

Atopy: Immunodeviation and environment

An increasing prevalence of atopic diseases especially in highly industrialized countries has been demonstrated by several studies. According to a study comparing 2510 children in 1964 and 3403 children in 1989, the prevalence of asthma rose from 4.1% to 10.2%, that of hay fever from 3.2% to 11.9%, and that of eczema from 5.3% to 12%.¹ In addition, a 20- to 60-fold variation in the frequency of asthma, rhinitis, and eczema has been reported among different countries, with the higher prevalence in Western industrialized countries.² The identification of factors influencing the risk for the development of allergic diseases is of obvious relevance for prevention programs. There is striking evidence that a genetic predisposition associated with an immune deviation in combination with specific and unspecific environmental factors ultimately leads to disease expression. A comparison of the different factors leading to an increase of allergic diseases is not possible yet, and each theory may be contradicted or disproved. However, there is convincing evidence that early childhood is the most susceptible period for sensitization to allergens and the induction of an imbalance of the T_H1/T_H2 immune response, ultimately favoring either long-lasting tolerance or allergy:

- The transient low IgE antibody response to certain foods and aeroallergens in early childhood as a normally occurring phenomena^{3,4}
- The causal relationship between early childhood pollen contacts and subsequent pollen allergy⁵
- Similar prevalence rates in West Germany (Hamburg) and East Germany (Erfurt) for people born before Germany was divided; in contrast, a significantly different prevalence for people born when Germany was divided.⁶ The similar genetic atopy predisposition supports the importance of the early life period and environmental factors.
- Animal experiments demonstrating the induction of IgE antibodies to a primary allergen exposure with low allergen amounts in newborn low and high IgE responder rats and a long-lasting tolerance in the low IgE responder rats by a second exposure but a boosting of

IgE production in the high IgE responder rat strain. A tolerance in these animals could be induced only by exposure to very high allergen amounts (~10,000-fold higher), in the low responders tolerance develops with doses down to the low nanogram level, whereas high responders require up to the high microgram level.^{7,8}

In industrialized countries young children spend most of their time indoors, favoring the importance of exposure to indoor allergens during this period of life. Accordingly, the significance of house dust mite allergens, pet allergens, or molds for the development of allergic rhinoconjunctivitis and allergic asthma is generally accepted. However, the significance of aeroallergens for the development of atopic dermatitis still is controversial but is supported by several observations:

- Higher amounts of specific IgE antibodies to mite body allergens than to major mite fecal allergen Der p 1 in serum samples from patients with eczema, but the inverse finding in patients with asthma indicate different routes of sensitization; Der p 1 allergen sensitization is thought to be induced by allergen inhalation, whereas sensitization to mite body allergens may be mediated by skin contact and further enhanced by a damaged skin barrier in patients with eczema⁹
- Eczematous skin lesions can be induced by patch testing with dust mite antigens. Mite antigen-bearing Langerhans cells were seen exclusively in the epidermis after 6 hours, and mainly in the dermis after 24 hours, suggesting that IgE-mediated contact hypersensitivity to mite antigens may develop and play a relevant role in atopic dermatitis.¹⁰ The specific nature of Der p 1-induced patch test lesions was supported by the detection of allergen-specific, IL-4-producing T cells in mite allergen patch test reactions capable of enhancing IgE production.¹¹ Moreover, there is evidence that the development of eczematous lesions in patients with atopic dermatitis is characterized by a sequential activation of T_H2 and T_H1 cells. In early atopy patch test lesions (24 hours) a prevalence of T_H2 cells was observed, whereas in chronic eczematous skin lesions or late atopy patch test sites (48-72 hours) mainly T cells exhibiting a T_H1 -type cytokine profile were detected.¹²
- Allergen inhalation has been suggested to cause exacerbation of atopic dermatitis in patients with asthma. Skin symptoms are significantly increased 1.5 to 17 hours after bronchial challenge with house dust mite, indicating that the respiratory allergen exposure is relevant in the induction and exacerbation of eczema in those patients who already have atopic dermatitis.¹³ House dust mite allergen avoidance prevents an

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increase in house dust mite-specific IgE serum levels in children sensitized to food but not to house dust mite. House dust mite avoidance reduced the activity of atopic dermatitis.^{14,15}

These data indicate an etiologic significance of aeroallergens for atopic dermatitis. In this issue Scalabrin et al (p 1273) and Schäfer et al (p 1280) demonstrate a strong association between sensitization to aeroallergens and atopic dermatitis. A correlation between the severity of atopic dermatitis and the degree of sensitization to aeroallergens in schoolchildren seems to indicate that the damage of the skin barrier may enhance the early epicutaneous sensitization to aeroallergens, especially to house dust mite or fungi. A higher degree of sensitization was associated with a corresponding pronounced clinical manifestation of atopic dermatitis.

