Recent Advances in Pediatric Allergy*

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In 1923 Coca and Cooke, two of the most important pioneers of allergology in the United States, enumerated a number of postulates defining an allergic or, more specifically, an atopic individual (Coca and Cooke, 1923). Atopy, a term coined by Coca, literally means "atypical," referring to a series of differences from the normal individual, partially proved and partially postulated. Today, I would like to examine those postulates with you in light of relatively recent clinical and experimental data which are fostering some changes in our understanding of the nature of the atopic state. Much of the information for discussion has been recently reviewed by Frick (1966; unpublished data).

Postulates

1) Atopy is an immediate hypersensitivity reaction limited to man;
2) There is a genetic predisposition to atopy;
3) Atopic individuals become sensitized "spontaneously" after the same natural exposures to antigens which are innocuous in most humans;
4) Atopic individuals form peculiar types of antibodies—skin-sensitizing antibody, or reagin, and blocking antibody.

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Veer, 1916; Spain and Cooke, 1924). On the basis of family studies relating to eventual development of atopic disease, they proposed that atopic constitution is inherited as a dominant trait, and that, with a bilateral family history of allergy (i.e., in both parents), there is a 70% chance of allergy developing in a given offspring. With a unilateral positive family history (i.e., in one parent) there is a 50%-60% chance of allergy developing in the child. They were unable to explain the fact that 38% of their patients had no family history of allergy. More recent studies have proposed that the atopic constitution is determined by a pair of recessive genes with incomplete penetrance, manifested in both homozygous and a certain percentage of heterozygous individuals. Differing estimates, ranging from 20%-40%, have been given for the degree of penetrance in numerous studies (Wiener, Zieve and Fries, 1936; Schwartz, 1952; Van Arsdel and Motulsky, 1959). This would account for the frequent occurrence of allergy in persons with a negative family history.

The important question of what is inherited has not been completely answered. From early studies it was clear that the tendency to become allergic and, thus, manifest disease was the inherited abnormality rather than specific sensitivities. For years the capacity to make reagins or skin-sensitizing antibodies has been considered the inheritable abnormality (Cooke and Vander Veer, 1916). Much work is forthcoming describing the physicochemical nature and activity of skin-sensitizing antibodies. The Ishizakas (1966) have clearly shown that these antibodies belong to a new class of immunoglobulins, which they have named IgE. This class has physicochemical and antigenic properties distinct from all the other recognized immunoglobulins—IgG, IgA, IgM and IgD. The Ishizakas (1968) have also reported evidence that the normal individual has IgE fixed to his skin. Hence, it appears that the atopic individual may have a quantitative abnormality in skin-sensitizing antibody production.

Salvaggio (Salvaggio et al., 1964; Salvaggio, 1966) showed that 60%–80% of a group of allergic individuals but only a few of the nonallergic controls developed positive immediate skin tests after being exposed, for a period of six months, to aerosol nasal inhalations of two unnatural antigens, beef ribonuclease and dextran. He suggested that this was because of increased nasal membrane permeability in the atotics. In addition, Rothberg and Farr (1965) demonstrated that adult allergic patients have a much higher incidence of antibodies to milk than controls, which suggests increased gut permeability to milk protein. Perhaps this increased permeability is genetically determined.

The third postulate, that atopic individuals become sensitized "spontaneously" after the same natural exposures to antigens which are innocuous in most humans, can be viewed in light of recent reports of asthma epidemics. These epidemics have raised the question of whether all humans, under sufficient allergen exposure, could be made to form atopic antibodies, thereby mediating clinical disease.

In one rural South African community, over 200 individuals living in the environs of a castor bean processing factory developed asthma, and many had positive skin tests to castor bean. Air pollution with castor bean waste appeared to sensitize a large number of the population (Ordman, 1955).

