

A study of the occurrence of atopic traits in patients with keratoconus

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The reported high frequency of atopic disease in patients with keratoconus seemed of interest because of a postulated membrane defect or peculiarity in atopic individuals. Accordingly, a group of 31 patients with keratoconus was compared with 30 unselected control subjects with respect to the occurrence of atopic traits as judged by: (1) the stated past or present occurrence of atopic manifestations in the subject or in his family; (2) the frequency and intensity of skin reactivity; and (3) the level of the total eosinophil count. The two groups exhibited no significant differences with respect to these except for a higher frequency of asthma in the keratoconus group and their families. Reasons are presented for questioning the relevance of this difference, and it was concluded that the two groups did not differ significantly with respect to atopic traits.

An association between keratoconus and atopic disease has been mentioned in the literature and has been considered significant since the publication by Hilgartner¹ in 1937. Since then there have been other reports²⁻⁷ of small numbers of keratoconus patients indicating the concomitant occurrence of atopic disease. In a more recent study,⁸ eczema was reported to be present in 32 per cent of one hundred keratoconus patients compared with an assumed incidence of 3 per cent in the general population. All of these publications, however, were based on histories elicited from the patients by ophthalmologists, and in none was there any control group for comparison.

The purpose of this study has been to determine the frequency of atopic traits among a group of keratoconus patients and to compare this with that obtained in a control group subjected to identical testing. Since earlier work had suggested that the nasal mucous membrane of atopic individuals is more permeable than that of nonatopic persons,^{9, 10} there also seemed to be the

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possibility that keratoconus represented a particular form of this membrane peculiarity. A recent report¹¹ describes an increased occurrence of respiratory allergy and skin reactivity to extracts of environmental allergens in anhydrotic congenital ectodermal dysplasia. It was postulated that either a common hereditary basis or enhanced absorption of inhaled allergens could explain this association.

SELECTION OF PATIENTS AND METHODS

All keratoconus patients participating in this study were patients from the Cornea Service of the Massachusetts Eye and Ear Infirmary. Fifty patients in whom the diagnosis of keratoconus had been established were sent a questionnaire asking them if they would be willing to participate in a clinical study relating to their disease. No indication as to the nature of the study was included in the correspondence in order to avoid the biased selection which might have resulted from the knowledge that testing for allergic disease was being contemplated. Eighty per cent of the patients contacted responded affirmatively.

Thirty-one from among these were referred to the Allergy Clinic of the Massachusetts General Hospital for assessment of atopic traits. A detailed family history was obtained, in which the presence or absence of atopic manifestations and the nature thereof, as stated by the patient, were recorded individually for the parents, aunts, uncles and siblings. Each patient was also carefully questioned with regard to past or present atopic manifestations, their nature, severity, and any treatment given therefor.

Difficulty was encountered in the selection of a group to serve as normal control subjects. Because awareness of the nature and purpose of the study might influence an individual's motivation in entering the study and thereby influence in turn the incidence of atopic traits in the control group, particular care was taken to obtain consent before the nature of the study was revealed. It was hoped that none would subsequently withdraw, and none chose to do so. Each control subject was then given a full description of the nature and purpose of the study, and each received compensation for the time required. The 30 subjects constituting the control group were drawn from among technicians in the hospital and from a fraternity at a neighboring teaching institution. So far as could be determined, selection was free from bias.

Skin tests were performed with pollens, molds, animal danders, house dust, and certain foods (Table I). These were first done by the "scratch" method. A drop of extract was placed on the skin, whereupon the point of a sterile, unused No. 20 hypodermic needle was drawn across the drop with sufficient pressure to leave visible scarification but not to induce bleeding. The reaction was recorded at the end of 20 minutes by a freehand drawing of the wheal and erythema. If the reaction was negative or doubtful, an intracutaneous test was done by injecting about 0.03 ml. of aqueous extract in the upper arm or in the back if the patient had been receiving therapeutic injections of allergenic extracts.¹² Readings were made after a period of 12 minutes, again by a freehand drawing of the wheal and erythema.

The pollen extracts, prepared in this laboratory, were freshly reconstituted

Table I. *Allergenic extracts used in skin tests*

<i>Pollens</i>	<i>Molds</i>	<i>Animal danders*</i>
Birch, oak, timothy, plantain, ragweed, willow, ash, maple, elm—all 1:10 w/v	Alternaria, Hormodendron, Penicillium*—all 1:40 w/v	Feathers, cat, dog—1:10 w/v

Each patient was tested with all the above by the "scratch" method. If no reaction, each patient and molds, 1:1,000 for house dust A, and 1:4,000 for house dust B. Each patient was also tested formed.

