

Studies on "intrinsic" allergic respiratory disease, with a hypothesis concerning its pathogenesis

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In an effort to shed some light on the pathogenetic mechanisms involved in the intrinsic allergic respiratory syndromes, the immune responses of 11 such patients have been compared with those of 6 atopic patients, following parenteral and intranasal immunization. All patients in both groups developed immediate wheal and erythema skin reactivity 3 weeks following subcutaneous administration of pneumococcal polysaccharide, which was passively transferrable to a nonsensitive recipient with 3 sera. The atopic group demonstrated clear-cut sensitization to intranasally administered ribonuclease, while the intrinsic group did not. We suggest that the intrinsic allergic respiratory syndromes do not involve reaginic antibody-antigen reactions as in atopic disease.

Asthma and rhinitis have for many years been subdivided into 2 patient groups: (1) the extrinsic, in whom the symptomatology is associated with known allergens, and (2) the intrinsic, in whom none of the known allergens is demonstrably involved.¹ Clinically, the two types resemble each other closely in the quality of their symptoms, physical findings, degree of eosinophilia, and reversibility of their disease by appropriate therapy, including adrenocortical steroids.² Pathologic findings are similar, with mucosal edema, hypersecretion of mucus, and infiltration with eosinophils being characteristic.^{1, 3} While the intrinsic group tends to have a less prominent family history of allergy and a somewhat later onset of disease than the extrinsic group, their most clear-cut distinguishing characteristic is the lack of immediate wheal and erythema skin reactivity to common inhalant antigens.¹⁻⁶ Although the pathophysiology involved

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in the extrinsic group has been clarified to some degree, much doubt still exists concerning the causal mechanisms involved in the intrinsic allergic respiratory syndromes. In an effort to elucidate some aspects of this problem, the immune responses of such patients were investigated, particularly with regard to their capacity to produce skin-sensitizing antibody following parenteral and intranasal immunization.

MATERIALS AND METHODS

Seventeen adult patients from the Allergy Clinic were skin tested during their initial evaluation with both the standard scratch and intracutaneous methods. Scratch tests were done on both forearms with the following allergens*:

1. Pollens (1:20)—short ragweed, timothy, plantain, birch, oak, willow, poplar, ash, maple, elm.
2. Foods (1:10)—milk, egg, wheat, chocolate, peanut, walnut, cottonseed, lobster, herring, salmon.
3. Molds (1:20)—*Alternaria*, *Hormodendrum*, *Penicillium*.
4. Miscellaneous inhalants (1:10)—two house dust preparations,† dog dander, cat dander, feathers.

Phenolized saline was used as the negative control, and reactions were measured after 20 minutes.

Intradermal testing was done on both upper arms, in areas which had not been previously injected with allergenic extracts, with the following allergens:

1. Pollens (1:200)—birch, oak, elm, ash, maple, poplar, timothy, plantain, short ragweed.
2. Molds (1:200)—*Alternaria*, *Hormodendrum*, *Penicillium*.
3. Dusts and danders—Endo house dust 1:4000, Hollister-Stier house dust 1:1,000, wool, feathers, dog dander, cat dander (all 1:100).

Histamine 1:10,000 was used as the positive control, and phenolized saline was used as the negative control. The reactions were measured after 12 minutes. After their initial evaluations were completed, the patients were divided into two groups, as follows:

Group I (extrinsic) consisted of 6 patients with known allergic rhinitis, bronchial asthma, or both, associated with clear-cut scratch test reactivity to 1 or more allergenic extracts and reversible obstructive airway disease.

Group II (intrinsic) consisted of 11 patients with rhinitis, reversible obstructive pulmonary disease, or both, who also had eosinophilia but lacked skin reactivity to all allergenic extracts with which they were tested intracutaneously.

The clinical features of both groups are summarized in Table I.

All patients were immunized with 80 μ g of Types II (S II) and VII (S VII) pneumococcal polysaccharide subcutaneously.‡ Three weeks later they were bled, the sera harvested, and skin testing carried out.

Later in the study, 5 patients from Group I and 9 patients from Group II

*Concentrations on a weight by volume scale.

†Purified allergenic house dust concentrate, 1:40, Endo Labs, Inc. and Hollister-Stier house dust 1:10.

‡Lederle Laboratories, Pearl River, N. Y.

