

An hypothesis for the development of atopic allergy in man

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Atopic allergy has long been recognized as a disease of immunologic origin. Most immunologists and allergists would now agree that the symptom complex seen in uncomplicated allergic rhinitis and bronchial asthma is in large part attributable to the activity of pharmacologic intermediates either released from mast cells or formed *in vivo* as a consequence of specific antigen-antibody interactions. These interactions involve a highly specialized and extraordinarily active antibody of a newly defined immunoglobulin class (IgE) (Ishizaka & Ishizaka, 1966, 1968; W.H.O., 1968) which has the capacity to sensitize cells for long periods of time for the subsequent triggering action of antigens. Immunoglobulin E is a normal constituent of human serum which is present at 1/40,000th the concentration of immunoglobulin G (Johansson, 1967). Recent studies suggest that IgE may be significantly increased in patients with atopic allergy (Johansson, 1967; Berg & Johansson, 1969; Schwartz & Buckley, 1971a; Kumar, Newcomb & Hornbrook, 1971; Yunginer & Gleich, 1971; Hogarth-Scott *et al.*, 1971) and that IgE levels rise with seasonal allergen exposure. It may be elevated as well in many other diseases, among which are severe liver disease, hypersensitivity aspergillosis, coeliac disease, visceral larva migrans, ascariasis, pulmonary haemosiderosis and rare forms of infectious disease (Buckley, Wray & Belmaker, 1971; Heiner & Rose, 1970; Johansson, Mellkin & Vahlquist, 1968). However, it has never been clearly understood why the specific antibodies of this class, which react with air-borne antigens and are responsible for the symptoms of hay fever and asthma, appear in only certain individuals exposed to these antigens. The present article advances a general hypothesis to explain one underlying basic abnormality leading to the development of IgE-mediated human atopic allergy.

The word atopy was first used by Coca & Cooke (1923) to describe allergic individuals with an hereditary background of allergic disease, and who demonstrated immediate weal and flare skin reactivity. Clinically, it refers to a group of illnesses, including infantile eczema, atopic dermatitis, seasonal and perennial allergic rhinitis, conjunctivitis, bronchial asthma, certain forms of 'food allergy', urticaria and nonhereditary

angioedema. Immediate local weal and flare reactions which result from the intracutaneous injection of antigen in an appropriately sensitized individual are also thought to be generally indicative of the atopic state. The heat-labile, passively transferrable serum antibody thought to mediate this type of skin reaction (and commonly referred to as reagin, or skin sensitizing antibody) has been shown to be of the immunoglobulin E class (Ishizaka & Ishizaka, 1966, 1968; W.H.O., 1968).

The clinical characterization of an individual as an atopic person depends on the presence of several features, including characteristic symptomatology, the existence of skin reactivity of the immediate weal-and-flare type, and a family history of atopic disease. Eosinophilia is common to all atopic disorders, and the level of circulating eosinophils parallels the severity of the patient's symptoms (Fowler & Lowell, 1966; Halle & Lowell, 1967; Lowell, 1967).

The familial clustering of atopic diseases suggests that an atopic tendency may be inherited (Sherman, 1965a). This genetic predisposition does not seem to determine the organ or tissue which is involved; not uncommonly a patient may have involvement of several organs at the same time (i.e. runny nose, itchy eyes and asthma) (Sherman, 1965a). Similarly, there is a great variability in the allergens to which an atopic will develop sensitivity. Most such individuals tend to develop sensitivities to an increasing range of allergens over the years. In practice, these four features (symptomatology, skin reactivity, family history and eosinophilia) are found in various combinations. 'Classical' atopic patients have all of these characteristics, while the non-atopic person has few or none. 'Asymptomatic atopy' can be said to exist in people who do not have overt symptoms but exhibit some degree of cutaneous reactivity, whether or not they have a positive family history of eosinophilia. This may be due to a low degree of sensitivity or to the presence of high titres of IgG 'blocking' antibody (Cooke *et al.*, 1935; Loveless, 1943; Lichtenstein *et al.*, 1968). Other factors, such as age and degree of exposure to allergens, may be important in determining the expression of clinical disease.

The manner in which a person develops atopic allergy is currently unsettled, but since the primary feature which distinguishes atopic from normal individuals is their altered reactivity to air-borne and ingested allergens, at least four hypotheses warrant consideration:

I. Predisposition of atopic humans to produce skin sensitizing antibody, due to hereditary differences in their immunologic apparatus.

II. The existence of enzymatic or related defect, allowing for prolonged retention of antigen with consequent heightened antibody production.

III. An enhanced reactivity to pharmacologic intermediates released from mast cells or formed *in vivo* as a result of antigen-antibody reactions.

