RELATIONSHIP BETWEEN ATOPIC DERMATITIS AND IMMUNOGLOBULIN E

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Coca and Grove (1925) concluded that serum factors, which they called reagins, were present in individuals with allergic respiratory disease. More than 40 years later, reaginic antibody was shown by Johansson and Ichizaka to belong to the immunoglobin E (IgE) class of immunoglobins. It has been established that the Fc component of IgE has an affinity for surface receptors on mast cells and basophilic leukocytes. After IgE has become fixed to these receptors, binding of appropriate allergen to the Fab component of the immunoglobulin initiates an inflammatory response via the release of pharmacologic mediators.

IgE is not unique to individuals with atopic disease. Nearly all persons have detectable serum levels of IgE. Plasma cells in lymphoid tissue draining mucosal surfaces have been shown to stain with fluorescein-tagged anti-IgE, suggesting that IgE is produced in these areas. Like other immunoglobulins, IgE enters the bloodstream, but unlike the others, the quantity present shows extreme variability. IgE has been found at concentrations of less that 2.4 ng/ml in normal adult serum. Recently a non-myeloma patient was discovered with a serum IgE level greater than 500,000 ng/ml. High IgE levels may be found in nonatopic individuals having several other conditions, including parasitic and fungal infections.

It is difficult to establish a mean value for IgE levels in normal nonatopic individuals. There are no technical problems in the quantification of IgE since the radioimmunoassay methods used are well standardized. One point of confusion exists in the nomenclature used to express IgE values. At present 2 measures are used, the nanogram and international unit (IU). One IU equals approximately 2.4 nanograms. A plausible reason for not having determined a mean IgE level in normal nonatopic individuals is the difficulty in excluding those persons who are atopic.

Atopy Defined

In order to classify properly a nonatopic person, a definition of atopy is needed. Besnier in 1892 first described and classified the prurigo group of skin diseases. He listed flexoral skin changes and certain respiratory diseases as belonging within a group, and suggested that these had an hereditary background. Subsequently, the concept of allergy and hypersensitivity was introduced. The term atopy (literally meaning "no place") was coined by Coca and Cooke (1923) to permit asthma and allergic rhinitis (conditions that did not fit into the existing classification of hypersensitivity diseases) to be categorized. Later studies revealed that atopic respiratory disease is associated with specific reaginic anti-

bodies transferable by the Prausnitz-Küstner method. These studies enabled Coca to include these antibodies in the definition of atopy. Wise and Sulzberger (1933) introduced the term atopic dermatitis for that type of eczematous process previously described by Besnier.[1]

The term atopy has been misused. At present most investigators restrict its use to the following: allergic rhinitis, allergic bronchial asthma, and atopic dermatitis.

Atopic Dermatitis

Atopic dermatitis is a form of eczema that can be distinguished by its morphological and constitutional manifestations. Several large population studies suggest a prevalence of atopic dermatitis ranging from 0.1% to 0.5%.[1] The onset of atopic dermatitis is before five years of age in the majority of individuals. Excoriations, prurigo papules, eczematous lesions and lichenification comprise the common clinical features of this disease. The predominant symptom is pruritus. Chronic prurigenous lesions in the flexoral areas are pathonomonic for atopic dermatitis. Most patients have spontaneous remission before the third decade. The histopathology of atopic dermatitis is not diagnostic, but is characterized by spongiosis, epidermal edema, and a dermal infiltrate of lymphocytes. Mast cells are also frequently seen.

With the concept of atopy, more specifically atopic dermatitis, now defined, it becomes important to determine what the mean IgE levels are in atopic and nonatopic individuals. An early comprehensive study of IgE levels revealed that an ostensibly normal population had a mean of 248 ng/ml with an upper confidence level of 1000 ng/ml. Another study found the mean level to be 179 ng/ml with 95% confidence limits extending up to 780 ng/ml. The mean serum IgE level in nonatopic persons is somewhere between 100–250 ng/ml. Recent studies of individuals considered nonatopic by a more rigorous definition reported values that fell below this level.[2] Further studies will have to be done in order to define what the normal IgE levels are in strictly nonatopic individuals.

There is agreement among investigators that IgE levels generally are elevated in persons with atopic diseases. A safe estimation would place the mean levels to be raised anywhere from 3 to 10 times the normal mean.[5] It appears that if individuals with a singular atopic manifestation are studied, the mean IgE is higher in those with atopic dermatitis than in those with either type of atopic respiratory disease. Several reports have shown that although the mean serum IgE level in patients with atopic dermatitis is unquestionably elevated, there are remarkable differences in individual levels.[2, 4, 5] Since atopic dermatitis patients differ from one another with regard to clinical manifestations and associated atopic conditions, some variation in IgE levels may be related to the following clinical parameters: (1) the severity of the dermatitis, and (2) the presence of coexistent atopic respiratory disease.

