

THE ROLE OF DUST MITES IN ATOPIC DERMATITIS: A Preliminary Report

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The ubiquity and the allergenicity of the dust mite makes it suspect as another "trigger" for exacerbations of the eczematous "twitchy skin" of atopics. The golden standard for contact allergens is the patch test; thus, the Eczema Committee of the American Academy of Allergy and Immunology decided on a protocol for patch testing with dust mite allergen, to be tested at six different sites, to evaluate the role of dust mites in atopic dermatitis. The rationale and preliminary impressions of this project are presented.

Atopic dermatitis (AD) is well recognized as the third component of the "atopic triad." Although the role of allergens as "triggers" for asthma and rhinitis is universally accepted, their role in AD remains a source of contention. This controversy may be due to the relative ease of identifying the secretagogue of IgE/mast-cell-induced immunologic reactions of respiratory allergy, and the less precise identification of the triggers of T-cell-induced immunologic reactions believed to produce eczema. A solution for the confusion may be the recent elucidation that many clinical syndromes are not restricted to a single Gell and Coombs immunologic response, but that they may be the result of an intricate interplay of several or all the immunologic responses.

Immunologic responses are the result of activation of the varied receptors on mast cells and T cells and the release of their respective inflammatory mediators. Dust mites, pets, and pollens are common triggers (type I IgE/mast-cell-mediated) of respiratory allergies, but their pathoetiologic role in AD is often questioned; however, recent evidence suggests that AD may represent the paradigm of an IgE-mediated T-cell (type IV) reaction, [3] supporting the potential for aeroallergens as another trigger of AD.

Type IV or delayed-type hypersensitivity is a T-cell driven immunological response to exogenous antigens (contact allergens, extracellular bacteria, bacterial toxins, dermatophytes) and endogenous antigens (viral and tumor). These antigens present to epidermal Langerhans' cells (LCs) in a haptenic state, and are delivered to draining lymph nodes, where they activate Th0 cells. This activation induces the differentiation of a clone of antigen-specific Th1 or Th2 cells that have the ability to "home" to the original skin site of incitement. Several factors influence Th cell differentiation into the polarized Th1 or Th2 pathway, including the cytokinal profile of "natural immunity" evoked by the different offending agents, the nature of their peptide ligand, the activity of some costimulatory molecules, and microenvironmentally secreted hormones, in the context of different host genetic backgrounds. ^[22] The release of Th1 and Th2 cell inflammatory mediators in the skin produce a spongiotic dermatitis, which clinically presents as a spectrum of eczematous eruptions. ^[22] Allergic contact dermatitis is the prototypic dermatologic (predominantly Th1) delayed-type hypersensitivity reaction. ^[23] While *irritant* contact dermatitis, which at times can be clinically indistinguishable from allergic contact dermatitis, is considered to be the result of direct damage of keratinocytes, and not a delayed-type hypersensitivity reaction, the mediators are released by nonspecifically activated T cells. Thus, eczematous eruptions can be the result of an allergenic or an irritating contactant. Allergic

contact dermatitis requires a latent period before the reaction is clinically apparent and is not dose-dependent, whereas irritant contact dermatitis occurs sooner, at the point of contact, and the spectrum of the reaction is directly dose-dependent.

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CHARACTERISTICS OF ATOPIC SKIN

