systemic treatment also under investigation is a chronic regimen of daily injections with interferon- γ . Results from a phase III trial are expected before the end of this year.

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HENOCH-SCHÖNLEIN PURPURA

Terri Finkel, M.D.

Henoch-Schönlein Purpura (HSP) is the most common childhood vasculitis, but its etiology remains unknown. Our group at National Jewish believes that certain strains of *streptococci* or *staphylococci* colonize patients, and produce toxins that act as superantigens to trigger the immunopathology of HSP. We are seeking specimens from suspected patients who are age 2-20 to help us test our hypothesis.

Once specific triggers are identified, patient education about allergen avoidance is of paramount importance.

About two-thirds of HSP patients have a mild, self-limited disease that does not require hospitalization or therapy, and resolves in 3-4 weeks with no significant sequelae. However,

about a third of patients have a recurrence within the first year following their initial episode.

About 7% of patients have severe gastrointestinal involvement, including hemorrhage or intussusception. The most devastating long-term morbidity is renal

involvement. Renal insufficiency develops in about 5% of cases, which can lead to end-stage renal failure.

HSP is relatively rare, with an estimated annual incidence of about 13.5 cases/100,000 children. Cases usually occur in clusters, most often during the winter, which suggests an infectious etiology. Half of all HSP patients have a preceding upper respiratory infection, often in association with a throat culture that is positive for group A β -hemolytic streptococci.

The diagnosis is usually straightforward because of the highly characteristic purpuric rash that develops on the buttocks and lower extremities; there is virtually no other disorder that mimics this rash. Rounding out the diagnostic triad is colicky abdominal pain and arthritis

We speculate that HSP develops when *streptococci* or *Staphylococcus aureus* on the pharynx, rectum, or skin of children produce pyrogenic exotoxins that mediate systemic inflammation. The exotoxins may act as superantigens, proteins that are potent stimulators of a broad spectrum of T cells and macrophages. Among the stimulated T cells may be autoimmune clones that attack

the patient's tissues and cause the disease's pathology.

Our study will investigate whether bacteria grown from the skin, pharynx, or rectum of

HSP patients secrete bacterial toxins that are known to act as superantigens. We plan to enroll over a two year period three groups of subjects who are between the ages of 2 and 20: 17 patients with a confirmed diagnosis of HSP based on an acute onset of palpable purpura, arthralgia/arthritis, and abdominal pain; 17 age-matched, normal, healthy control subjects; and 17 pediatric patients with systemic lupus erythematosus, who will serve as a disease control group. Patients with a prior history of HSP will not be excluded.

Serum specimens, throat, rectal, and skin cultures will be collected from all participants.

When clinically indicated, a skin biopsy will also be collected.

Patients with a suspected diagnosis of HSP based on the diagnostic triad need not come to Denver to participate; specimens can be submitted by their primary care physician. Follow-up serum specimens and interval histories will also be obtained from the HSP patients. Patients will be compensated for their participation.

If this study and follow-up investigations document a role for bacteria in the etiology of HSP, one practical implication will be that children diagnosed with the disease should be treated with an antibiotic to help clear their superantigen-producing infection.

Contact Dr. Terri Finkel, (303) 398-1408, or through LungLine, (800) 222-LUNG and then page.

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The most devastating long-term morbidity is renal involvement. Renal insufficiency develops in about 5% of cases, which can lead to end-stage renal failure.

If this study and follow-up investigations document a role for bacteria in the etiology of Henoch-Schönlein Purpura, one practical implication will be that children diagnosed with the disease should be treated with an antibiotic.

A highly characteristic purpuric rash develops on the buttocks and lower extremities; there is virtually no other disorder that mimics this rash.

Dr. Richard S. Farr

This issue is dedicated to the memory of Dr. Richard S. Farr. Dr. Farr died on May 21, 1997. He was chairman of the Department of Medicine at National Jewish from 1969-1977.

Dr. Farr completed his M.D. degree at the University of Chicago in 1946 and interned at the Naval Medical Research College. Much of his career was spent at the University of Chicago where he served as Head of the Section of Clinical Immunology. After 7 years at the Scripps Clinic and Research Foundation, first as Head of the Division of Allergy, Immunology and Rheumatology and then as Chairman of the Department of Medicine, in 1969, he came to Denver as Head of Allergy and Immunology and later as Chairman of the Department of Medicine at National Jewish.

Among his many accomplishments were Presidency of the Academy of Allergy and Clinical Immunology in 1969 & 70, receipt of the Distinguished Service Award from the University of Chicago in 1975 and Honorary Fellowship in the Canadian Society of Allergy and Immunology. A lectureship at the American Academy of Allergy and Clinical Immunology is given each year in his honor.

Dr. Farr was a distinguished scientist and physician. As a scientist, he was the first to discover that lymphocytes recirculate. He is best known for the development of a sensitive method for measurement of antibody reactions with antigens, a method which could be used to measure amounts of antigen or antibody in any given preparation. This method, which is known as the "Farr Assay", was crucial to the development of quantitative immunology and laid the ground work for others to invent the radioimmunoassay, a technique which earned its inventors a Nobel Prize from which, in this writer's opinion, Dr. Farr was unjustly excluded.

As a physician, Dr. Farr was a skilled practitioner and a caring and understanding individual. He had an amazing ability to understand the strengths and weaknesses of his patients, and to use this understanding in the design of their treatments. Dr Farr had a turn of phrase

which was reminiscent of Will Rogers. He put this to good use in his lectures describing the states of mind of his patients who found themselves categorized as "Humpty Dumpty" or "Eeyore" He coined the evocative and accurate term "twitchy lung" to describe the lungs of asthmatic patients. He had a 48 hour rule, which many of us have used since in trying times, 2 days time-out to be put to use before responding to any particularly annoying situation.

Those of us who were lucky enough to know and work with Dick Farr loved him for his kindness, absolute integrity and loyalty. We felt we had the privilege of sharing his idea that life and science were adventures of discovery to be enjoyed together.

National Jewish was a poorer place on the day Dr Farr left Denver. The world is now a poorer place for his death.

Contributions may be sent to the Richard S. Farr Memorial fellowship Savings Account 6053-008676
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