

Aeroallergen Contact Dermatitis

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Introduction

The role of inhalant allergens in causing or triggering skin lesions in atopic dermatitis (AD) has been considered since the 1930s. Until recently, inhalant allergens were attributed, at best, a modest function as provocateurs of skin lesions either through inhalation or as contact allergens or irritants by a minority in the field of allergy and dermatology. Inhalant allergens, especially house dust mite allergens, have been studied extensively in asthma and allergic rhinitis in the context of IgE immediate-type reactions, and a good correlation of clinical symptoms with corresponding skin-prick tests and specific IgE serum levels has been shown (1). Such immediate skin reactions to inhalant allergens together with high specific IgE levels are good markers of the atopic status and a common feature in AD. However, they were considered to be irrelevant to the skin symptoms; in AD patients, eczema/dermatitis lesions have clinical and histologic features similar to those of contact dermatitis, a prototype for delayed hypersensitivity reactions. In contact dermatitis, one defined allergen is capable to elicit the effector phase of the reaction. In AD, the existence of such contact reaction to common inhalant allergens *in vivo* is assumed (e.g., for dust mites in beddings), but remains difficult to establish.

In the last decade, as witnessed by the number of articles published, airborne allergens in contact dermatitis and AD have received much more attention. For AD, this arousal of interest came from clinical patch-testing studies with inhalant allergens in association with laboratory arguments, suggesting that delayed IgE-dependent contact mechanisms may cause or exacerbate dermatitis. The use of the term aeroallergen has thus gained support instead of inhalant allergen,

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which was related to a specific route of entry and the implicit assumption that pathogenic effects were targeted mostly to the bronchial and upper airways mucosae.

This article focuses mostly on those arguments, based on aeroallergen contact reactivity, which try to reconcile the delayed nature of eczema in AD and the well-known increased immediate IgE responses characteristic of atopy, and discusses the relevance of the tests to the pathophysiology of the disease.

Historical Perspective

Observations that suggested a link between aeroallergens and AD were described in early reports (e.g., Rost [2]). These reports noted that seasonal flares occur in AD and that avoidance of environmental allergens (especially house dust) in hospitals or in "allergen-free rooms" can lead to improvement of skin lesions in the absence of other therapies. As with food allergens, studies of common aeroallergens as etiologic factors in AD were common in the first half of this century (3–7). Early investigators speculated that exacerbations of dermatitis to specific allergens might be masked if the cutaneous responses were delayed. Tuft (8) reported on patients, sensitive to house dust from their own home, some of whom were cured after cleaning the house. He later reported on the influence of ragweed in seasonal flares (9). Simon (10,11) investigated human dander and showed that a high percentage of children with AD had positive patch tests (PT) to dander extracts.

Lacking in all these studies was a clear demonstration that selective avoidance followed by controlled allergen exposure causes AD exacerbations. This is necessary to establish that the reaction has the specificity and memory features of an immunologic/allergic manifestation. The opinion that such contact reactions were allergic was not validated by leading authorities like Sulzberger (12), who considered them to be manifestations of irritancy/toxicity rather than allergy. Furthermore, the papular/follicular reactions caused by dander were considered by Nexmand (13) as nonspecific.

The interest in that question waned until the 1970s for several reasons analyzed by Platts-Mills et al. (14), the main reason being that specific desensitization did not help the patients, and thus the specific diagnosis of allergen sensitivity in patients with AD was not perceived as leading to useful change in treatment. Second, in the mid-1960s, foods were acknowledged as a cause of AD in children in some countries, but few allergists or dermatologists recognized a role for aeroallergens or foods in adults with AD. However, Uehara and Ofuji (15), pursuing previous experiments on delayed intradermal reactions to human dander, made an important contribution in a large study of