Table I. *Clinical characteristics*

<i>Group</i>	<i>I (extrinsic)</i>	<i>II (intrinsic)</i>
<i>Age</i>		
Mean	36.5	52
Median	37	54
Range	29-44 years	26-64 years
<i>Sex</i>		
Male	2	6
Female	4	5
<i>Syndromes</i>		
Rhinitis only	1	1
Asthma only	0	1
Rhinitis and asthma	5	9
Nasal polyposis	0	3
<i>Duration</i>	all > 4 years	all > 2 years
Eosinophils (No./mm. ³)	all > 250	all > 450

were given weekly nasal inhalations of crystalline ribonuclease (RNase) from bovine pancreas, salt, and protease free.* The antigen was dispensed from a Holmspray No. 600 Nasal Atomizer. Each week both patient groups were given 3 intranasal inhalations in each nostril weekly for a 4 month period. Each spray delivered approximately 0.35 mg. of antigen. This is a gross approximation, since some material trickled from the nostrils at the time of each patient treatment. Development of skin reactivity was assessed at monthly intervals.

Skin testing

Intradermal tests were done with approximately 0.02 ml. doses of S II and S VII, 80 μ g per milliliter and RNase, 0.1 mg. per milliliter. The diameters of the areas of edema and erythema were recorded after 15 minutes. Saline controls were done in all cases. These skin tests were performed on all subjects before immunizations were carried out. Reactions were graded as follows:

- = < 4 mm. edema, 0 erythema
- + = 4 to 8 mm. edema, up to 10 mm. erythema
- ++ = 4 to 8 mm. edema, 10 to 20 mm. erythema
- +++ = 8 mm. edema, > 20 mm. erythema
- ++++ = > 8 mm. edema, > 25 mm. erythema

Passive transfer studies

Skin-sensitizing antibody was measured by the Prausnitz-Küstner method. Blood was collected in sterile tubes and allowed to clot. After standing overnight at 4° C., sera were harvested. Then, 0.1 ml. of undiluted serum was injected into the skin of a nonsensitive recipient. The sites were challenged 48 hours later with approximately 0.02 ml. of S II, in a concentration of 80 μ g per milliliter. Reactions were read after 20 minutes. Appropriate controls were carried out.

*Mann Research Laboratories, New York, N. Y.

Table II. Skin reactions to subcutaneous Types II and VII pneumococcal polysaccharide

Group	Patient	Response to S II (80 mg./ml.) skin test		Response to S VII (80 mg./ml.) skin test	
		Before	After	Before	After
I (extrinsic)	1	++	++	—	+++
	2	—	+++	—	++++
	3	—	+	—	+++
	4	—	++	—	++
	5	—	++	—	+++
	6	—	+++	N. D.*	N. D.*
II (intrinsic)	1	—	++++	—	+++
	2	±	++++	—	++++
	3	—	++++	—	++++
	4	—	+	—	+
	5	—	++	—	++++
	6	—	+++	—	++
	7	—	+++	—	+++
	8	—	+	—	++
	9	—	+	—	+
	10	—	+	—	+
	11	—	+++	—	+++

*N.D. = Not done.

RESULTS

Wheal and erythema reactivity to pneumococcal polysaccharide

Table II lists the results obtained on immunization with S II and S VII pneumococcal polysaccharide. Of the 6 subjects in Group I, all but one lacked prior reactivity to either antigen; in one subject a positive intradermal test to S II was elicited. None of the Group II subjects had skin reactivity on initial testing. Three weeks following immunization, all subjects in both groups had converted to a skin reactive state, with no difference noted between groups in degree of response.

Ribonuclease inhalation

Table III records the results of serial skin testing in both study groups. It is evident that the atopic Group I responded early with development of nasal symptoms, as well as skin reactivity. By the third month, 4 out of 5 subjects were skin test positive.

In contrast, all of Group II remained unresponsive, both clinically and by skin test after 3 months. At the end of the fourth month of study, only 2 patients out of 9 had become skin reactive. It has been previously noted⁷ that skin reactivity can follow repeated skin testing with RNase; it seems most likely that this explains the two conversions in Group II.

Skin-sensitizing antibody

Serum from 2 patients from Group I and one from Group II were tested for the presence of passive-transfer antibody to S II; positive results were obtained

Table III. *Skin reactions to ribonuclease during intranasal administration*

Group	Patient	Preimmunization	Period (months)			
			1	2	3	4
I (extrinsic)	1	—	—	+	++++	
	2	—	—	—	—	
	3	—	—	+	+	+++
	4	—	+	++	+	
	5	—	—	—	+	
II (intrinsic)	1	—	—	—	—	—
	2	—	—	—	—	—
	3	—	—	—	—	—
	4	—	—	—	—	—
	5	—	—	—	—	—
	6	—	—	—	—	+++
	7	—	—	—	—	—
	8	—	—	—	—	—
	9	—	—	—	—	++

with all three 48 hours after injection. This Prausnitz-Küstner phenomenon was abolished by preheating the serum at 56° C. for 3 hours prior to intradermal injection.