The discovery of the high-affinity IgE receptor (FcεR1) on LCs of patients with AD provides a mechanism for LCs to accept and then present IgE allergens to receptive sensitized T cells^[6] and mast cells. T-helper lymphocytes with Th2 characteristics predominate in the skin lesions of AD.^{[4] [7]} Recently, Thepen et al^[28] have demonstrated a biphasic response to aeroallergens in AD.^[28] They found that an early predominance of Th2 cells in AD, with their cytokine profile of interleukin IL-4 and IL-5, helps initiate an IgE/mast cell-eosinophil allergen-triggered reaction. Although IL-5 induces a tissue eosinophilia (the source of eosinophilic major basic protein [EMBP] found in the dermis of subacute and chronic AD lesions),^[16] IL-4 contributes to mast cell activation and the release of mediators (especially histamine), which may play a role in AD. In addition, Th2 cells require an exogenous pulse of IL-4 to initiate their differentiation and the subsequent synthesis of specific cytokines. Mast cells also release more IL-4 upon activation,^[11] and it may act as that essential activator. It is also likely that histamine, the predominant mediator released by IgE-induced mast cell degranulation, can cause a pruritus, which when scratched can produce the eczematous lesions, a phenomenon recognized as "Koebnerization." In the later or chronic phase of AD, the usual allergic contact IFN-γ-producing Th1 cells appear and eventually predominate over Th2 cells.^[28] Because the mediators released from both types of activated T cells are able to produce an eczematous (spongiotic) reaction, a concomitant type of contact- (allergic or irritant) triggered cause for AD is very conceivable (Fig. 1) (Figure Not Available).

Figure 1. (Figure Not Available) Proposed immune response to **dust mite** in subset of atopics. *Afferent limb*--a haptenated **dust mite** antigen gains entrance to the epidermis and is picked up by Langerhans cells (LCs). The haptenated LCs migrate to a draining lymph node. Presentation of the **dust mite** hapten to Th0 cells in the lymph node sensitizes Th2 and later Th1 cells as a clone of hapten-specific Th1 (and Th2) cells. *Efferent limb*--the sensitized t cells, which possess skin specific homing receptors, are guided to the hapten-provoked skin site, whereby they recognize the specific **dust mite** hapten presented to it by LCs, causing them to release their specific cytokines, including IL-4 and IL-5. (*From Allergy and Clinical Immunology International 9(2)37-40, March/April 1997; with permission.*)

Atopy

The genetic predisposition for atopics to produce increased amounts of IgE antibodies in response to allergen, which then may attach themselves to (the atopics increased number of) mast cells, gives rise to their many positive skin and radioallergosorbent test (RAST) tests. These positive IgE tests merely reflect the afferent limb of a possible immunologic response, and often are false-positives, as many atopic patients have positive skin or RAST tests with no associated allergic symptoms. Thus, a positive skin or RAST test does not always mean that the allergen

will trigger a type I immunologic response, but the positive tests serve better as markers of the atopic diathesis. Because the highest IgE levels have been noted in patients with atopic dermatitis, the author proposes the paradoxical question of whether the diagnosis of atopic dermatitis should be made without ever demonstrating this marker for "atopy" in patients labeled with the diagnosis of AD?

Pruritus

The diagnosis of atopic dermatitis cannot be made if there is no history of itching!

G. RAJKA

"Atopic dermatitis is an itch that erupts, rather than an eruption that itches" is one of the most frequently quoted dicta in dermatology. Atopic patients have "itchier" skin than nonatopic patients, as confirmed by a questionnaire distributed to consecutive patients in the author's office. The patients were divided into three groups: (1) those with no personal or family history of atopy (68 patients), (2) those with respiratory allergies but no history of eczema (123 patients), and (3) those with eczema, with or without respiratory allergies (91 patients). When asked if they believed their skin itched more than normal, the affirmative responses by respective groups were 6%, 14%, and 82%, respectively.

Alloknesis, which is defined as the phenomenon of cutaneous hyperaesthesia by O. Hagermark, better describes the itch of atopic dermatitis.^[21] Atopic patients do not have a lowered itch threshold, but rather they perceive many normally nonpruritic stimuli as itching. The latter was reaffirmed by C.F. Wahlgren in his report of common provokers of itch in atopic dermatitis: heat and perspiration, 96%; wool, 91%; emotional stress, 81%; certain foods, 49%; alcohol, 44%; and "common cold," 36%^[22] (and to these the author would like to add **dust mite** in a third of patients with AD). It is noted that most patients with AD report increased itching when in contact with certain topicals (soaps, cosmetics, perfumes, tobacco smoke, etc.) or when they ingest vasodilating stimuli (spicy foods, alcohol). The author deems these patients as having a "twitchy skin syndrome" akin to asthmatic patients who are dubbed as having a "twitchy lung syndrome."