IV. The existence of a local defence barrier defect, allowing for increased absorption of antigens across mucosal surfaces and/or more efficient contact between antigen and immunologically competent cells.

The above hypotheses are not mutually exclusive and all may contribute in part to the development of the atopic state.

In regard to hypothesis I, Coca & Cooke (1923) and Sherman (1965b) suggested that atopy is a unique disease. They pointed out that atopy seems to be limited to human beings, and involves reactions to usually innocuous antigens. They suggested that atopy represents an abnormal immune response, with the production of an unusual

immunoglobulin. Other data challenge these assumptions. Dogs (Patterson, 1960) and horses (Lowell, 1964) have been described in which atopic-like hypersensitivity was detected, while subhuman primates have been passively sensitized (Patterson, Pruzensky & Chang, 1963; Patterson *et al.*, 1965) with atopic human serum. Homocytotropic antibody has also been described in several other species (Bloch, 1967).

Atopy, then, is not a peculiarly human condition. More importantly, the capacity to produce skin sensitizing antibody is not limited to atopic individuals. Non-atopic, as well as atopic, individuals respond to parenteral immunization with protein and polysaccharide antigens by the production of skin sensitizing antibody and weal and flare reactivity (Leskowitz & Lowell, 1961). No differences exist between atopic and non-atopic individuals in their dose-response production of skin-sensitizing antibody following parenteral immunization with pneumococcal polysaccharide (Schwartz & Terr, 1971). Furthermore, anaphylactic hypersensitivity to insect stings, drugs and foreign sera occurs commonly in otherwise non-atopic people and the antibodies responsible for these conditions are indistinguishable from those occurring in atopic disease (Schwartz & Terr, 1971; Alexander, 1955; Brunner, 1934; Baron & Brunner, 1942; Coca, Walzer & Thommen, 1931; Davidson, Baron & Walzer, 1947; Schwartz & Kahn, 1970). Thus, an allergic diathesis does not seem to be an absolute prerequisite for the development of immediate hypersensitivity, provided that efficient and prolonged methods of immunization are employed.

On the other hand, recent studies in inbred rodent strains have contributed greatly to our understanding of genetic control of the immune response, by showing preferential reagin formation in response to repeated minute doses of hapten-protein conjugates (Levine & Vaz, 1970; Vaz & Levine, 1970; McDevitt *et al.*, 1971), which can be correlated with major histocompatibility types. These latter findings, together with the demonstrations of increased serum and secretory IgE content plus specific antibody in atopic individuals, favour the first hypothesis in suggesting a genetic capacity to mount an IgE response to repeated low doses of antigen. However, recent tests of association between HL-A histocompatibility antigens and immediate hypersensitivity reactions to allergens in man revealed no significant correlation (Marsh, Hsu & Bias, 1972), although studies on larger numbers of patients and more inbred human populations are necessary.

Attempts to demonstrate subtle and complex relationships between histocompatibility antigens, immune responsiveness and susceptibility to atopic disease will no doubt occupy a considerable portion of future research in human atopy.

The second hypothesis, namely prolonged retention of antigens for periods of time sufficient to allow antibody production, is difficult to verify but does not appear likely, in view of the similar immunologic response of atopic and normal individuals to parenterally injected protein and polysaccharide antigens (Leskowitz & Lowell, 1961; Schwartz & Terr, 1971; Salvaggio & Leskowitz, 1965; Kuhns, 1962; Kuhns & Pappenheimer, 1952; Salvaggio, Castro-Murillo & Kundur, 1969).

Hypothesis III, an altered reactivity to pharmacologic intermediates released by antigen-antibody reactions in atopic individuals, may represent one of several 'basic' underlying defects associated with the atopic state. Indeed, a voluminous literature attests to the fact that bronchial asthma is associated with a functional imbalance of the autonomic nervous system, namely that partial beta-adrenergic blockade is a cause of bronchial hyperreactivity in man (Reed, 1968a, b; Szentivanyi, 1968).

Differences in the physiologic reactivity of certain organs to chemical mediators

