

Hymenoptera sensitivity

II. The role of atopy in the development of clinical hypersensitivity

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The present study assesses the relationship between the presence of the atopic state and the occurrence of insect-sting hypersensitivity. Despite the use of broad criteria for the definition of atopy, 14 of 41 individuals with systemic insect-sting hypersensitivity were found to be nonatopic. The authors suggest that atopy is not a prerequisite for the development of other types of anaphylactic hypersensitivity.

The clinical importance of hypersensitivity to the stinging Hymenoptera group of insects has been widely recognized in recent years. Although diagnostic modalities are of limited value at this time,^{1, 2} much has been accomplished clinically and experimentally toward furthering our knowledge of this disease state.³ Furthermore, immunotherapy of patients with systemic hypersensitivity to these stinging insects is of proved value.⁴

The term atopy, first used by Coca and Cooke⁵ in 1923, is applied to a constellation of clinical features, including a personal history of one or more of the following: infantile eczema, atopic dermatitis, allergic rhinitis, seasonal or perennial allergic asthma, and urticaria, especially the type specifically related to exposure to particular allergens. Frequently there is a family history of one or more of these syndromes,⁶ and blood eosinophilia is the rule.⁷ There is great variability in the allergens to which an atopic individual develops sensitivity, but they are typically antigens which are presented to the subject at mucosal surfaces (respiratory and/or gastrointestinal).

However, the pathogenetic mechanisms involved in the development of human allergic disorders, including insect hypersensitivity, are still unclear. Hereditary influences apparently play an important role in the development of hay fever and allergic asthma,⁶ but by uncertain means. It has been suggested that the ability to produce skin-sensitizing antibodies (i.e., reagins) is geneti-

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cally determined,⁸ but there are recent data to suggest that all people (allergic or normal) can produce these antibodies.⁹⁻¹¹ Indeed, it is uncertain whether or not atopic individuals are the only ones who are capable of developing immediate hypersensitivity following exposure to any type of environmental antigenic stimulus.

The present study is an effort to determine the relative susceptibility of allergic and nonallergic individuals to stinging-insect allergy. Thus, an investigation is made of the coincidence of atopy and clinical Hymenoptera sensitivity.

METHODS AND MATERIALS

We divided 52 patients with Hymenoptera sensitivity into 2 groups, 41 with systemic and 11 with local hypersensitivity, based on clinical history. Those with systemic reactions included patients who, following a Hymenoptera sting, developed one or more of the following: urticaria, angioneurotic edema, asthma, hypotension, or collapse with unconsciousness. In addition, many experienced dizziness, thickened speech, nausea, a sense of constriction in the chest, and other vague symptoms of a generalized reaction. The local reactors included patients who developed immediate and progressively severe edema involving at least half of the entire extremity that was stung but who did not develop any of the systemic problems just described.

A careful history was obtained in order that the incidence of atopy could be determined. For this study, those individuals who had a past history or a family history of hay fever, asthma, or atopic eczema were considered atopic, as were patients who were negative in this regard but who later proved to have significant positive skin test reactions to various inhalants and foods. A history of hypersensitivity to drugs and insect stings was not considered to represent evidence of atopy, since these antigens are usually introduced parenterally rather than transmucosally, as are pollens, molds, danders, dust, and foods. The family history was broad in content so as to include the history of allergy in siblings, parents, grandparents, and aunts and uncles. Patients were skin tested by the scratch and intradermal methods with grass, tree, ragweed, fungal, animal dander, and house dust antigens. Extracts of feathers, wheat, milk, egg, peanut and salmon were also used. All antigens were purchased from Hollister-Stier Company. Intradermal tests were done with 0.01 to 0.02 ml. of 1,000 protein nitrogen units (PNU) per milliliter solutions.

All 52 patients were skin tested with a whole-body mixture of bee, wasp, yellow jacket, and hornet in Coca's solution (Hollister-Stier). The intradermal tests were done with 0.01 to 0.02 c.c. of the 1:100 w/v concentration of the whole-body Hymenoptera mixture. Coca's solution was injected as a control, also in the volume of 0.01 to 0.02 c.c. These tests were performed intracutaneously on the lateral surface of the arm at a site which had not previously been used for any allergy or other type injection. Reactions were read at 15 minutes only, delayed reactions not being investigated or recorded. The immediate reactions were graded according to wheal size as follows: (negative) 0 to 4 mm.; 1+, 5 to 8 mm.; 2+, 9 to 12 mm.; 3+, 13 to 16 mm.; and 4+, > 16 mm. Flare formation and pseudo-

pod, if any, were not considered in the measurement of the wheal but were recorded separately.

Conjunctival testing was also done with mixed insect antigen. A 1:10 concentration of the Hymenoptera was employed in a 1 c.c. tuberculin syringe (without a needle), and one drop of antigen was placed in the lower conjunctival sac of one eye. Reactions were read after 5 and 10 minute intervals and recorded as follows: 1+, congestion of the sclera and lower conjunctiva with slight redness and swelling of the caruncle; 2+, more diffuse and intense scleral redness; 3+, extremely diffuse and intense scleral redness with marked involvement of the upper palpebral conjunctiva; and 4+, chemosis of conjunctiva and caruncle.²

RESULTS

Of the total population of 52 study patients, there were 31 men and 21 women, ranging in age from 6 to 70. Forty-one of these patients had systemic Hymenoptera hypersensitivity. Based on the results of examination of these patients by personal and family history and allergy skin testing, they were divided into 2 groups, 26 being atopic and 15 nonatopic. Of the 15 nonatopic patients, one had recurrent idiopathic urticaria. Thus, with the use of highly stringent criteria, it can be said that 14 (34 per cent) of this group of systemic reactors were definitely nonatopic. It is of interest that although several of the atopic patients had a personal history of drug allergy, none of the nonatopic patients did (Table I).