*Obtained from Hollister-Stier Laboratories, Spokane, Wash.

†Obtained from Endo Products Laboratories, Summit, N. J.

Table II. *Sex and age distribution*

	<i>Control</i>	<i>Keratoconus</i>
<i>Sex</i>		
Males	20	19
Females	10	12
Total	30	31
<i>Age</i>		
Mean	21.9	29.2
Median	20	26
Range	15–36	14–58

Table III. *Numerical scores assigned to reactions obtained by skin test*

	<i>Pollens</i>	<i>Molds, danders and house dust*</i>
Scratch		
Intense	10	10
Moderate	5	10
Intracutaneous		
Greater than that to histamine†	3	5
Equaling that to histamine	2	3
Less than that to histamine	1	2
No response	0	0

*The extracts of molds, danders, and house dust gave less intense reactions, in general, than did the extracts of pollens, and for this reason higher scores were arbitrarily assigned to them.

†See Table I.

each month from stock extract which had been dried from the frozen state after filtration through a sterile bacterial filter. Cultures made during bottling prior to freezing of the extract gave no growth after 5 days at 37° C. All extracts had been shown to be capable of giving intense reactions by scratch test in appropriate patients. Stock extracts of Alternaria and Hormodendron were prepared from cultures grown in this laboratory, extracted, and lyophilized in the same manner as the pollens.

<i>Foods*</i>	<i>House dust</i>	
	<i>A*</i>	<i>B†</i>
Wheat, milk, eggs, peanut, fish, cottonseed, walnut—all 1:10 w/v	1:10 w/v	1:40 w/v Of concentrated solids

was tested intracutaneously with this extract in a final dilution of 1:200 w/v for all the pollens with histamine 1:10,000 w/v as the base. Intracutaneous tests with food extracts were not per-

Table IV. *Occurrence of atopic manifestations by history*

	<i>Rhinitis</i>	<i>Asthma</i>	<i>Eczema</i>	<i>Total individuals</i>
Control	14 (2)*	1 (0)†	2	14
Keratoconus	16 (2)	5-7 (2)	3	18

*Numbers in parentheses indicate individuals who received injection therapy for allergic rhinitis.

†Numbers in parentheses indicate individuals in whom asthma was current.

Table V. *Skin test scores*

	<i>Mean</i>		<i>Median</i>		<i>Range</i>	
	<i>Control</i>	<i>Keratoconus</i>	<i>Control</i>	<i>Keratoconus</i>	<i>Control</i>	<i>Keratoconus</i>
Pollens	15.3	15.2	2	2	0-85	0-64
Molds	2.6	2.1	2	1	0-12	0-7
Animal danders	4.9	6.2	1	1	0-21	0-22
Totals	29.0	30.9	15	17	0-114	0-108

Table VI. *Skin test scores*

<i>Total skin test score in the range</i>	<i>Controls</i>	<i>Keratoconus</i>
1-30	19 (0)*	20 (0)
30+	11 (7)	10 (9)

*Numbers in parentheses indicated subjects describing clinical manifestations characteristic of allergic rhinitis.

A total eosinophil count was done in each patient with venous blood obtained before skin testing. With the exception of 5 patients in the keratoconus group and 2 subjects in the control group, the blood samples were obtained between November and February. There is little likelihood, therefore, that the two groups differed significantly in regard to environmental exposure to pollens and molds at the time they were seen. Blood was drawn to the 0.1 mark on the white cell-

counting pipette and diluted with an eosin-acetone-water solution drawn to the 1.0 mark. Both sides of a Fuchs-Rosenthal counting chamber were filled, and, after settling of the cells, all 32 squares were counted. Total eosin-staining cells seen multiplied by 1.56 gave cells per cubic millimeter in the blood sample.¹³

The distribution of sexes in the two groups and the mean, median, and range for ages are given in Table II. The two groups were similar but differed in that the patients in the keratoconus group were somewhat older and the age range was greater than that in the control group. Except for age and certain features to be described, no significant differences in the characteristics of the two groups were recognized. Statements regarding the presence or absence of rhinitis, allergic rhinitis, asthma, and eczema were accepted at face value. Since urticaria is especially difficult to classify and is only occasionally clearly atopic, urticaria was omitted from consideration.