Epidemiologic studies of asthma and allergic rhinitis have suggested another intriguing question: Is asthma an infectious disease? Smith, at the University of Iowa, has performed two surveys. In the first, she studied 1,760 rural families (Smith and Knowler, 1965a). In the second, every fourth household in Iowa City was canvassed, all socioeconomic groups being included (Smith and Knowler, 1965b). She found that when one member of a family pair with a negative family history for allergy married an allergic individual, there was a fourfold to fivefold or 20% increase of allergic disease in the nonatopic spouse within five years after marriage. Furthermore, when the mother was the allergic individual, there was a five times greater incidence of allergy in the children than when the father was originally allergic. Previous genetic studies mentioned earlier in my paper revealed that approximately 50% of the children in the family with one affected parent are potentially allergic. According to Smith's epidemiologic data, when the mother was the original allergic family member, 50% of the later allergic spouses developed allergy at about the same time as the offspring. This would suggest transmission of the atopic condition by an infectious agent of low virulence and communicability, with intimate contact over a long period of time being required for transmission.

The physicochemical nature of allergens is currently under intense investigation. It appears that there are some striking similarities among rather diverse naturally occurring substances which produce skin-sensitizing antibody in man (Frick, 1966). In general, their molecular weight is between 10,000 and 40,000. They have a low nitrogen content, usually between 1% and 13%, but a high carbohydrate content. Berrens, in Holland (Berrens and Bleumink, 1965; Bleumink and Berrens, 1966), has purified several common allergens, including horse dander, tomato atopen and milk. He has found that they all contain an N-glycosidic protein-sugar linkage and that, with aging or browning, as in the case of tomatoes, a particular rearrangement occurs in the sugar moiety of the carbohydrate-protein complex. An enol form results, producing the allergenic component of the mole-
cule. This, then, raises the question of whether atopic persons are deficient in handling this kind of molecule. Do they have a genetic enzyme defect, as in the inborn errors of metabolism, and does the previously mentioned increased membrane permeability relate to this?

The fourth postulate deals with the formation of peculiar types of antibodies—skin-sensitizing and blocking. Atopic sensitization develops following natural exposure to allergens in patients with an atopic constitution; allergic disease develops following repeated exposure to the allergen after skin-sensitizing antibody has formed (Boyden, 1963). The demonstration of a similar mast cell-sensitizing antibody in the rat by Becker and Austen (1966) and the production of a heat labile, gamma 1, anaphylactic-type antibody in the Hemophilus pertussis-treated mouse (Fishel, Szentivanyi and Talmage, 1964) have suggested the presence of reagin-like antibodies in other species. The mechanism which triggers the formation of this kind of antibody is being vigorously sought.

Specific treatment of allergic disease with immunizing injections of allergens has been shown to produce a blocking gamma G type of antibody. This type of antibody subsequently prevents allergen-reagin interaction (Boyden and Roth, 1963). Studies have not shown a close correlation between the titer of blocking antibody and the absence of clinical disease. Sherman (1968) has shown that the skin-sensitizing antibody titer itself significantly diminishes in patients receiving allergy injections for a number of years. The decrease in skin-sensitizing antibody content correlates with clinical improvement, suggesting either the production of immune tolerance or an actual desensitization (Claman, 1964). The latter hypothesis is supported by the diminishing in vitro release of histamine from sensitized leukocytes in treated allergic patients as compared with controls (Lichtenstein, 1968).

Altered Autonomic Reactivity

As a final consideration I would like to review with you a theory proposed by Cookson and Reed (1963), suggesting that asthmatics have an imbalance of sympathetic nervous system adrenergic receptors with a partial beta-adrenergic blockade.

In 1948 Ahlquist described two types of adrenergic receptors, which he named alpha and beta on the basis of their responses to various amines. Endogenous mediators for alpha receptors are epinephrine and norepinephrine; for beta receptors, epinephrine. Thus, epinephrine has both kinds of activity. Acetylcholine stimulates the cholinergic receptors of the parasympathetic system. Norepinephrine has been shown to be a pure alpha stimulator; Isoproterenol, a beta stimulator; and methacholine, a cholinergic stimulator (Innes and Nickerson, 1965).