In the group with local insect hypersensitivity, 9 of the 11 were atopic, whereas 2 lacked both a personal and family history of allergy and lacked skin reactivity to the panel of test allergens (Table I).

Skin and conjunctival testing of both systemic and local Hymenoptera-sensitive groups with insect antigens failed to distinguish between those who were atopic and those who were nonatopic (Table II). The high incidence of positive skin tests in the systemic reactors is in confirmation of our earlier findings.^{1, 2}

The age and sex distribution of both atopic and nonatopic groups of insect-sensitive patients were comparable. It should be emphasized that the 16 nonatopic insect-hypersensitive patients were entirely lacking in skin reactivity to the inhalant and food allergens employed in skin testing.

Table I. *Relationship between the presence of atopy and insect-sting hypersensitivity*

<i>Atopy</i>	<i>Insect hypersensitivity</i>	
	<i>Systemic</i>	<i>Local</i>
Personal	4 (10%)	5 (45%)
Familial	9 (22%)	0
Personal and familial combined	13 (32%)	4 (36%)
Nonatopic*	14 (34%)	2 (18%)
Total	41	11

*Including negative skin test results with pollen and food antigens.

Table II. *Conjunctival and skin reactivity to insect allergens in atopic and nonatopic patients with insect hypersensitivity*

<i>Atopy</i>	<i>Positive reactions to insect allergens*</i>			
	<i>Systemic group</i>		<i>Local group</i>	
	<i>Skin test†</i>	<i>Eye test‡</i>	<i>Skin test†</i>	<i>Eye test‡</i>
Personal	4/4 (100%)	2/4 (50%)	5/5 (100%)	3/5 (60%)
Familial	8/9 (89%)	4/9 (44%)	0	0
Personal and familial combined	13/13 (100%)	7/13 (54%)	4/4 (100%)	3/4 (75%)
Nonatopic	14/14 (100%)	10/14 (71%)	1/2 (50%)	1/2 (50%)

*Mixed whole-body extract in Coca's solution.

†Intracutaneous 0.01 to 0.02 c.c. 1:100 w/v.

‡One drop of 1:10 w/v into conjunctival sac.

DISCUSSION

The present study reports that 14 of 41 (34 per cent) patients with systemic hypersensitivity and 2 of 11 (18 per cent) patients with local hypersensitivity to Hymenoptera are nonatopic, as judged by their lack of personal or family history of atopy and their complete lack of skin reactivity to the inhalant and food allergens used in skin testing. This finding supports and strengthens previous reports which had suggested that allergy to insect stings can occur in nonatopic subjects¹² and enables us to discard the notion that an allergic diathesis is a prerequisite for the development of other types of anaphylactic sensitivity.^{3, 13, 14} Unfortunately, a large enough control population could not be evaluated in sufficient detail to allow comment on the concept that insect allergy is more likely to occur in atopic than in nonatopic individuals.³ Reports from other centers suggest that by using various diagnostic criteria,^{15, 16} the over-all incidence of atopy in the general population ranges from 9 to 50 per cent. Thus, it may be that our insect allergic group has a higher incidence of atopy than normal, but this is unclear.

For some time it was widely thought that atopy was due to the reaction of an abnormal immune mechanism to natural exposure to antigen, with the production of abnormal types of antibodies (i.e., skin-sensitizing antibodies, reagins). Anaphylaxis, on the other hand, had been felt to be the reaction of a normal immune mechanism to an artificially imposed, unnatural exposure to antigen.^{13, 14} However, recent evidence indicates that these concepts need revision. Bloch¹⁷ has pointed out that the anaphylactic antibodies and skin-sensitizing antibodies of any given mammalian species are the same. It has been shown that the immunologic response of normal and atopic individuals to parenteral immunization is similar⁹ and that all individuals are capable of producing skin-sensitizing antibodies.^{10, 11, 18} Still unsettled are the questions of whether reagins constitute only one immunoglobulin class (IgE) or whether they can be heterogenous, and whether atopic persons differ from normal persons in their quantitative production of reagin following appropriate immunization (natural or artificial).

There is good evidence to suggest that the basic differences between normal and atopic individuals involve the manner in which ingested or inhaled antigens

are handled when they contact mucosal surfaces. Intranasal instillations of the purified protein bovine pancreatic ribonuclease or the polysaccharide dextran induce immediate wheal and flare skin reactivity in atopic but not in normal persons.^{19, 20} That this is not due to the presence of inflammatory changes in the nose is suggested by the finding that patients with vasomotor rhinitis do not respond immunologically to intranasal instillation of ribonuclease.¹⁸

Similarly, the higher incidence of anti-milk protein antibodies in atopic individuals than in normal persons²¹ further suggests a basic difference in mucosal handling of antigens in atopy. Thus, it is suggested that atopy and anaphylaxis are different clinical expressions of basically similar immune mechanisms. The finding that substantial numbers of nonatopic individuals can become anaphylactically sensitive to Hymenoptera stings supports both this belief and the membrane hypothesis presented above.

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