Skin tests were scored numerically with regard to intensity as shown in Table III. Reactions to the pollens were in general much more intense than those to mold, dander, and dust extracts.

Criteria for atopy

It has not seemed useful to attempt to classify each subject in this study as atopic or nonatopic, because atopic traits, rather than being present or absent, occur in greater or lesser degree in the population. These traits include: (1) such clinical manifestations as hay fever and asthma, often occurring on exposure to airborne or ingested allergens and eczema; (2) the presence in close relatives of similar clinical manifestations; (3) "immediate" type of skin reactivity to extracts of airborne and some other biological substances; and (4) blood eosinophilia, perhaps only present at times when significant allergenic exposure is taking place.¹³ These four criteria were tallied for each subject.

RESULTS

The number of individuals who stated that they had or had had hay fever, asthma, or eczema is shown in Table IV. The numbers for hay fever were the largest and closely similar, with 14 and 16 in the control and keratoconus groups, respectively. Two in each group had been skin tested and had received injections of allergenic extracts in the past. The greatest difference was seen in the stated incidence of asthma, one in the control group describing this as having occurred in the past and 5 or 7, depending how the answers were interpreted, in the keratoconus group. Two of these had had asthma in the recent past. The incidence of a history of "eczema" was 2 and 3 in the control and keratoconus groups, respectively.

Scores for the results of skin testing, as shown in Table V, were similar for the two groups, and no significant differences were recognized. All those stating that they had seasonal hay fever or asthma had scores exceeding 30. As shown in Table VI, among these there were 7 and 9 in the control and keratoconus groups, respectively, whereas there was none among those in either group with scores below 30. Thus intense skin reactivity appeared to be a meaningful indication of the likelihood of seasonal atopic disease, and there were equal num-

Table VII. *Total eosinophil count*

	<i>Control</i> (cells/mm. ³)	<i>Keratoconus</i> (cells/mm. ³)
Range	22-438	20-650
Median	135	170
Mean	172	197

Table VIII. *Stated occurrence of atopic disease among the families*

	<i>Rhinitis</i>		<i>Asthma</i>		<i>Eczema</i>		<i>Total</i> <i>individuals</i>	<i>Family</i> <i>"pool"</i>	<i>%</i> <i>Atopic</i>
	<i>No.</i>	<i>%</i>	<i>No.</i>	<i>%</i>	<i>No.</i>	<i>%</i>			
Controls	21	8.9	4	1.7	2	0.9	25	236 (36)*	10.6
Keratoconus	15	4.9	16	5.2	5	1.6	30	305 (33)	9.85

*Numbers in parentheses refer to members of the families concerning whom the subjects expressed ignorance as to the presence or absence of allergic rhinitis, asthma, or eczema.

bers exhibiting such reactivity (19 and 20, respectively) in the control and keratoconus groups.

In this analysis, 4 in the keratoconus group having intense skin reactivity to cat or dog dander or both also described hay fever or asthma on exposure to cats or dogs. On the other hand, there was none in the control group describing symptoms on such exposure even though the over-all intensity of skin reactions to these extracts in this group was equal to that in the keratoconus group. This difference between the two groups will be discussed.

The ranges, medians, and means for the total eosinophil counts in the two groups are given in Table VII. No significant differences were recognized, although values in the keratoconus group were slightly higher than those in the control group.

The stated instances of hay fever, asthma, and eczema among the parents, uncles, aunts, and siblings of those in the two groups are given in Table VIII. Those instances in which the subject had no direct or indirect knowledge of the presence or absence of atopic disease in members of the family (usually aunts or uncles) were omitted from the pool of family members on which the frequency of the various syndromes was based. Thus the occurrence for the control group is based on a pool of 236 instead of the actual total of 272 family members, and for the keratoconus group these numbers were 305 versus 338. The stated number of individuals among family members reported by the subjects to have one or more of the syndromes was 10.6 per cent in the control group and 9.85 per cent in the keratoconus group. A family history of hay fever was greater in the control group, and that for eczema was small in both groups. However, there were 16 family members reported to have asthma in the keratoconus group versus 4 in the control group — a threefold difference when the numbers in the two pools are taken into account.

