

## Atopic dermatitis: Triggering factors

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Atopic dermatitis is a hereditary disorder, frequently associated with allergic rhinitis and bronchial asthma. The disease may be influenced by many triggering factors such as irritants, aeroallergens, food, microbial organisms, sex hormones, stress factors, sweating, and climatic factors. Moreover, it is important to be aware of contact allergy as a complicating factor. This review deals with recent clinical, experimental, and some therapeutic data on these triggering factors. (J AM ACAD DERMATOL 1994;31:467-73.)

Although atopic dermatitis (AD) is a common disease, its pathogenesis is still obscure.<sup>1-4</sup> Genetic factors underlie the development of the disease,<sup>5</sup> and the role of genes on chromosome 11q13 is currently under investigation.<sup>6,7</sup> However, environmental influences frequently seem necessary to provoke the disease.<sup>5,8</sup>

The central, but not necessarily the primary, event in AD is the itching. Patients appear to have a reduced itch threshold and a more prolonged itch duration to pruritic stimuli than normal,<sup>9</sup> probably as a result of the inflammatory reaction in their dry or eczematous skin. This reduced itch threshold is considered by some as a hallmark of AD, just as increased bronchial reactivity is characteristic of bronchial asthma.<sup>9</sup> Moreover, patients with AD seem to have an "itchy skin." Mechanical stimuli (e.g., friction, touch) near eczema lesions are perceived as itch rather than touch.<sup>10</sup> The mechanism of this is not known but may be caused by an altered central processing of mechanoreceptive input.<sup>10</sup> As a result there is a vicious circle of itching, scratching, and aggravation of eczematous lesions. A variety of triggering factors<sup>8</sup> may provoke itching.

There is also growing evidence that allergic mechanisms could also be of pathogenic significance in AD. Therefore, in analogy with the classification of allergic rhinitis and asthma, Wüthrich has proposed for this type the term *extrinsic* AD; the term *intrinsic*

AD applies to those cases in which there is no evidence of "allergic" influences.<sup>11</sup>

This article reviews important trigger factors.

### IRRITANTS

There is a tendency for itching and/or an eczematous reaction to develop after contact with irritants.<sup>10,12</sup> Intolerance to wool<sup>13,14</sup> and to lipid solvents, especially soaps,<sup>15</sup> have been included as minor diagnostic criteria for AD by Hanifin and Rajka.<sup>16</sup> Disinfectants (e.g., chlorine in swimming pools) are frequently not well tolerated. Occupational irritants may produce major problems, particularly on the hands,<sup>17</sup> and cigarette smoke may provoke eczematous lesions on the eyelids.

The reason that patients with AD have irritable skin is not clear. It may be secondary to the dryness of their skin, which is probably related to disturbances in lipid content and hydration of the epidermis.<sup>18</sup> A low-grade inflammatory reaction is present in this dry skin.<sup>19</sup> These findings evidently are related to the impaired barrier function of the skin in AD, allowing irritants to act more intensely.<sup>20</sup> Finally, an increased releasability of histamine and possibly other mediators may be factors.<sup>10</sup> Here disturbances of cyclic adenosine monophosphate c-AMP phosphodiesterase activity might be important.<sup>3</sup>

The avoidance of irritating factors, the use of mild skin cleansing agents, and regular applications of a hydrating cream can help prevent exacerbations of AD.<sup>9</sup>

### AEROALLERGENS

Enthusiasm for the role of allergic factors has varied, and the importance attributed to aeroaller-

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gens, nutritional, or microbial allergens has waxed and waned.<sup>21</sup>

The most important aeroallergen appears to be the house dust mite. Many patients with AD have specific anti-IgE antibodies to house dust mite antigens, and in many cases the concentrations of these are higher than those to other allergens.<sup>21</sup> As early as 1932, Rost<sup>22</sup> demonstrated that the eczema of some patients allergic to the house dust mite would lessen significantly if they remained in a room free of mites. More recent studies confirm these findings,<sup>21, 23-28</sup> but not others.<sup>29</sup> Carefully designed studies, such as that done by Sanda et al.,<sup>28</sup> are needed to evaluate the practical relevance of house dust mite elimination measures in the treatment of AD. At present, the role of the house dust mite in exacerbations of AD is still controversial. The concentration of house dust mite antigens detected in the beds of patients with AD was found to parallel the severity of the disease,<sup>30</sup> whereas others could not demonstrate a correlation.<sup>31</sup> However, a lack of synchronicity of the measurements was an important flaw in the latter study.