contact reactions on intact skin to human dander. These authors demonstrated clearly the increased prevalence of such reactions in patients with AD, detailing the clinical and histologic pattern of the tests, and discussing their link to intradermal delayed reactions (16). Mitchell et al. (17) performed a controlled study in small group of patients tested with a battery of common aeroallergens including house dust mites and its purified antigen P1, grass pollen, guinea pig dander, and cat dander. This report showed that patch reactions to P1 antigen were not found in nonatopic controls and that such reactions are mostly correlated to skin-prick tests, but not specific to AD since four of six atopic volunteers with a history of asthma or rhinitis had positive P1 antigen PT. In their study, Mitchell et al. abraded the epidermis before patch testing to reproduce the scratching of the disease and this issue proved later to be a subject of controversy. These two groups of investigators, however, opened a new era in the field of contact dermatitis because at least 16 articles were devoted to the subject of patch testing with house dust mite allergens, outdoor allergens, and animal danders since that time (reviewed in ref. 18). Delayed cutaneous reactions to *Pityrosporum ovale*, which might be one of the antigens of human dander, have also been studied (19). During the same period, case reports, clinical studies (20–25), and epidemiological studies (26) have brought further arguments for a role of aeroallergens in aggravating AD.

Patch Testing with Aeroallergens

Methods

Several approaches have been used by investigators for testing and have been reviewed thoroughly by De Groot and Young in 1989 (27). We have reviewed recent studies and made remarks based on two large multicenter studies in which we have participated (18,28).

The first controversial area concerns skin preparation since investigators have used either intact skin (16,18,28–38) or skin abraded by scratching (39) or stripping (17,40–43). Enhancement of intensity of positive reactions by stripping 10 layers of the stratum corneum with cellophane tape was noted first by Uehara and Ofuji (16) and did not increase the frequency of positive reactions in patients with AD and normal controls. Van Voorst Vader et al. (43) considered on the contrary that the proportion of specific reactions were greater on 15X tape-stripped skin. For their proponents, methods causing abrasion make sense because contrary to fat soluble low mol-wt chemical compounds used for conventional patch testing, allergens are both water soluble and of high mol-wt and could not cross the stratum corneum to reach antigen-presenting cells (14). These authors also consider that

scratching marks in AD patients reproduce these experimental conditions, hence rather speculating about a secondary aggravating factor rather than on a primary mechanism in inducing eczema. On the contrary investigators who have obtained positive results on intact skin with concentrations of aeroallergens which parallel those found in the environment of the patients are inclined to think that the defect in skin permeability barrier in AD patients (44) allows the passage of aeroallergens through the stratum corneum (30). They also argued on the practical point of view that contact allergists are best trained to perform PT without abrasion (28).

The type of antigen, the preparation of the antigen, its concentration and vehicle, the amount of solution applied, and the material used for testing have varied considerably according to investigators. De Groot and Young (27) summarized the variables in their article and showed, for example, that investigators have used everything from basic commercial prick testing solutions to pure mite dry powder. With antigens, a comparable unit measurement system is not available among commercially available products. Dosage of D pter-1 antigen for dust mites in commercial extracts has been performed in the Castelain et al. study (28) and the optimized range of concentration for use on unabraded skin with the classic Finnchamber™ technique was approx 10 µg/mL. A modification of the repeated open application test technique has been used by Norris et al. (32) followed by occlusion and referred to as "Challenge test."

Several sites were tested. Flexor areas were used by Norris et al. (32) and Gondo et al. (40). Uehara and Ofuji (16) and Räsänen et al. (37) used the inner anterior side of the arm. The general opinion remains that the skin of the upper back remains the best site for patch testing and allows to use enough space especially for testing in combination contact allergens (18).

Results

As shown in Table 1, and as expected based on the considerable variations noted in the Methods, the results show positive PT for aeroallergens in general and also for house dust mites in isolation in 10–100% of AD patients. Further sources in variations not mentioned in the Methods section include the selection of patients by prick testing or IgE levels and the time of reading. Some variations were expected owing to changes in climate and environment in different countries, and some studies have addressed only relevant prevalent environmental allergens like birch pollen (37). For indoor allergens, which are common in most dwellings like house dust mites, the magnitude of variations does not reflect environmental conditions but strengthen the case for a standardization in methods.