DISCUSSION

The pathophysiology of atopic respiratory disease had been considered to involve the development, in genetically susceptible individuals, of an immune response to usually innocuous antigens, with the production of antibodies belonging to the class referred to as reagins.⁶ Leskowitz and Lowell⁸ have shown, however, that atopic and normal individuals respond in a similar fashion, both quantitatively and qualitatively, to parenteral immunization with dextran and Type II pneumococcal polysaccharide. Salvaggio and Leskowitz⁹ have shown the same with alum precipitated RNase. The fact that skin reactivity to RNase was passively transferred indicates that normal, as well as atopic, individuals make reaginic antibody under appropriate circumstances.

On the other hand, strong evidence exists that atopic patients respond to intranasal instillations of antigen quite distinctively. Immediate type skin sensitivity can be readily induced in atopic subjects by intranasal administration of RNase, dextran, and Keyhole Limpet Hemocyanin (KLH). Whereas, in nonatopic subjects this is achieved only irregularly, if at all, and only following prolonged exposure. In the latter instance (KLH), the data are less clear since repeated skin tests alone produce active sensitization. Nonetheless, the level of immune response was greater in the atopic than that in the control group.¹¹ It is of further interest that Farr and co-workers have reported a much higher incidence of anti-milk protein antibodies in the atopic than that in normal subjects.^{12, 13}

While other possibilities exist, we have adopted as a working hypothesis to explain these data the concept that the fundamental distinction between atopic and normal subjects lies in the way in which antigens contacting mucosal surfaces are handled. In the atopic patients antigen penetrates in an immunogenic form, while in normal individuals it either fails to penetrate or is degraded. The

net result of the mucosal defect is that atopic subjects develop an immune response to antigens lodging on their mucosa in sufficient quantities for sufficient periods of time. Because of the exquisite sensitivity of the technique for detecting the skin-sensitizing antibody, this is the most apparent immunologic response.

What, then, is the basic defect in "intrinsic" asthma? It has often been suggested that bacterial allergy exists in this syndrome, but the evidence has been contradictory and inconclusive.^{4, 6} The lack of skin reactivity in intrinsic allergic respiratory disease, while frequently taken to imply an as yet unknown allergen, has suggested to us that this disease differs pathogenetically from "extrinsic" asthma and rhinitis. That there is no inherent inability in these patients to produce skin-sensitizing antibody is indicated by the normal development of wheal and erythema skin reactivity upon immunization with S II and S VII. Moreover, such reactivity was transferable in three subjects by the Prausnitz-Küstner technique at 48 hours and was abolished by heating the serum at 56° C. for 3 hours, thus fulfilling the conventional criteria for reaginic antibody.

It is also unlikely that the responsible allergen has simply not yet been discovered. Most atopic patients, when tested in the manner described, react to several inhalant allergens rather than to a single, isolated antigen. Moreover, the range of allergens to which they become sensitive tends to increase with time and exposure. The failure of patients with intrinsic asthma to exhibit skin reactivity to common inhalant allergens, as well as to intranasal RNase administration, suggests strongly that in this respect they behave much more like normal individuals than atopic patients with extrinsic asthma. It is of considerable interest that their failure to develop skin reactivity exists in the face of symptoms of rhinitis, conjunctivitis, and asthma, much like that exhibited by patients with extrinsic allergic disease. It has always been a moot point of much concern to us whether the ability to become sensitized via mucosal contact with antigen was the cause of atopic allergy or the result of an increased permeability produced by the disease. The results reported here lend further credence to the hypothesis that the mucosal defect may well be the cause of atopic disease. Although, a prospective study in which subjects are tested before they develop clinical disease obviously would be of interest.

Strong circumstantial evidence has been accumulated to show that many of the clinical features of extrinsic allergic syndromes involve one or more of the known pharmacologic mediators, including: histamine, serotonin, slow-reacting substance, and plasma kinins.^{6, 14, 15} In atopic allergy these are presumed to be, in part, the consequence of reaction of antigen with reaginic antibody fixed to target cells (e.g., mast cells).

We would like to suggest that the presence of similar symptoms and eosinophilia in intrinsic asthma indicates that common pathways are being followed; but these are being initiated by nonimmunologic stimuli, such as, infection, temperature and humidity changes, and air pollutants. Whether the pathogenesis of intrinsic asthma involves the absence of a cellular or serum inhibitor or some other genetic defect, as in hereditary angioneurotic edema,^{16, 17} is a matter for future study.

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