have been clearly demonstrated. Provocative inhalational and parenteral challenge of atopic asthmatic, and non-atopic individuals with histamine, acetyl-beta-methylcholine, and related agents results in significant bronchoconstriction in the former and none in the latter (Townley, Dennis & Itkin, 1965; Curry, 1946a, b; Dautrebande & Philpott, 1941; Tiffeneau & Beauvallet, 1945). Furthermore, the cyclic AMP system seems to control several inflammatory responses mediated by leucocytes (Lichtenstein, Henney & Bourne, 1972). Drugs which affect this system can induce quantitative changes in the number of immunocompetent cells (Morse, 1965; Fichtelius & Hassler, 1958) and can influence *in vitro* immunoglobulin synthesis by human peripheral lymphocytes (Smith, Sherman & Middleton, 1972). However, other evidence suggests that beta-adrenergic blockade *per se* cannot explain all features of respiratory, cutaneous, and gastroenterologic atopic diseases involving direct organ system contact with exogenous allergens. Atopic and non-atopic individuals respond equally to skin testing with histamine, serotonin, and the histamine releasing compound 48/80, and plasma histamine concentrations in allergic patients are normal (Leskowitz & Lowell, 1961; Farmer, 1945; Lecomte, 1957; Beall, 1963). Also, the heightened bronchoconstrictive response to histamine and related compounds is not limited to atopic asthmatics with intense Type I weal and flare skin reactions, since abnormal responses are noted in 'intrinsic' asthma, and to a lesser extent in patients with 'idiopathic' obstructive bronchitis and emphysema (Parker, Bilbo & Reed, 1965; Klein & Salvaggio, 1966). In addition, a heightened state of pharmacologic reactivity cannot fully explain other forms of human atopic disease such as allergic rhinitis, where bronchial hyperreactivity is considerably less than that noted in asthma (Townley *et al.*, 1965).

Considering these facts, the basic difference still emerges that under conditions of prolonged exposure to comparatively small amounts of antigen, such as exposure via respiratory tract mucosa, atopic individuals develop weal and flare skin reactivity and reaginic antibody under circumstances where the remainder of the population fail to respond. It seems apparent that the natural circumstances under which this basic difference occurs consist almost exclusively of mucosal contact with antigens such as pollen, animal dander, fungal spores and foods, which are normally inhaled or ingested. No unusual degree of exposure to antigen seems necessary and atopic and normal individuals presumably inhale and ingest the same quantities of allergens throughout their lives.

With these facts in mind, and with the lack of convincing evidence for hypotheses I, II and III to explain all features of development of the atopic state, we set out to test the fourth hypothesis (i.e. the possibility that the basic difference between atopic and normal individuals lies in their mode of handling antigens which come in contact with mucosal surfaces).

Using purified proteins and polysaccharides, we found that intranasal instillation of these antigens more readily induced immediate weal and flare skin reactivity in atopic individuals than in normal subjects (Salvaggio *et al.*, 1964, 1966, 1969). Although our subjects were tested when no atopic symptoms were present, it was possible that the differences in sensitization observed using intranasal routes of immunization were the result of inflammatory changes induced in the nose by the underlying allergic disease, rather than the cause of the allergy. Evidence that this was not likely came from a study of individuals with vasomotor rhinitis due to 'intrinsic' allergy (Schwartz, Leskowitz & Lowell, 1968). Attempts to sensitize such individuals by intranasal instillation of the antigen bovine ribonuclease failed, despite the existence of perennial

rhinitis. The absence of skin reactivity to common allergens in these subjects suggested further that their disease might not be due to specific immunologic reactivity as in atopic allergy, and raised doubts about their ability to make skin sensitizing antibody. However, Berg & Johansson (1969) have demonstrated detectable levels of skin sensitizing antibody in the blood of such individuals, and Schwartz *et al.* (1968) have demonstrated that they could in fact produce specific reagins after parenteral immunization with pneumococcal polysaccharide. This existence of an ability to synthesize skin sensitizing antibody, coupled with a failure to develop sensitivity when antigen is given intranasally, led us to conclude that subjects with 'intrinsic' allergy more closely resembled normal than atopic individuals in respect to the functioning of their mucosal surfaces, and that their disease differed in a fundamental way from atopic allergy. Of chief interest here, however, is the observation that vasomotor rhinitis *per se* did not lead to early sensitization by mucosal contact with antigen, in the absence of some underlying defect.

How then might one account for the observed differences in immune response between atopic individuals (with broad patterns of Type I skin reactivity), and non-atopic individuals (including persons with 'intrinsic' asthma and/or 'vasomotor' rhinitis, who lack Type I skin reactivity).

One possibility is that local antibody production to common inhalant allergens might differ qualitatively such that different immunoglobulin classes of antibodies are produced. This could account for the group differences noted above. Thus, atopic individuals might respond to natural transmucosal immunization with inhaled or ingested allergens by excessive local production of IgE antibody and normal individuals might develop a predominant 'protective' serum and secretory IgA response. 'Intrinsic' asthmatics might represent a third type of reactivity, perhaps characterized by a 'pure' autonomic nervous system defect, or the development of another as yet undescribed type of anaphylactic (reaginic) antibody.

Another closely related possibility is that the basic abnormality in atopy lies in other aspects of handling allergens which come in contact with mucosal tissues (i.e. enhanced local antigen 'processing', or defects in certain 'protective' proteins in mucosal secretions which might facilitate more efficient antigenic stimulation of the normal immune apparatus).