In nonatopic subjects, the largest study including 398 controls showed for D pter-1 PT only 0.75% of positivity (28). In the pioneering work of Uehara and Ofuji (16), 3% of nonatopic controls patch tested ($n = 31$) reacted to human dander. For asthma/rhinitis controls without AD, only limited information is available (17,29,32,36,40,41) on a total of 81 patients with a wide array of methods used. Without abrasion, the number of positive aeroallergen PT is low (around 3%), but seems higher (15%) after abrasion. Thus, the name "atopy patch test" proposed by some for aeroallergen PT (34,38) seems appropriate because of its good specificity. However, its sensitivity to detect the atopic status seems low especially in pure mucosal atopic patients. Larger scale studies are needed to compare prick and PT in this last category of patients.

Clinical Interpretation of Patch Tests

Most authors have used the guidelines of the ICDRG (International Contact Dermatitis Research Group) to read the tests at 2 d, but it should be emphasized that 4-d readings are crucial to detect false-positive responses which are weak and disappear at the late reading (28). Persistence of positive tests for several days, 1 wk or longer leading to lichenified plaques or patches of scratched papules, has been noted (16). The aeroallergen PT are not as frequently vesicular like contact allergy conventional PT. In the Castelain et al. series (28), around half of positive readings were vesicular, corresponding to 11.2% of clinically eczematous reactions in the AD population patch tested with aeroallergens. Micropapular, follicular tests are most prevalent, and represent the majority of positive reactions recorded in children in our series (18) (Fig. 1). This clinical pattern is frequently occurring naturally in AD on the trunk and is referred to as follicular AD. Similar patterns have been described in allergic contact dermatitis from nickel, neomycin, and formaldehyde and yield no support to the nonspecific irritant theory (45).

Histopathology

Pathology studies have demonstrated eczema lesions (spongiosis and migration of mononuclear cells), which predominate at the upper portion of hair follicles, with similar changes around sweat glands in the epidermis, delineating a predominant folliculoporal pattern (16). Based on histologic studies using semithin sections, Mitchell et al. (17) emphasized a similarity between this delayed reaction and the well-known basophil delayed experimental hypersensitivity in the guinea pig (Jones Mote), which involves both T-cells and anaphylactic antibodies. However, other investigators (29,41) have not reproduced these data. The presence of eosinophils in the infiltrate, a finding which could discriminate between classic contact allergy and aeroallergen

Table 1
Aeroallergen Patch Tests in AD: Studies with Abraded vs Nonabraded Skin^a

Study	Number of AD patients tested	Allergens tested	Patients with positive patch tests, %	Patients with positive prick tests, %	Patients with concordant patch-prick tests, %
Uehara and Ofuji (1976) (16)	181	HD	66	ND	NE
Mitchell et al. (1982) (17) ^b	10	Der P1	100	100	100
Young et al. (1985) (41) ^b	18	HD Der P1	94 HD, 100 Der P1	100 HD	100 Der P1
Gondo et al. (1986) (40) ^b	1	<i>D. farinae</i>	1	1	100
Reitamo et al. (1985) (29)	17	BP, HDM	BP 35, HDM 18	BP 76, HDM 53	BP 46, HDM 33
Desager et al. (1987) (31)	22	HDM, CD, DD, GP, WP, TP	41 at least one positive PT	ND	NE
Adinoff et al. (1988) (30)	10	Alternaria According to environment	100	100	100
Bruynzeel-Koomen et al. (1988) (41) ^b	15	HDM, GP	HDM 80, GP 26	HDM 100, GP 86	HDM 100, GP 30
Norris et al. (1988) (32)	30	HDM	33	100	33
Langeland et al. (1989) (34)	35	HDM, Timothy P BP, Cladosp	17	NE	85

Tanaka et al. (1989) (35)	20	DP, DF	DP 70, DF 65	ND	NE
Kieffer et al. (1990) (19)	55	P. ovale	13	65	77
Van Voorst Vader et al. (1991) (42) ^b	21	HDM	28	ND	NE
Räsänen et al. (1992) (37)	10	BP	10	100	10
Imayama et al. (1992) (43) ^b	130	HDM	39	ND	NE
Seidenari et al. (1992) (36)	47	Gramineae	14	ND	NE
Castelain et al. (1993) (28)	355	HDM	21	42	20
Darsow et al. (1993) (38)	29	HDM, CD, GP	?	ND	NE
Cabon et al. (1995) (18)	59	9 aeroallergens	29	7-70 ^c	20

^aAbbreviations: BP, birch pollen; CD, cat dander; DD, dog dander; DP, *D. pteronyssinus*; GP, grass pollen; HD, human dander; HDM, house dust mite; NB, not done; NE, not evaluated; TP, tree pollen; WP, weed pollen; ?, unknown.