Eczema (Spongiosis)

The Koebnerized-eczema (spongiotic dermatitis) of AD, which has features found in virtually any other eczematous eruption, is considered the result of the discharged T-cell inflammatory mediators, a common denominator of all eczematous eruptions. But, as stated previously, the unique preponderance of allergen-specific Th2 cells in atopic dermatitis (at least in the early phase of AD) instead of Th1 cells as in contact dermatitis interjects another set of triggers and an alternative pathway producing the eczema.

The characteristic pattern of chronologic presentation and evolution of clinical AD comply with the basic properties of atopy, pruritus, and Koebnerized eczema.^[23] Thus, the eczema is localized to the site, triggered by the "itch" and responsive scratch! Removal of the provocation or the cessation of scratching almost always results in the resolution of the eczema. The "minor" signs and symptoms described for AD are genetic markers seen more frequently in atopic patients, but are also seen in individuals without the atopic diathesis.^[24] Many of the minor findings contribute to the "twitchability" of the atopic skin, especially the xerosis.

THE ROLE OF DUST MITES IN ALLERGIC DISEASE

The role of house dust in sensitizing asthmatic patients was first reported in 1921.^[13] The association between house dust sensitization and asthma was subsequently repeatedly confirmed, and treatment of asthma with hyposensitization to house dust extract is widely practiced.^[18] It was not until 1967 that Voorhorst et al^[31] identified the most important single source of house dust allergen to be the **dust mite** *Dermatophagoides*. It was then discovered that beds and overstuffed furniture are the main foci for breeding of mites. The bed provides the mites ample food in the form of human skin scales and other organic debris. Fomites (pillows, mattresses, sofas, carpets, etc.) also provide a physical habitat that offers optimum conditions for the culture of **dust mites** (a temperature of 25°C and relative humidity >70%^[33]). Green et al^[9] have reported that mite numbers and mite-allergen levels in dust from carpets or seating in public buildings are much lower than levels in private homes. Frequency of cleaning or vacuuming and air-conditioning might be important controlling factors. Platts-Mills^[19] noted that mite counts, however, are not suitable for assessing mite-allergen exposure on a routine basis. His studies on seasonal variation revealed that mite allergens remain high for months after the fall in mite numbers. It is now known that the major respiratory allergens from the mites (*Dermatophagoides* spp) are *Der pI* and *Der pII*,^[17] and they may persist long after the death of the mite.

A basic tenet of managing patients with allergies is the importance of removing the identifiable allergen. In 1932, Rost^[23] reported that patients with eczema improved when they lived in a dust-free environment, a finding confirmed by many investigators.^{[14] [15] [26] [29]} Despite a fairly impressive amount of evidence supporting a role for **dust mite** allergens in AD, there remains considerable skepticism regarding their relevance in the management (partially perhaps as a reaction to the overenthusiastic proselytizing on the part of allergists!); however, there were important issues undermining the skepticism:

- The misconception by nonallergists that it is virtually impossible to create a dust-free environment
- The house dust antigen used for skin testing was a poorly defined mixture, and **dust mites** were only recently identified
- Intradermal testing with house dust antigen produced the short-lived (type I) urticarial reaction, and not an eczematous (type IV) reaction
- Allergen-specific immunotherapy was not helpful in the management of AD^[20]
- Most patients with AD have multiple factors contributing to their symptoms, and careful attention to *all* the causative factors is required for successful management.