The way aeroallergens aggravate AD is still a matter of debate. More than 30 years ago, Tuft<sup>32</sup> and Storck<sup>33</sup> provoked exacerbations of skin lesions by inhalation of house dust or pollen extract, respectively. However, there is also evidence that allergen penetration through the skin may occur. Eczematous lesions can also be provoked by applying house dust mite allergens to the skin for 1 or 2 days with a patch test<sup>34</sup> or by repeated applications.<sup>35, 36</sup> In one case report the concentration of specific IgE to house dust mite antigens paralleled the severity and extent of the eczema, whereas specific IgE to other aeroallergens did not. The interpretation of this finding was that large amounts of house dust mite antigen may be scratched into the skin during clinical exacerbations.<sup>37</sup> In addition, the presence of house dust mite antigens in the epidermis of AD lesions and patch-test reactions to house dust mites has been demonstrated.<sup>35, 38, 39</sup>

Other aeroallergens such as pollens,<sup>11, 25, 26, 40-42</sup> allergens from pets,<sup>25, 26</sup> from molds,<sup>26</sup> or human dander<sup>43</sup> may contribute to provoking AD in the same way.

If there are strong indications of aeroallergen exacerbation of skin lesions, measures for allergen elimination should be considered. Hyposensitization in its classic way<sup>44</sup> or, as recently described, with complexed allergens<sup>45</sup> may be effective, but cannot be regarded as an established therapy for AD. It re-

mains to be determined which subgroups of patients will benefit from measures that interfere with aeroallergen-induced reactions.

## MICROBIAL AGENTS

### *Staphylococcus aureus*

An excellent review of the possible role of *Staphylococcus aureus* is given in a recent article by Neuber et al.<sup>46</sup> *S. aureus* is the predominant skin microorganism in AD lesions in about 90% of patients.<sup>47</sup> It is also significantly increased in nonaffected skin.<sup>48</sup> Normally, *S. aureus* represents less than 5% of the total skin microflora in persons without AD.<sup>47, 48</sup> This overgrowth of *S. aureus* in AD has been attributed to a diminished antibacterial function of the skin caused by altered sebum and sweat secretion.<sup>47, 48</sup> Greater adherence of *S. aureus* to atopic skin caused by a changed or improved access to certain proteins (e.g., fibronectin) or to enhanced HLA-DR expression as well as changes in the microbial defense mechanisms are further factors.<sup>49</sup>

There is experimental evidence that *S. aureus* also may contribute to the development of eczema via allergic mechanisms:

- Anti-IgE antibodies against *S. aureus* have been detected.<sup>50, 51</sup>
- *S. aureus* can induce IgE production by B lymphocytes in vitro, whereas it suppresses IgA and IgG production.<sup>52</sup>
- *S. aureus* enhances the expression of CD23, the low-affinity receptor for IgE, on B lymphocytes and Langerhans cells.<sup>52</sup>
- Enterotoxins released by some staphylococci may function as superantigens by themselves<sup>53-56</sup> or indirectly via the intermediate of cellular superantigens.<sup>57</sup> Superantigens are potent T-cell stimulants that are able to join MHC class II molecules on antigen-presenting cells with T lymphocytes bearing a T-cell receptor with a particular  $V\beta$  region.<sup>57</sup> At least in mice, superantigens seem to stimulate Th2 lymphocytes preferentially,<sup>54</sup> which are believed to be important in the pathogenesis of AD.

Staphylococci evidently are involved in exacerbations of AD, as it is a common experience that AD may dramatically lessen when antibiotics are administered systemically or topically.<sup>47, 58, 59</sup> However, there is still discussion whether such therapy is also effective in patients in whom *S. aureus* can only be cultured from the skin without clinical evidence of infection.<sup>58</sup>

### ***Pityrosporum* yeasts**

The data concerning the relevance of *Pityrosporum* yeasts as a provocative factor are less conclusive. This organism was thought to be one of the most important factors in provoking the so-called head-and-neck variant of AD.<sup>60</sup> This yeast, a normal inhabitant of most humans, is highly lipophilic and therefore predominates in these seborrheic regions.

Prick or intracutaneous tests,<sup>60-64</sup> patch tests,<sup>63, 64</sup> histamine release tests,<sup>61</sup> and lymphocyte transformation tests<sup>63</sup> with extracts of *Pityrosporum* may give positive results in patients with AD, and specific IgE antibodies to *Pityrosporum* have also been demonstrated.<sup>51, 61, 62, 64</sup>

However, in recent studies<sup>63, 64</sup> a definite correlation between clinical severity, test results with *Pityrosporum ovale* extracts and the response to antimycotic treatment could not be found. Moreover, it is our experience that not every patient with AD of the head and neck improves with such treatment.