Against this general concept are the findings of similar secretory and serum IgA concentrations and secretory IgA blocking anti-ragweed activity in normal and atopic subjects (Turk, Lichtenstein & Norman, 1970; Buckley, Dees & O'Fallon, 1968; Huntley & Lyster, 1963; Momma, 1965; Hobday, Cak & Turner, 1971). Also, serum concentrations of exocrine IgA, which might reflect mucous membrane permeability, are not elevated in atopic asthmatics, as opposed to non-atopic children (De Vald & Newcomb, 1972) and the distribution of immunoglobulins, including IgE, as demonstrated by immunofluorescent and radiographic studies of mucosal biopsy specimens is similar in atopic and non-atopic subjects (Callera *et al.*, 1972).

In support of this concept, however, are other reports of serum IgA deficiency in a significantly higher proportion of individuals with atopy and autoallergic diseases in comparison with the population at large (Cassidy *et al.*, 1969; Amman & Hong, 1970; Schwartz & Buckley, 1971b; Kaufman & Hobbs, 1970) and the converse findings of elevated serum IgE plus specific IgE nasal secretion reaginic activity predominantly in atopic individuals (Johansson, 1967; Berg & Johansson, 1969; Schwartz & Buckley, 1971a; Kumar *et al.*, 1971; Yunginger & Gleich, 1971; Hogarth-Scott *et al.*, 1971;

Arbesman, Tse & Wicher, 1970; Dolovich, Tomasi & Arbesman, 1970). In addition to these findings, and our previous demonstrations that atopic subjects respond to intranasally administered allergens with enhanced development of Type I skin reactivity when compared to normal subjects, other data support this general hypothesis. There is a higher incidence of anti-milk protein antibodies in atopic than in normal individuals. Further, there are the 'allergic' gastroenteropathies associated with milk intolerance, asthma, rhinitis, eosinophilic intestinal mucosal infiltrates and gastrointestinal protein loss, and an unconfirmed report of an increased prevalence of allergic disease in anhydrotic congenital ectodermal dysplasia (a disease associated with hypoplastic changes in respiratory mucosa) (Rothberg & Farr, 1965; Waldmann *et al.*, 1967; Vanselow *et al.*, 1970).

In summary then, while by no means conclusive, considerable evidence suggests that atopic allergy may be a disorder involving anaphylactic (reaginic) antibody, in which a genetically influenced behaviour of mucosal membranes, substances in mucosal secretions, or quality and quantity of local antibody producing cells to inhaled or ingested antigens is the predisposing factor permitting more efficient contact between antigens lodging on these surfaces and immunologically competent cells. A local defect of this type might merely represent another expression of the reported alterations in the skin of atopic individuals (Prose, 1965; Wheatley, 1965).

In addition to the amount of factual material it encompasses, the value of a hypothesis may be measured by the number of testable experiments it suggests and we should like to list a few that might prove productive.

1. Direct assay of mucosal permeability should be possible with sufficiently sensitive detection systems. Thus, one might apply small amounts of radioactively labelled antigens to mucosal surfaces and count directly the penetration of antigen either in *in vitro*, biopsy specimens or *in vivo* fashion.

2. Prospective studies may be undertaken, in which children early in life are tested for sensitizability by intranasal administration of a bland non-recurring antigen. Predictions could then be made as to the probability of atopy developing in later life and statistical verification obtained.

3. Studies of nasal secretions of atopic and normal individuals for content of non-antibody substances such as alpha₂-mucosal component and lysozyme might be fruitful. Such substances are present in all epithelial secretions (Masson *et al.*, 1965a, b) and might play prominent roles in digesting surface lipids and polysaccharides of ragweed and other airborne allergens, with subsequent effects on the amount of soluble proteins released onto mucosal surfaces.

4. Quantitative, developmental, or functional group differences in 'protective' IgA subclasses or structural abnormalities in secretory component or 'J' component (O'Daly & Cebra, 1971; Mestecky *et al.*, 1971) undetectable by routine serum or exocrine IgA quantitation might be present in atopic subjects. Such abnormalities could facilitate antigen penetration of mucosal surfaces and warrant study.

5. Further immunofluorescent and radiographic histologic studies to determine the balance between IgE and IgA producing cells in mucosa-associated lymphoid tissues of atopic and normal individuals, and on the conditioning of these cells by pharmacologic factors might explain the abnormal immune response of atopic individuals to allergens applied to mucosal surfaces in combined immunologic and pharmacologic terms.

Finally, if this type of local defect is indeed proven to be the precipitating defect in atopic sensitivity, the theoretical possibilities of selectively altering membrane permeability by topical or systemic treatment, of influencing local antigen processing, or of inducing local immunity by selective stimulation of secretory IgA cells carry the implication of a preventive approach to this noisome disease.

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