

A familial tendency toward skin sensitivity to ragweed pollen

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A study was undertaken to establish whether or not the ability to develop skin-sensitizing antibodies to ragweed pollen is familial. The frequency of positive intradermal skin tests to ragweed pollen extract was compared in the parents and sibs of children with ragweed hay fever and positive skin tests and the parents and sibs of children without ragweed hay fever and with negative skin tests, selected without reference to a family history of allergy. The frequency of positive skin tests to ragweed pollen extract was found to be higher in the sibs of children with positive skin tests and symptoms of ragweed hay fever (28.0 per cent) than it was in sibs of children with negative skin tests and no ragweed fever (4.8 per cent). The frequency of positive skin tests to ragweed pollen extract was higher in the sibs of children with positive skin tests and symptoms of ragweed hay fever when at least one parent had a positive skin test (48.5 per cent) than it was when neither parent had a positive skin test (14.3 per cent). These findings clearly demonstrate that the ability to form skin-sensitizing antibodies to ragweed pollen is familial and probably genetically determined. The ability to develop a positive skin test to grass pollen extract was also found to be familial.

Although most physicians acknowledge a familial predisposition to allergy, some remain unconvinced,¹ and there is very little conclusive evidence to settle the question. Part of the trouble comes from the lack of a clear-cut definition of allergy, and part from the lack of family studies with adequate controls.

Many investigators have approached the problem by simply classifying individuals into those who have at least one affected relative (positive family history) and those with no affected relatives (negative family history). If the proportion of individuals with a positive family history is higher for a group of

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allergic patients than it is for a group of nonallergic individuals, a familial tendency is assumed.²⁻⁶ However, the validity of this approach depends on whether the control families are comparable to the allergic families in size, age distribution, ethnic composition, and so forth, and whether they are studied just as intensively as the allergic families, since the proportion of positive family histories the investigator obtains depends on how carefully he looks and how distant the relatives are that he includes in the family. It is not generally recognized that with a condition as common as allergy, the proportion of positive family histories of allergy would be high even if there were no familial tendency. For instance, with a 16.7 per cent frequency of allergy in the population and an average family size of 10 relatives, 84 per cent of all individuals, allergic or not, would have a positive family history by chance alone.⁷

Even if a familial tendency were demonstrated by this approach, the proportion of positive family histories contributes no information about the mode of inheritance of the disease. It is better, therefore, to indicate the proportion of affected individuals in each category of relative—sibs, parents, children, and so forth—for a group of allergic probands (index cases) and a group of control probands. One can then see whether the frequency of the condition is highest in the first-degree relatives of the allergic probands and decreases with decreasing degree of relationship, and whether for each category of relative it is higher in the allergic probands' relatives than in the control probands' relatives.^{8, 9} From the proportions of affected relatives in each category certain inferences can then be made about the mode of inheritance.

The allergic probands, who are necessarily affected by definition, should not be included in the data from which the proportion of affected relatives is calculated. For instance, Viswanathan and Bharadwaj¹⁰ stated that the frequency of asthma in the sibs of asthmatic individuals with normal parents is 18.6 per cent, but they included the asthmatic probands themselves among the sibs. When the probands are removed, the value for the sibs becomes 7.2 per cent, which is about the same as their control value.

Genetic analysis of "allergy" is further hampered by the variability of symptoms in allergic patients, variation in exposure to allergens, and lack of a simple reliable test that would classify individuals into two discrete groups—allergic and nonallergic.

It is not surprising, therefore, that opinions vary widely as to the mode of inheritance of allergy. They include autosomal dominant,^{4, 5, 11} dominant with reduced penetrance,⁹ autosomal recessive,^{10, 12} a recessive locus for each of hay fever, asthma, and eczema,¹³ an autosomal locus with early onset of allergy in homozygotes for one allele and late onset of allergy in 18 per cent of the heterozygotes,⁸ and multiple additive genes.⁷ It has also been pointed out, correctly, that a familial tendency does not necessarily mean an inherited predisposition.¹⁴

The relatively few family studies that have made use of skin testing have almost all shown a higher frequency of positive skin tests in the near relatives of allergic probands than in a more or less suitable control population; however, these studies have not clarified the mode of inheritance.

Brem and Colmes¹⁵ did scratch tests with thirty-five allergenic substances on 40 allergic patients and on 17 members of 4 control families of unspecified nature. They found a higher frequency of positive scratch tests in the relatives of the allergic patients than in relatives of the control subjects, but the investigators did not state whether the control families were comparable to the allergic families. Bissell¹⁶ tested the near relatives of 11 allergic patients with fourteen allergens and found that the relatives tended to react to the same allergens as the patients, but he suggested that more cases were needed to confirm this impression. In a large study of asthmatic and control probands, Schwartz⁹ found no difference in the number of relatives with at least one positive reaction to twenty-two allergen extracts among 81 near relatives of asthma probands (21 per cent) and 127 near relatives of nonallergic control probands (18.1 per cent). Critz¹⁷ found a higher frequency of positive scratch tests for various antigens in the parents of allergic children than in the parents of control subjects, but the control children were selected on the basis of having no personal or family history of allergy. If there is a relation between allergy and positive scratch test, this procedure would result in a control group with a frequency of scratch tests much lower than that of the general population and, in any case, not comparable with the parents of the allergy group.

Undaunted by this confusion, we have carried out a pilot study designed to answer the following questions:

1. Is the prevalence of ragweed hay fever higher in the near relatives of probands with ragweed hay fever and a positive skin test for ragweed pollen than in the near relatives of probands with no ragweed hay fever and a negative skin test (the control group)?
2. Is the prevalence of positive skin tests for ragweed pollen higher in the parents and sibs of children with ragweed hay fever and a positive skin test than in the parents and sibs of the control probands?
3. Is the prevalence of positive skin tests for grass pollen and egg albumen higher in the parents and sibs of children with ragweed hay fever than in the parents and sibs of control probands?