In 1982, Mitchell et al reported consistent eczematous reactions in some patients with AD following the application of a purified mite allergen directly to the skin for a prolonged period. Subsequently, many other investigators^{[7] [12] [25] [30]} have applied **dust mite** patch tests to patients with AD and reported similar (positive) results in a subset of patients.^[5] Unfortunately, because no standardized house **dust mite** patch test was established, and because all studies used

different materials and methods (i.e., some applied to "stripped" skin, others to intact skin, and others pricked the patch test site), the reported results were difficult to interpret. All reported studies convincingly found no correlation between the serum IgE level (or skin or RAST test) and the patch test reaction for **dust mite** antigens. Ring et al ¹⁸ have documented a more specific role for aeroallergens (animal dander and house **dust mite**) in patients who have an air-exposed pattern of atopic eczema (Fig. 2) (Figure Not Available) .

Figure 2. (Figure Not Available) Number of patients with positive atopy patch test restrictions and pattern of atopic eczema. *Group I:* patients with eczematous skin lesions predominantly located in air-exposed areas. *Group II:* control patients with atopic eczema. Solid area = positive; white area = negative. (From Ring J, and Abeck D: *The atopy patch test as a method of studying aeroallergens as triggering factors of atopic eczema. Dermatological Therapy I: July 22, 1996; with permission.*)

When the author patch tested patients with that air-exposed pattern of AD, 17 of 22 (77%) patients were positive to dust mite, but when all the atopic patients were included, only 18 of 54 (33%) were positive. This emphasizes that basic rule of all allergic contact dermatitis, namely that dermatitis occurs at the site of contact!

The reported success in the management of AD by eliminating **dust mites** from the bedroom, combined with the 47% incidence of positive **dust mite** patch testing of patients with AD (Table 1), certainly supports a potential role of **dust mites** in the pathogenesis for a subset of patients with AD. Of significance is the improvement reported by most of the investigators, when patients with AD were placed in a "dust-free" environment whether positive or negative to **dust mite** patch testing. The author has also found that patients who were dust-mite-test-negative (intradermal or patch) also improved in a dust-free environment. This latter finding supports the role of the **dust mite** also acting as an irritant.

A DUST MITE PATCH TESTING STUDY

In 1994, the Eczema Committee of the Dermatologic Disease Interest Group of the American Academy of **Allergy** and Immunology proposed a multicenter study to determine the incidence of **dust mite** contact

	Patients	Dust Mite	
Name	with AD	Patch	IgE+
Yamada N et al	11	9 (82%)	11
Manzini BM et al	313	122 (39%)	121
Wananuku S et al	30	21 (70%)	same as controls
Castelain M et al	357	75 (21%)	Not related
Wakugaw AM et al	9	6 (67%)	9
Vincenzi C et al	86	37 (43%)	
Imamama et al	130	51 (39%)	32
Darsow U et al	36	33 (92%)	

	Patients	Dust Mite	
Name	with AD	Patch	IgE+
Darsow U et al	57	30 (53%)	
Ring J et al	26	18 (69%)	
Beltrani VS	22 (H&N)	17 (77%)	12
Beltrani VS	54 All AD	18 (33%)	34
Totals	1009	420 (42%)	

allergy in patients with AD, and to compare it with the rate of incidence of a nonatopic population. This study is still in the process of investigation, and the results will be presented when statistically significant numbers are attained.