DISCUSSION

The incidence of atopic disease and skin reactivity in response to testing with allergenic extracts has been reported by several workers. The findings will be

influenced by the manner in which the data are gathered and by the source, concentration, and activity of the extracts used. For this reason we assume that it would be unreasonable to attach significance to differences between our findings in the keratoconus group and findings of others who have carried out studies to determine the incidence of atopy in selected or unselected populations.

The responses obtained by a personal and family history will be influenced by the individual's concern with illness and past medical experience. Because of the ophthalmologic disease, the keratoconus group undoubtedly had had much more frequent and intense contact with physicians than the control group. They would have been questioned repeatedly concerning any past or familial hay fever, asthma, or because of the reported high incidence of atopic disease among those with keratoconus. They surely differed from the control group in this respect, and the finding of more frequent reported occurrence of atopy in the families of patients with keratoconus than among the controls can be attributed wholly or in part to this difference in past medical experience. This difference may also explain in part the greater reported occurrence of asthma among patients with than among those without keratoconus. In the present study, the number of those with hay fever and eczema was about the same, and the total number of individuals describing one or more atopic syndromes, past or present, was not very different in the two groups. It was interesting that among the keratoconus group, there were four who described the past occurrence of asthma or rhinitis on exposure to cats or dogs, whereas there was none in the control group. A possible explanation for this difference is the probable tendency for those with keratoconus to avoid outdoor activities because of the eye condition and therefore to be subjected to greater indoor exposure to household pets than the control subjects.

In light of the above considerations, it is questionable whether the small observed differences can be considered meaningful. Furthermore, the over-all reported incidence of one or more atopic syndrome in the families of the two groups was almost exactly the same, namely, very close to 10 per cent. Thus it seems unlikely that a real difference between the two groups existed with respect to the reported occurrence of atopic disease.

No significant difference between the groups was seen in the response to skin testing and in the total eosinophil counts. Here the influence of irrelevant factors was absent or much less. The difference between the groups was indeed so small as to suggest completely similar populations with respect to these procedures.

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REFERENCES

1. Hilgartner, H. D., Hilgartner, H. L., Jr., and Gilbert, J. T.: Keratoconus successfully treated with organotherapy, radium and shortwave diathermy, *Amer. J. Ophthalm.* 20: 1032, 1937.
2. Bereston, E. S., and Baer, R. L.: Keratoconus associated with atopic dermatitis, *Arch. Derm. Syph.* 46: 358, 1942.

3. Brunsting, L. A., Reed, M. B., and Bair, H. L.: Occurrence of cataracts and keratoconus with atopic dermatitis, *Arch. Derm.* 72: 347, 1955.
4. Galin, M., and Berger, R.: Atopy and keratoconus, *Amer. J. Ophthal.* 45: 904, 1958.
5. Spencer, W. H., and Fisher, J. J.: The association of keratoconus with atopic dermatitis, *Amer. J. Ophthal.* 47: 332, 1959.
6. Ridley, F.: Scleral contact lenses in keratoconus, in *Twentieth International Congress of Ophthalmology, 1966. Symposium: Contact lenses*, Basel, 1967, S. Karger AG, p. 163.
7. Ridley, F.: Contact lenses in treatment of keratoconus, *Brit. J. Ophthal.* 40: 295, 1956.
8. Copeman, P. W. M.: Eczema and keratoconus, *Brit. Med. J.* 2: 977, 1965.
9. Salvaggio, J. E., Cavanaugh, J. J. A., Lowell, F. C., and Leskowitz, S.: A comparison of the immunologic responses of normal and atopic individuals to intranasally administered antigen, *J. ALLERG.* 35: 62, 1964.
10. Schwartz, H. J., Leskowitz, S., and Lowell, F. C.: Studies on "intrinsic" allergic respiratory disease, with a hypothesis concerning its pathogenesis, *J. ALLERG.* 42: 169, 1968.
11. Vanselow, N. A., Yamate, M., Adams, M. S., and Callies, Q.: The increased prevalence of allergic disease in anhydrotic congenital ectodermal dysplasia. Presented at the 25th Annual Meeting of the American Academy of Allergy, March 17-19, 1969, Bal Harbour, Fla.
12. Lowell, F. C.: The effect of subcutaneous injections of allergenic extract on the local reactivity to intracutaneously injected extract, *J. ALLERG.* 34: 35, 1963.
13. Lowell, F. C.: Clinical aspects of eosinophilia in atopic disease, *J. A. M. A.* 202: 109, 1967.