^bStudies with abraded skin.

^cAccording to allergen tested.

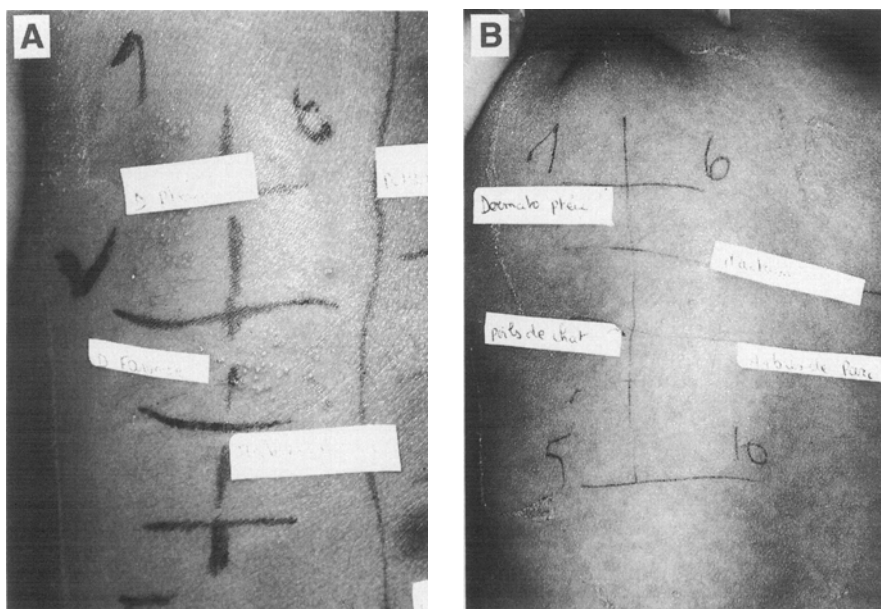


Fig 1. Clinical and pathological features of aeroallergen patch tests: **(A)** Typical papular follicular pattern in a 7-yr-old girl with AD at 48 h: ++, *D. pteronyssinus*; ++, *D. farinae*; +, garden trees (park trees: mixture for maple tree, horse chestnut tree, plane tree, locust tree, and Indian tree). Clinical data: severe lichenified AD (first visit SCORAD 70), no asthma. Allergy data: Contact allergens: +, potassium bichromate; +, 0.6% PPD black rubber mix; ++, lanolin alcohol 30%; ++, nickel sulphate. Concordant aeroallergen prick tests (plus positive gramineae). Total IgE 2578 KUI/L, RASTs *D. pteronyssinus* and *D. farinae* > 300 SU/mL. Improved during the following year with avoidance of contact allergens (SCORAD 45 1 1/2 yr later). **(B)** Multiple positive aeroallergen PT in a 7-mo-old boy breast-fed for 5 mo with moderate AD (first visit SCORAD 35) involving mostly face and extensor aspects of limbs since 3 mo and with first attack of wheezing at 7 mo during patch testing: Patch tests: +, *D. pteronissymus*; ±, plantain; erythema, cat dander; +, garden trees. Other data: negative prick tests to the same allergens; positive prick tests to eggs, milk. Total IgE 76 KUI/L RASTs: eggs 28 SU/mL cow's milk 4.9 SU/mL (casein 11.8 SU/mL), *D. pteronissymus*, *D. farinae* < 1.4 SU/mL. Strict avoidance of milk and eggs with topical treatment. Clearance of AD at 2 yr. Asthma requiring inpatient treatment three times since age 1.

contact dermatitis was noted by several investigators (17,39,41). Moreover, close contact between Langerhans' cells (LC) and eosinophils have been noted within the epidermis using electron microscopy (41). The dermal mononuclear infiltrate also contains activated eosinophils in early (4–6 h) biopsies and later mostly CD4 lymphocytes and CD1a+ antigen-presenting cells (±9,34,41).