Patients to be tested were to fulfill the Hanifin and Rajka ^[10] criteria for the diagnosis of AD. Age- and sex-matched nonatopic controls would be recruited. Each patient answers a questionnaire concerning their general health, severity and distribution of disease, and response to all previous therapy. All patients in the study are patch tested with a 20% suspension of mite bodies in petrolatum (the mite bodies were provided by Miles Laboratories, Bayer Corporation, Spokane, WA), as reported by C. Vincenzi et al. ^[10] A control patch will contain the vehicle only. The antigen and control will be pricked, with a Prick Lancetter (Center Laboratories, Port Washington, NY), and then placed under large Finn Chambers (Center Laboratories, Port Washington, NY) and held in place with Scanpore Hypoallergenic Tape (Center Laboratories, Port Washington, NY). The patch test is to be applied only to "uninvolved" skin of the back. The patient is instructed to keep the area dry and return for removal of the patch and a reading at 48 hours, with a subsequent reading at 96 hours. The patch test sites are to be read at 15 minutes after removal, and the reading will be on a 0 to 3 scale, as described by the American Contact Dermatitis Society. Patients are also to be prick tested to standardized mixed **dust mites** (*Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*) and a histamine control. The prick tests are to be read at 15 minutes as millimeters of wheal and millimeters of erythema. Several patients with positive **dust mite** patch tests will collect vacuum containers (ALK Indoor Allergen Analysis Kit) from their bedrooms for **dust mite** counts.

In testing controls, the author included the "**dust mite** patch" to the



Figure 3. A 44-year-old woman with an eyelid dermatitis of many years duration, which was controlled with the daily application(s) of 1% hydrocortisone cream. Patient was advised to create a dust-mite free environment following an "**allergy** work-up" for her perennial rhinitis. With the encasement of her pillows and mattress, the eyelid dermatitis resolved completely, and she required no topical therapy subsequently.

standard (Hermal) patch test tray when testing patients suspected of having allergic contact dermatitis. Surprisingly, several patients reacted positively to the dust mite patch! It was noted that all those in this group who reacted to the dust mite patch were atopic, several of whom also had a positive prick or intradermal dust mite reaction. Another startling finding was the disappearance of a chronic eyelid dermatitis, when a patient created a mite-free home environment for her dust-mite-induced perennial rhinitis. Subsequently, 12 other patients with chronic eyelid dermatitis (Fig. 3) were tested, and 6 reacted positively to the dust mite patch, but to no other contactant! None of these patients had evidence of eczema anywhere else on their body, but all the reactors were atopic with a history of rhinitis or asthma.

The possibility of whether the **dust mite** causes "chronic" localized eczematous reactions in atopics is now being evaluated.

CONCLUSION

Patch testing with **dust mites** can be most important in the identification of dust-mite-contact-sensitive individuals. Although this was first reported in 1982, it was not until the last decade, with the identification of the **dust mite** and its specific antigens, that many investigators have pursued the role of contact **allergy** in AD. [Table 1](#) summarizes the recently reported cases, but each investigator used a different preparation and different method, and most selected patients with AD at random; thus, evaluating their conclusions becomes confusing. (The author patch-tested five patients with both the petrolatum vehicle and an aqueous preparation of *D. Pteronyssinus* and *D. Farinae* 10,000 protein nitrogen units (PNU), and found one patient elicited an irritant reaction to the aqueous preparation and no reaction to the petrolatum preparation. Three of the five patients tested reacted positively to the petrolatum preparation. This suggests that the contact allergen may be different than the IgE antigen!) As stated previously, the author noted a relationship between the distribution of the eczema and positive **dust mite** patch tests. Imayama et al ^[2] also noted a higher incidence of positive results in patients whose eczema was predominantly on areas of the body (face, head, neck, extremities) in contact with fomites, whereas patients with eczema predominantly of the antecubital and popliteal fossa were almost all negative.

Recognizing that the role of **dust mites** in AD deserved more precise evaluation, a multicenter protocol using identical antigenic material and a uniform method was undertaken by the Dermatologic Disease Interest Group of the American Academy of **Allergy** Immunology and Asthma (AAAIA). The participating centers are Columbia-Presbyterian Medical Center of New York; National Jewish Center for Immunology and Respiratory Medicine, Denver, CO; The Johns Hopkins University School of Medicine, Baltimore, MD; Oregon Health Sciences University, Portland, OR; The Brenham Clinic, Brenham, TX; and the University of Medicine and Dentistry of New Jersey. The author's preliminary impression seems to support the published reported conclusions; however, the final results will be statistically analyzed and subsequently reported.

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