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HYPOTHESIS-DETERMINANT FACTORS IN THE MANIFESTATIONS OF ATOPIC DISEASE

By

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Various theories have been proposed to explain the occurrence of atopic disease in a substantial segment of the population (12, 20, 22). Many of these theories implicate a qualitative or quantitative defect in the IgA immune response as an integral component in the development of atopy. Certainly, our current concept of the secretory immune system postulates a protective role for secretory IgA. A defect at this level of immune response could present the organism with potentially harmful antigens, both natural and artificial, that are ordinarily neutralized and eliminated by this system. It is less easily understood how a defect in the serum IgA system could act in a similar manner unless there is a concomitant defect in the secretory IgA system; at least one study (23) has suggested this possibility. Unfortunately, attractive as these theories are, none has satisfactorily explained the development of atopy, and it is unlikely that IgA is the sole factor in the pathogenesis of atopic disease.

Any proposed unifying concept for the development of atopic disease must explain the complex natural history of allergic manifestations in atopic persons. It has been recognized for many years that certain atopic conditions are most commonly found at certain ages (7). A patient may have atopic eczema during early infancy, asthma during childhood ("outgrowing" this during later childhood), and seasonal pollinosis during late adolescence or early adulthood. This

same patient may later have late-onset asthma, after age 40 years, and his problem now may be "intrinsic" and unrelated to any obvious external antigenic stimuli. In our hypothetical patient, the early manifestations of atopic disease may be related to foods, the childhood and adolescence problems related to inhalants, and the late-onset problem unrelated to identifiable extrinsic antigens.

A unified theory for the development of atopic disease may be composed of three separate elements that together determine the manifestations of atopy in a given patient: 1) a genetic propensity to produce IgE antibodies in response to low-dose exposure to various antigenic determinants, 2) permeability of the gastrointestinal and respiratory tract mucosa that is inversely related to the maturity of the organism, and 3) a metabolic or homeostatic defect leading to instability of the target organ.

Such a theory stresses that sensitization is related to absorption of antigenic macromolecules across the respiratory and gastrointestinal epithelium. The degree of absorption of macromolecules is inversely related to the maturity of the mucosal barrier, and it is likely that the degree of maturity varies with individuals although following the same general principles in the population (17).

In the immature state, the gastrointestinal and respiratory mucosa presents an indiscriminate and inadequate barrier to antigenic macromolecules (16). Consequently, antigenic materials cross the epithelial barrier regardless of their state of intrinsic antigenicity. During this stage of development the absorption of these macromolecules is predominantly determined by the relative masses of the materials presented to the organism. Foods are obviously most important during the first few months of life because of the large relative proportion of protein presented to the mucosal barrier (21). Most food allergens are of low intrinsic antigenicity during this period.

Correspondingly, the respiratory mucosal barrier offers poor resistance against antigenic materials of low immuno-

genicity such as house dust, environmental inhalants, and molds. Pollens may also cross this barrier but only as part of the indiscriminate absorption of macromolecules rather than as a function of the high intrinsic antigenicity of pollen antigenic determinants. Respiratory infections may create a condition of the mucosal barrier conducive to antigenic transmigration—thus explaining their common occurrence in infantile asthma (3).

Once antigenic macromolecules are absorbed, allergen-specific IgE antibodies are produced and appear in the secretions. These antibodies are capable of further interaction with antigen, which releases mediators that induce further permeability of the respiratory or gastrointestinal mucosa (10). Under these conditions the atopic individual may continue to absorb antigenic macromolecules across the respiratory epithelial membrane into adult life (4). Thus, a cyclic phenomenon is set into motion which tends to perpetuate the state of sensitization.

In the more mature state, the respiratory and gastrointestinal mucosa is impermeable to all but the most highly antigenic protein materials. Examples would be ragweed across the respiratory mucosal barrier and allergens from various "high index" food such as shellfish, berries, and nuts across the gastrointestinal mucosa. The antigens important during infancy and childhood tend to be greater in number and lower in intrinsic antigenicity (for example, foods, molds) whereas, in adult life, allergens of high intrinsic antigenicity, although fewer in number, are more important.

The role of IgA in the pathogenesis of infantile atopy is not entirely clear. One study (23) suggested that a transient deficiency at age 3 months would predispose infants to the development of atopic disease. However, another study (2) found no relationship between the presence or absence of IgA in the cord serum and the subsequent development of asthma or atopic eczema during infancy. It is possible that the absence of secretory IgA is a special circumstance which is conducive to the production of nonreaginic serum antibodies of the IgG

class but these antibodies do not appear to be a significant factor in most allergic persons (5, 17). Furthermore, atopic patients have normal secretory IgA levels even during childhood (1, 19).

All infants are exposed to potentially antigenic materials. However, only those genetically programmed to produce IgE molecules in abundance will do so under the conditions of normal low-dose environmental exposure (13). Those who are not genetically programmed to produce specific IgE antibodies will produce IgG antibodies which bind the antigenic macromolecules and are rapidly cleared by the reticulo-endothelial system of the liver and spleen. Thus, the absorption of macromolecules is neutralized in these persons. On the other hand, those with an inherited genetic predisposition will respond to this universal challenge with the formation of antibody molecules that are of appropriate specificity and affinity and that are potentially capable of producing atopic disease. It is not uncommon to find family members without overt atopic disease but who have both *in vivo* and *in vitro* evidence of allergen-specific IgE antibodies (6). Thus, a third factor is required to cause atopic disease.

Persons with a genetically directed IgE-type response may manifest atopic disease if they have the appropriate defect in their homeostatic mechanisms. It has been postulated (22) that there is a state of partial beta-blockade that, in the asthmatic patient, renders the lung hyperresponsive to various antigenic and nonantigenic stimuli. It is conceivable that this metabolic defect is present in other tissues of the body such as the skin, upper respiratory tract, and gastrointestinal tract. In addition, other aberrations of the adrenergic and cholinergic autonomic nervous system may contribute to metabolic instability in the atopic person (15).

Thus, the manifestations of atopic disease are to a significant degree determined by complex interaction of these three factors. Moreover, these three factors vary as a function of age. Both total and allergen-specific IgE antibodies are age-related, with little or none present at birth and peak levels

noted during adolescence (8, 11). With increasing age, the levels of IgE gradually decline (9). The permeability of the gastrointestinal and respiratory tracts is clearly age-related, being greatest in the newborn and much less in the mature individual (17). The influence of age on the metabolic instability characteristic of atopic disease is less well defined but it is entirely conceivable that "intrinsic" asthma is the consequence of a severe metabolic defect in conjunction with minimal influence of the other two factors. By the same token, the passive infusion of reaginic antibody in large amounts could produce typical allergic reactions without the other two factors (14, 18).

SUMMARY

It is postulated that both the initiation and the perpetuation of atopic disease occur as a result of a complex interaction of a genetically determined IgE response, increased permeability of the gastrointestinal and respiratory tracts, and an inherent metabolic instability that may be either localized or generalized. These three factors vary as a function of age and serve to explain the complicated natural history of allergic manifestations in atopic persons.

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