During recent years several epidemiologic evaluations focusing on the role of nonspecific factors in the pathogenesis of atopic diseases have been performed. The increased atopy prevalence correlated with cigarette smoke, drugs (β -blockers, progesterone, among others), and nutrition in the prenatal period, fetal stress in the perinatal period, viral infections, lack of infections with parasites or helminths, exposure to indoor and outdoor environmental factors and allergens, and immunization especially with vaccines with aluminum hydroxide as adjuvants in the postnatal period.¹⁶⁻¹⁸ These data are in correlation with our current knowledge of the T_H1/T_H2 paradigm.¹⁹ Thus infections with intracellular pathogens such as bacteria and leishmania, among others, trigger a T_H1 immune response by inducing specific cytokines (IFN- γ , IL-2, IL-12), whereas extracellular pathogens such as helminths and allergens, among others, induce a T_H2 immune response characterized by the production of other cytokines (IL-4, IL-5, IL-10), which are responsible for many of the pathologic findings seen in atopic diseases such as hyper-IgE production, eosinophilia, and down-regulation of the T_H1 response. Moreover, bronchial infection with viruses such as respiratory syncytial virus or pertussis through inducing Type I IFN- α , which inhibits IL-12 production, was found to costimulate a continuing T_H2 response and thus aggravate symptoms of atopy.^{20,21} There is also recent evidence indicating that dendritic cells, which are required for the initiation of T-cell activation, also provide T cells with specific signals leading either to T_H1 or T_H2 immune response. Accordingly, there are 2 subsets of dendritic cells: DC1 produces IL-12, skewing T cells toward T_H1 differentiation, whereas DC2, lacking IL-12, favors T_H2 development.²²

These findings may allow the following speculation, which ultimately could provide a possible explanation for the increasing prevalence of atopic diseases. This involves the existence of 2 different populations, 1 with a normal immune response being able to generate a T_H1 as well as a T_H2 response. The other group exhibits a T_H1/T_H2 imbalance resulting in a T_H2 predominance that may be genetically determined. In the early childhood in healthy individuals the immune response is shifted toward T_H2 . Control of an overwhelming T_H2 response is

achieved by appropriate T_H1 triggering signals such as bacterial antigens. In the absence of these signals, contact with allergens such as cow's milk and aeroallergens, among others, may result in a strong and uncontrolled T_H2 response with IgE production, eosinophilia causing and aggravating symptoms of atopic diseases.^{23,24} This view recently was supported by a Japanese study showing an inverse association between delayed hypersensitivity to mycobacterial tuberculosis and atopy. Thus positive tuberculin reactions correlated with a lower incidence of asthma, serum IgE levels, and T_H1 immune response.²⁵ Furthermore, specific oligonucleotides (CpG motives) derived from bacterial DNA are very strong inducers of T_H1 cytokines such as IFN- γ ^{26,27} and treatment of mice with CpG oligonucleotides was able to inhibit allergic airway inflammation.²⁸ Similar findings have been reported after infection of mice with *Mycobacterium bovis*-BCG.¹⁷ Similarly, in individuals with a genetically determined deficiency to develop a sufficient T_H1 immune response, T_H2 triggering allergens will provoke a poorly controlled T_H2 response, subsequently leading to atopy because in these patients T_H1 triggering signals are not able to generate an appropriate T_H1 immune response that is able to control T_H2 development. They only poorly will respond to therapeutic regimens aiming to stimulate T_H1 activation such as CpG.

On the basis of this hypothesis, another possibility further explaining the increasing prevalence of atopy should be discussed. Individuals with a defect T_H1 immune response in addition to being prone to the development of allergies also may be more susceptible to severe bacterial and viral infections because of the lack of IFN- γ , IL-12, and IL-2, which are required for the activation of cytotoxic cells.¹⁷ Thus it may be speculated that these patients, before the availability of efficient antibiotics, died early in life from infectious diseases. Consequently, these individuals in many cases have not been able to transmit their inherited immune deviation to their children. This ultimately, until the end of the first half of this century, may have resulted in a selection of a population with an effective T_H1 immune response, whereas most T_H2 responders were not able to survive. After antibiotics were available on a large scale, this natural selection was modified, ultimately leading to an increasing population with a genetically determined predominant T_H2 response who are prone to the development of atopic diseases. In some of these individuals the lack of T_H1 triggers resulting from "sterile conditions" in which children are raised may have resulted in a further enhancement of allergies.²⁴ Although this hypothesis formally needs to be proved and in some regards may be speculative, it seems to be compatible with many of the current pathogenetic aspects of this complex disease.

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