It is possible that in a subclass of patients with AD, treatment with topical or systemic antiyeast preparations<sup>60</sup> may be beneficial, but more precise studies are needed to define more accurately which patients might benefit.

### **Other microorganisms**

*Candida albicans*<sup>65</sup> and perhaps *Trichophyton*<sup>66</sup> may be triggering factors for AD, but their actual importance, as well as that of other microorganisms, remains to be established. Particularly in children, infections (e.g., of the respiratory tract) may provoke exacerbations of AD.<sup>9</sup>

### **FOOD**

Whether foods can provoke exacerbations of AD has been another point of controversy, but we now know that they definitely can contribute. However, the question is: How frequently and to what extent do foods cause exacerbations of eczema?

Foods can provoke both allergic and nonallergic reactions.<sup>67</sup> Allergic reactions are evidently not infrequent in children. The standard work in this field has been done by Sampson and his associates (summarized in Sampson<sup>68</sup>). They tested 320 patients with extensive AD with double-blind, placebo-controlled food challenges. Positive reactions were recorded in 63% of the patients, most were skin eruptions (75%), but gastrointestinal symptoms (41%), upper respiratory tract symptoms (36%), and sometimes wheezing (10%) also occurred. Most patients reacted only to one or two food items. The

foods provoking most reactions were eggs, peanuts, milk, fish, soy, and wheat. Those with positive provocation tests almost always had positive skin tests to the causative food, but the reverse was not true. However, others have found food challenges are frequently positive in the absence of positive skin tests or demonstration of specific IgE by a radioallergosorbent test (RAST).<sup>69, 70</sup>

Signs pointing to a food-induced reaction are urticarial lesions, an exacerbation of eczema, gastrointestinal or respiratory tract symptoms, or anaphylactic reactions temporally related to eating. However, many patients reacting to food are not aware of their hypersensitivity.

When provocation tests were repeated 1 to 2 years after starting an elimination diet, 42% had lost their sensitivity.<sup>68</sup> Milk and soy allergy usually disappeared with aging, whereas egg and fish allergy had the tendency to remain. Before food challenges are performed for diagnosis, a history has to be taken and skin tests as well as a determination of specific IgE antibodies (e.g., RAST) have to be done. Direct application of the native food to the skin<sup>71</sup> or with a scratch test probably is more reliable than testing with commercial extracts. The results of RAST tend to be less reliable.<sup>72</sup> Although extensive studies have not yet been conducted in adults, it generally is thought that IgE-mediated food allergy is of less importance in them. A few recent studies suggest that more importance in adults<sup>73</sup> and in children<sup>74</sup> should be assigned to reactions provoked by preservatives, colorants, and other substances of low molecular weight present in food. In addition, nonspecific flushing reactions from alcoholic beverages or spicy or hot food have to be considered.<sup>67</sup> The patient's history is crucial for interpreting such reactions because there are no skin or other laboratory tests. In patients with severe eczema, provocation tests are the only way to identify the causative agents,<sup>67, 73, 74</sup> although they have to be interpreted critically.<sup>75</sup> Undirected elimination diets without identification of eliciting items have to be avoided; beyond being unnecessary unpleasant restrictions for the patient, they may cause social isolation, particularly in children, or nutritional deficiencies, or even lead to anaphylaxis after uncontrolled reintroduction of a nontolerated food.<sup>67</sup>

### **HORMONES**

Women frequently report fluctuations of the clinical course of AD indicating hormonal influences. Menstruation, pregnancy, parturition, and

menopause may be associated with exacerbations. However, an opposite effect is also possible, and the effects may vary, even in the same patient.<sup>76</sup> Unfortunately, no therapeutic measures are known to influence the course of AD exacerbated by hormonal factors.

## PSYCHE

Stressful life events often precede exacerbations of AD. Daily emotional stress can trigger the itching and scratching, and some studies have suggested that AD has a psychophysiologic component.<sup>77, 78</sup> On the other hand, severe disease and its unpredictable course impose a great psychologic burden on the patient, which is experienced as anxiety.<sup>77-79</sup> However, these influences seem to differ from one patient to another and different subgroups can be distinguished with regard to psychologic disability.<sup>80</sup>

Learned maladaptive behavior may be important in the maintenance of AD.<sup>79</sup> In childhood a disturbed parent/child relationship, in particular, may be crucial, and it is important to consider this possibility. Some children learn to manipulate parents by their scratching and sleeplessness.<sup>79</sup> Moreover, parental behavior may also create problems because they may provide inadequate information and may not follow therapeutic instructions.<sup>81</sup>

Psychophysiologic interactions evidently occur in AD,<sup>78</sup> but their mechanisms are not yet well understood. The disturbances in the adenylyclase-cyclic adenosine monophosphate system<sup>78</sup> or the action of neuropeptides,<sup>82</sup> such as vasoactive intestinal polypeptide<sup>83</sup> or substance P,<sup>84</sup> have been suggested as possible links. Recently a close anatomic relation between mast cells and nerve endings<sup>85</sup> and an increased number of immunoreactive nerve fibers in AD<sup>86</sup> have been demonstrated, which suggests a potential role of innervation and neuropeptides for the disease.