The action of these receptors on different organs depends upon their concentration in a given organ—e.g., the blood vessels of the skin have alpha receptors primarily, and stimulation causes constriction. Skeletal muscle blood vessels, on the other hand, respond by dilation in response to beta stimulation. The heart is largely regulated by beta receptor stimulation for increase in heart rate, stroke volume and force of contraction. Slowing of the heart rate occurs with vagal cholinergic stimulation. The lungs respond to beta stimulation by bronchodilation, and there are few alpha receptors present except in blood vessels. Vagal cholinergic influences would bring about bronchoconstriction. Thus, there is a neat balance between the adrenergic alpha and beta receptors and the cholinergic parasympathetic receptors. Alpha receptors may be blocked by Dibenzyline and Regitine with resulting imbalance of the adrenergic system due to beta enhancement. The beta receptors may be blocked by agents such as Dichloroisoproterenol, propranolol and pronethanol, leaving the alpha system unchecked. Atropine blocks the cholinergic receptors (Innes and Nickerson, 1965).

As an experimental model for anaphylaxis, the H. pertussis-treated mouse has heightened sensitivity to histamine and other amines of importance as mediators in allergic asthma (Fishel, Szentivanyi and Talmage, 1964). The response seems to be mediated through a partial blockade in the beta receptors, with alpha receptor overactivity or enhancement (Fishel, Szentivanyi and Talmage, 1962, 1964; Fishel and Szentivanyi, 1963). This is supported by beta blockade with Dichloroisoproterenol increasing histamine sensitivity in the untreated mouse and alpha blockade with Dibenzyline decreasing sensitivity to histamine in H. pertussis-treated mouse. Various metabolic effects, including flattening of the glucose tolerance test, are also noted after beta blockade in the normal mouse and the H. pertussis-treated mouse. The latter fails to respond to epinephrine with hyperglycemia (Fishel and Szentivanyi, 1963). Whereas, as mentioned previously, normal mouse and man produce IgG antibodies in response to most antigens, an additional antibody is produced by the mouse after treatment with H. pertussis; it is a 7S gamma I anaphylactic type of antibody and is comparable to IgE or reagin in man (Mota, 1967). The relationship between production of this antibody and the apparent imbalance in the adrenergic receptors is not clear at this point.

Various investigators have shown that the asthmatic man is much more sensitive to bronchospastic effects of histamine and acetylcholine administration than the normal control is (Curry, 1946; Curry and Leard, 1948; Tiffeneau, 1958). Compared with normal controls,
this response in asthmatics may be variably enhanced by beta-adrenergic blockade with agents such as propranolol (Zaid and Beall, 1966). Ouellette and Reed (1965) have further shown that asthmatics have marked increase in response to methacholine after influenza vaccine. They suggest that this is an endotoxin-like toxic effect of the vaccine acting through the autonomic nervous system and propose this as a mechanism whereby acute respiratory infections provoke asthma. Clearly bacterial products do alter autonomic nervous system reactivity, and such mechanisms may be operative in conjunction with antigen-antibody reactions in allergic individuals (Szentivanyi and Fishel, 1965).

A number of altered metabolic effects have also been noted in asthmatic man consistent with a partial beta-adrenergic blockade, but absolute proof is lacking that this mechanism is of fundamental pathophysiological importance in asthmatics, and, in view of other conflicting data (Zaid and Beall, 1966), it must remain only an attractive hypothesis.

Summary

Evidence has been presented to indicate that atopic disease is not limited to man but occurs in subhuman primates. The genetic transmission of allergy may relate to altered membrane permeability or an enzymatic defect, with inability to handle certain N-glycosidic protein-sugar linkages occurring in the atopics of nature. The suggestion that an infectious agent transmits allergic disease has been examined. Finally, in vitro and animal experimental models of anaphylaxis closely akin to atopy and the effects of manipulation of the autonomic nervous system in laboratory animals and man have been discussed.

References