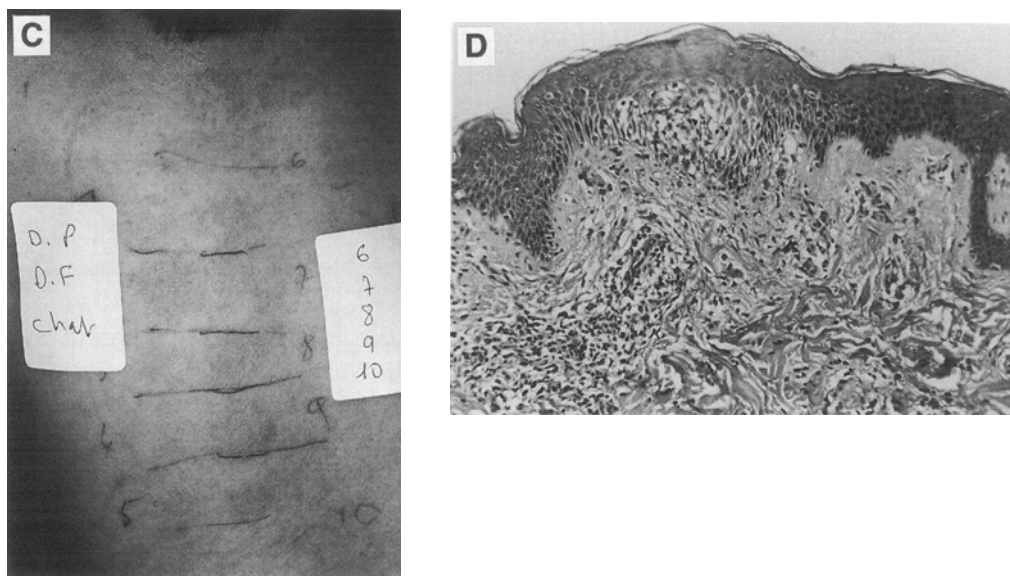


Fig. 1. (continued) (C) Multiple positive aeroallergen PT at 48 h in a 2-yr-old boy with severe AD (first visit SCORAD 75): +, *D. pteronyssimus*; ++, *D. farinae*; +, cat dander; ++, 6 (mugwort); ++, 7 (plantain); ++, 8 (garden trees); ++, 9 (damp area trees). Other data: Prick tests positive for *D. pteronyssimus*, pork, wheat flour. Positive food challenge with wheat flour, negative for pork; IgE 3300 KUI/L, RASTs *D. pteronyssimus* 0.46 PRU/mL, negative for cat dander, mugwort, plantain, wheat. Clear improvement following avoidance of wheat. (D) Histopathology of *D. pteronyssimus* patch test 200 IR (stallergenes) on intact skin in an adult AD patient at 48 h. Eosinophils are present in the epidermis and in the dermal infiltrate (H & E stain 100×).

Children Series

Few patients have been tested in the pediatric age group. However, positive aeroallergen PT have been noted as early as 1 yr of age and around 30% of patients have at least one positive test in our experience in the Bordeaux area, dust mites being the most prevalent (18).

Standardization

As noted, this issue is crucial to validate the current effort to assess PT reactions to aeroallergens (38). When allergens, vehicles, and concentrations are agreed on, the major problem will remain the large-scale preparation of reagents using standardized, tried, and tested semi-industrial methods (e.g., for classic PT products) (28). Currently the production of individual units in syringes for small-scale studies may cause uneven dispersion of antigen leading to false-positive or false-negative reactions (28).