Again, there is agreement among investigators that the highest mean IgE levels are found in those individuals with atopic dermatitis who also have a history of allergic respiratory disease. There has also been a correlation between the severity of atopic dermatitis and the mean IgE level.[1, 2, 4, 5] However, some patients with severe and extensive atopic dermatitis have been found with low normal levels.

One of us (HEJ) reported a consistency

between the frequency of positive allergen skin tests in atopic respiratory disease patients and the IgE levels. This relationship was not found in patients with atopic dermatitis who did not have an associated atopic respiratory disease.[2]

When anti-IgE antibody is injected into the skin of nonatopic persons, it binds with mast cell fixed IgE and results in an urticarial response. In atopic dermatitis patients, this reaction is not correlated with the serum IgE level.[1] This may be because serum IgE levels reflect "excess" IgE above that required to saturate cell surface receptors.

IgE Association

Considering the previously mentioned findings, the question now arises as to whether IgE is involved in the pathogenesis of the atopic diseases. There is abundant evidence which strongly suggests that IgE is involved in the pathogenetic mechanisms of atopic respiratory disease. There is no appealing evidence that IgE causes atopic dermatitis, although there is an association between (1) higher serum levels and severe or extensive skin disease, and (2) claims that IgE levels may parallel disease activity in some individuals.[3] These associations prompted us to attempt an explanation of how IgE could cause chronic skin changes characteristic of atopic dermatitis.

It is well known that IgE fixes to basophiles and tissue mast cells and that stimulation with the proper antigen causes the release of such vasoactive substances as histamine, heparin, SR-A, and eosinophil chemotactic factor. These in turn produce the classic wheal and flare reaction, an evanescent phenomenon. It is most difficult to envision that this IgE-mast cell-pharmacologic mediator system could produce the chronic skin manifestations and histopathologic changes of atopic dermatitis.

Recent work has shown that certain lymphocytes possess the ability to fix antibody to their surface, and following binding with the proper antigen, initiate the mechanisms of antibody-dependent cell-mediated cytotoxicity (ADCMC). Evidence also suggests that small- to medium-sized lymphocytes have IgE on their surface, although it is not known whether the anibody was synthesized by that cell or bound to its surface.[7] In atopic dermatitis, it is conceivable that IgE, once present on the surface of a type of lymphocyte, arms that cell for ADCMC. Then, following confrontation with the necessary antigen, this effector-cell would initiate a cytotoxic process within the skin. Alternatively, the ADCMC mechanism could be activated by the movement of unarmed lymphocyte subtypes into the skin where they bind with Fc components of an in-situ fixed antibody-antigen complex. As in the first case, where antibody was present initially on the effector cell, the cytotoxic damage to the skin would follow.

Any of several antigens might be involved in the ADCMC mechanism which we are suggesting could cause atopic dermatitis. Considering that stratum corneum is an effective barrier to foreign macromolecules, it would appear likely that the responsible antigen would be present in the internal milieu of the skin. If this were the case, atopic dermatitis could be classified as an autoimmune disease.

We are not aware of experimental evidence that IgE actually arms K effector cells for ADCMC or that cells capable of ADCMC are even present in atopic skin. We are also not aware of evidence which suggests what the responsible antigen might be. Neverthe-

less, if one is to base speculation as to the pathogenesis of atopic dermatitis on the observed facts, that is, an elevated IgE level, a lymphocyte infiltrate, and a chronic eczematous process, ADCMC is an acceptable working hypothesis. Other mechanisms involving IgE might be operative but one should keep in mind that IgE may not play any role in the pathogenesis of atopic dermatitis.

Conclusions

We believe that there is a significant relationship between serum immunoglobulin E and atopy and that many patients with atopic dermatitis have large quantities of IgE in their skin and serum. As to the role of IgE in the pathogenesis of atopic dermatitis, we can only speculate at this time. However, further research should soon begin to bridge this gap.

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VD Among the Commanches

The Mexicans' most effective retaliation against the Commanches, ironically, was involuntary. Nineteenth-century Mexico was still scourged by epidemics of all kinds, and the more the people penetrated south the more exposed they became to the diseases of civilization. For the first time, smallpox, measles, and cholera appeared among the Nermernuh; in 1816, and again in 1839, smallpox wiped out whole bands. Furthermore, venereal disease was rampant among the *mestizo* population, and now this plague too was visited on Commanches. Syphilis became endemic, and Commanche sexual habits spread it like a conflagration through some bands. Thus the warriors who raped across northern Mexico, carrying off children and women to their camps, unknowingly loosed frightful consequences on their own people. By the 1830's and 1840's, there was frequent evidence of epidemic disease and venereal maladies north of the Red River.—*T. R. Fehrenbach: Commanches: The Destruction of a People, New York, Alfred A. Knopf, 1974, p. 259.*