A thorough psychologic evaluation and specialized care and/or changes in the social or familial situation may help to manage patients with severe AD. Relaxation exercises and/or sedatives may be of help in preventing severe attacks.

## SWEATING

Although there are no unequivocal experimental data on the effect sweating has on atopic eczema, it is well known that sweating may cause itching and, secondarily, eczema.<sup>9</sup> Studies concerning sweat gland function in atopic eczema are contradictory.

An increase in sweat production has been reported by some, but several recent studies have indicated a reduced sweat production (reviewed in Parkkinen et al.<sup>87</sup>).

The way sweating causes pruritus is not known. Sulzberger et al.<sup>88</sup> suggested that a rapid and excessive absorption of sweat droplets by the stratum corneum occurs in dry keratotic skin, producing periporal edema. Parakeratotic plugging of the sweat duct ostium has been demonstrated. Because of poral closure a leakage of sweat through the duct wall may provoke an irritant reaction with pruritus, urticaria, or a condition resembling miliaria. Others propose that there is increased sweat production, as a consequence of an enhanced sensitivity of the parasympathetic part of the autonomic nervous system because of sympathetic blockade (Sventivanyi's theory).<sup>9</sup> Some studies also suggest that constituents of sweat can provoke allergic reactions.<sup>89</sup>

The avoidance of activities or circumstances that may induce intense sweating is the only possible way to prevent this trigger factor. Anticholinergic drugs or sauna therapy, as done in Scandinavian countries,<sup>9</sup> do not seem to be helpful or, at least, need to be better evaluated.

## CLIMATE

There are clear seasonal influences on the course of AD. In some patients AD worsens during the winter months, others experience exacerbations during spring or autumn, and in some the disease worsens in the summer.<sup>9</sup> Moreover, a change of environment may influence the disease.<sup>25, 26</sup> Stays at the seaside or in the mountains, particularly above 1500 m, are frequently associated with improvement of the skin condition.<sup>90</sup>

Exposure to the sun generally is beneficial,<sup>9</sup> but some patients will experience worsening of exposed skin areas during sunny months.<sup>91</sup> Some have actinic prurigo<sup>91, 92</sup> or a polymorphous light eruption,<sup>91</sup> but some experience a true exacerbation of their AD. This has been called photosensitive AD and may progress to chronic actinic dermatitis. In photosensitive AD routine phototesting usually gives normal results, but lesions may sometimes be induced with UVB.<sup>93</sup>

Different factors like antigen exposure,<sup>25, 26</sup> sweating, UV exposure, low air humidity during the winter months, and cold winds that dry the skin may, therefore, contribute to seasonal influences on AD.<sup>9, 90</sup>

For severe cases of AD climatotherapy (in the mountains or at the seaside) may bring a period of dramatic relief. For every patient with AD, holidays in regions where the climate is favorable should be recommended. Moving permanently to regions with another climate has been reported to be beneficial.<sup>25, 26</sup>

## COMPLICATING CONTACT ALLERGY

It is important to keep in mind the possibility of contact allergic reactions,<sup>94, 95</sup> particularly to ingredients in skin care products. If, when correctly performed, treatment does not result in the expected improvement, the possibility of a contact allergy to topical preparations, including the corticosteroids,<sup>96</sup> should be considered. Clothing, airborne, or hematogenous contact dermatitis, which may closely mimic AD, have to be excluded.

## CONCLUSION

Many factors, allergic or nonallergic, may influence the course of AD. They differ from one patient to another and possibly during the course of the disease in the same patient. The cornerstone for identifying possible triggers is thorough history taking. This becomes mandatory if the disease cannot be controlled by a basic treatment with "skin care" measures and occasional therapy for relapses with topical corticosteroids, and, if needed, antihistamine agents.

At present, no standardized test scheme, like that for rhinitis or asthma, is available to trace possible triggers of AD. Diligent studies are required to find out which patients might benefit from the elimination of individual elicitors of disease. The individual patient, whose disease is refractory to conventional basic therapy, should be examined carefully and critically with regard to such provocation factors.

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