Relevance, Correlations, and Avoidance-Challenge Studies

As stated earlier, studies on both abraded and nonabraded skin show a good specificity for the atopic status, and possibly a better one for AD. However, is the observed reaction a nonspecific manifestation of the "irritable" skin in AD patients or not? This controversy is not completely closed, but several arguments are pleading against the irritant theory: the clinical pattern that mimics the clinical presentation of the disease with itchy follicular papules; the histologic features and especially the eosinophils migrating in the epidermis; and the challenge and passive transfer studies (29,34,39,46). All these arguments indicate that the effector phase of a delayed immune reaction can be elicited through contact with aeroallergens but they do not show that this mode of reaction is relevant to the constitution of skin lesions *in vivo*. Correlation studies are thus interesting to investigate more accurately the relevance of such findings. Imayama et al. (44) conducted a study investigating IgE for house dust mite, PT, and clinical presentation. In this well-designed series of 130 patients, no correlation was noted between specific IgE levels to house dust mites and positive PT to the same antigen, however, they confirmed that higher specific IgE levels correlate with respiratory atopic disease. The authors were able to establish a correlation of the clinical cutaneous profile with the results of specific house dust mite IgE levels and of house dust mite PT, and distinguished four categories of patients. In a study of our group of 59 children (18), a series of correlations was examined for PT to a series of aeroallergens. Concerning site of lesions, no particular feature was striking when comparing positive and negative PT groups. Lichenification predominated in the PT-positive group, and erythema plus edema/papulation was more frequent in the PT-negative group (Table 2). However, overall no significant statistical difference concerning extent or type of lesions was noted based on the SCORAD index (47), but the tendency toward more lichenification in PT-positive patients was in agreement with Imayama et al.'s study (43) as well as another previous Japanese study (16). Furthermore, the following items were studied in positive- and negative-PT groups: family history of asthma, rhinitis, or AD; early onset of AD or respiratory symptoms; total serum IgE levels; contact allergy to an ICDRG panel; and exposure to environmental factors. Similarly, no correlation was established with PT positivity (18).

In contrast, a study on carefully selected patients with concordant-specific IgE prick and PT to aeroallergens has suggested a good correlation between environmental allergens exposure and corresponding PT and a good response of AD to avoidance of the offending allergen (30). Challenge studies with repeated open application of allergens

Table 2
Type of Lesions According to Four Groups of Patients Using Skin Tests
and Clinical Data Based on the SCORAD Index (47)^a

Clinical signs	Patch +, prick + ^b	Patch +, prick - ^c	Patch -, prick + ^d	Patch -, prick - ^e
Lichenification predominating	3	2	2	0
Erythema, edema, and papulation predominating	1	3	6	7
Equal number of lichenified lesions and erythema, edema, and papules	7	0	8	4
Xerosis predominating	1	0	1	3

^aFrom ref. 18.

^b*n* = 12.

^c*n* = 5.

^d*n* = 17.

^e*n* = 14.

(32,39) are positive in some selected sensitized prick test-positive patients, worsening AD lesions, whereas in atopic pure respiratory controls with positive prick test to the same allergen have only urticaria and pruritus and no eczema (32).

Based on these data, the overall relevance of positive aeroallergen PT in AD patients remains difficult to establish. IgE-specific levels, prick, and PT are concordant in only a minority of patients. Careful avoidance/challenge tests studies should be ideally performed in patients with concordant and discordant types of responses to address the issue of relevance. But for now, patients with concordant prick and PT to aeroallergens and predominant cutaneous symptoms are good candidates to be put on a specific avoidance regimen when feasible.

Delayed Hypersensitivity, IgE and Late Reactions to Aeroallergens

The delayed epicutaneous responses to aeroallergens noted in one third to one fourth of AD patients on intact skin raise new questions about the pathophysiology of this disease in which abnormalities have been noted in immune responses.

Is Sensitization with Aeroallergens Through Skin Possible in AD Patients?

A host of articles have been published on the suppression of delayed hypersensitivity in AD (21 from 1937–1979 according to Clark's review [48]). More recent data indicate that the severity of the dermatitis correlates with a blockade of sensitization with potent allergens (49), which is reversible on treatment of AD. Recent large-scale studies in contact dermatitis clinics show either a similar or slightly decreased rate in contact allergy among atopics (50), when compared with nonatopics (51), but a decreased rate among patients with active AD (51,52). Thus, the sensitization via skin by aeroallergens remains possible since, even if depressed, delayed-type hypersensitivity is not completely impaired, especially in mild and moderate forms of AD.

How Are IgE-Mediated Reactions Related to Delayed Cutaneous Aeroallergen Hypersensitivity?

Effector cells for immediate IgE-mediated reactions are mast cells or basophils that can release inflammatory mediators on cross-linking of surface bound IgE by allergens. Mitchell et al. (17) suggested that the so-called IgE-mediated late-phase response (53) was involved, and that the effector phase, including the recruitment of eosinophils could be explained by dermal mechanisms once the antigen has reached this level. Gondo et al. (39) provided evidence of such a transepidermal passage using ferritin-mite conjugate. A major advance was the discovery of IgE bound to epidermal LC by Bruynzeel-Koomen et al. (55), which was a step necessary to understand the *in situ* priming of T-lymphocytes when the epidermis is exposed to aeroallergens. Her group later showed that only IgE-bearing epidermal LC could present house dust mite antigen to T-cells using proliferation assays (54). Bieber and his group (56) studied IgE-binding molecules on human LC and found three types of molecules susceptible to bind IgE, namely the low-affinity receptor FcεRII/CD23, the high-affinity receptor FcεRI, and the IgE-binding protein εBP. CD23 bound to LC is a good candidate for aeroallergen presentation and soluble CD23 released by LC may influence the regulation of IgE synthesis. FcεRI could be a candidate for initial events within the epidermis during challenges (56). However, the IgE-bearing LC are not specific for AD since they are found in other inflammatory skin diseases and in correlation with IgE serum levels (57).

Thus, based on this brief summary, aeroallergens could induce cutaneous delayed reactions either directly through sensitization and later elicitation via epidermal LC, and this mechanism could be

enhanced by the abnormal barrier function of AD patients or as inhaled allergens reaching the skin via the blood stream and acting on dermal effector cells. Recent studies on food allergens (58) point out possible mechanisms for specific homing in the skin of sensitized T-lymphocytes and may provide clues for the preferential localizations of eczematous lesions. The variation in sites during life of AD lesions could be related to maturation of the epithelial barrier (59).

Is There a Link Between Delayed IgE-Mediated Reactions and Impaired Delayed Cellular Immunity?

The development of the Th1–Th2 imbalance theory in atopy (reviewed by Plaut [60]) has provided new insights for this phenomenon. It has been shown that house dust mite-specific T-cell clones from skin of patients with AD have a Th2 profile when stimulated by house dust mite antigen (61). This Th2 profile, which is characterized by the secretion of IL-4, IL-5, IL-6, IL-10, and IL-13 may explain most of the cellular events of the IgE-mediated late phase, especially the recruitment of eosinophils and mast cells. It may also explain the functional impairment of Th1-driven reactions like contact allergy and antiviral immunity. However, recent *in situ* studies in the skin of AD patients indicate that this model may be an oversimplification (62).

Conclusion

The recent advances in the field of aeroallergen contact dermatitis have provided new concepts that may help in managing patients with AD. First, progress should be made in improving our tools for patch testing with aeroallergens, and a consensus would be welcome for the standardization of allergens and testing methods. More epidemiological and follow-up studies are needed to assess the relevance of aeroallergen PT data. It seems reasonable to admit from the literature reviewed that a subset of patients with AD can improve with a manipulation of their environment, like a subset seen mostly in infants and young children improves after selective avoidance diets. However, in other patients, delayed responses to aeroallergens may have no relevance and could indicate merely the existence of other IgE-dependent mechanisms contributing to late-phase reactions in atopy. This phenomenon might be considered as a further marker of the atopic status, left sometimes undetected when only intradermal tests are used. The awareness of the development of IgE-dependent mechanisms via the epidermis may encourage the prevention of AD in predisposed individuals by reinforcing the epidermal barrier (63), especially in infancy, for example, by using large amounts of emollients, among other usual measures to decrease exposure to common aeroallergens (64).

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