MATERIALS AND METHODS

Group RH-H (ragweed hay fever—hospital)

Fifty probands were chosen consecutively, without knowledge of their family history, from the files of The Montreal Children's Hospital Allergy Clinic. The subjects were 5 to 15 years old, had lived with their families in Montreal (which has a high ragweed pollen count) for at least 5 years, and had clinical ragweed hay fever and positive skin tests to ragweed pollen extract. Thirty of the probands had asthma as well.

Group RH-P (ragweed hay fever—private)

Twelve probands were chosen, without reference to the family history, from the private practice of one of us (H. L. B.). They were the first 12 patients seen who met the above criteria and did not come simply for injections.

Group C (control)

The 50 control probands were the firstborn members of twins who had previously been ascertained by Dr. J. D. Metrakos and registered in the Department of Medical Genetics for other purposes. The control probands were in the same age group, did not have ragweed hay fever, and had negative skin tests to ragweed pollen extract. The secondborn twins were excluded from the analysis.

The family of each proband was visited by one of us (E. I. K.), and a family history was obtained, usually from the proband's mother. A form containing a list of detailed questions about allergy symptoms was filled out by the interviewer for each near relative, confirmed by direct interview whenever possible, and reviewed by two allergists (H. L. B. and A. E.). Both parents and all available sibs over 4 years of age were skin tested by intradermal injection (0.02 ml.) at four separate sites with ragweed pollen extract (100 protein nitrogen units per cubic centimeter), grass pollen extract (100 protein nitrogen units per cubic centimeter), egg albumen (1,000 protein nitrogen units per cubic centimeter), and buffered saline at the distal site. Any reaction with a wheal 4 mm. or more in diameter accompanied by erythema was considered positive, when the saline test site was negative. In almost all cases the result was unequivocal.

RESULTS

The families of the three groups did not differ significantly in average age of proband, average maternal and paternal age, mean age of sibs, and mean sibship size. The control probands had a higher mean birth rank (3.2) than the hay fever probands (RH-H, 2.4; RH-P, 1.5), presumably because of the known association of twinning with maternal age.¹⁸ There was an extraordinary and unaccountable excess of males in Group RH-H sibs (sex ratio, 2.1). A similar excess of males in the probands (sex ratio, 2.6) is consistent with the known excess of males in the hospital patient population.¹⁹

Symptoms

Although the data suggest that the frequency of allergic symptoms is higher in the near relatives of ragweed hay fever probands than in control relatives, the differences are not consistent—for example, the difference between control mothers and RH-H mothers as regards ragweed hay fever symptoms is actually in the direction opposite to expectation. In view of the well-known unreliability of even the most carefully taken histories of allergies, we do not consider these data trustworthy, and will say no more about them.

Skin tests

The results of the skin tests are presented in Table I.

Tests with egg albumen

There was no evidence of an increase in positive skin tests for egg albumen among near relatives of ragweed hay fever probands; the frequency was very low in all three groups.

Table 1. *Skin tests in mothers, fathers, and sibs of probands*

	Group RH-H		Group RH-P		Group C	
	No.	% positive	No.	% positive	No.	% positive
<i>Ragweed pollen</i>						
Mothers	50	24.0	12	50.0*	50	16.0
Fathers	50	28.0	12	66.6*	50	18.0
Sibs	82	28.0*	16	37.5*	124	6.5
<i>Grass pollen</i>						
Mothers	50	12.0	12	33.3*	50	6.0
Fathers	50	10.0	12	58.3*	50	10.0
Sibs	82	14.6*	16	37.5	124	4.8
<i>Egg Albumen</i>						
Mothers	50	2.0	12	0	50	2.0
Fathers	50	2.0	12	0	50	6.0
Sibs	82	1.2	16	0	124	1.6

*Differs from the control value at the 1 per cent level of significance.

Tests with ragweed pollen extract

The most striking difference was the high frequency of positive reactions in the parents and sibs of Group RH-P (ragweed hay fever probands from a physician's private practice). Even with the small number concerned, the figures are significantly different from those of the control subjects ($p < 0.01$). Furthermore, the fathers and combined parents differ significantly from those of Group RH-H (ragweed hay fever probands from the hospital). We are unable to explain the difference between the values for the private practice and those for the allergy clinic group. An effort was made to select probands without regard for their family history, but perhaps the nature of a private practice makes it more likely than a hospital clinic population to include familial cases. For instance, a parent already in the habit may bring a child to the allergist for testing because of very mild symptoms; symptoms not severe enough to require bringing the child to the clinic. Other differences of race, social class, and so forth, may also be relevant. We shall, therefore, limit further considerations to Groups RH-H and C.

In the Group RH-H the proportion of sibs with positive tests for ragweed (28.0 per cent) is significantly higher than that for the control sibs (6.5 per cent), thus demonstrating a familial tendency. The frequency of positive skin tests in the sibs of probands who have asthma as well as hay fever (32.5 per cent) is not significantly higher than it is in the sibs of probands without asthma (Table III). The values for the mothers and fathers in the ragweed group (24.0 and 28.0 per cent) are essentially the same as those for the sibs. However, the value for the control parents (17.0 per cent) is significantly higher ($p < 0.02$) than that for the control sibs (6.5 per cent), suggesting that the probability of becoming sensitized increases with age. Classification of relatives by age group (Table II) suggests that there is little change in the response of sibs between ages 5 and 15, a peak response in the parents at about 30 to 39 years, and a decreasing frequency in older individuals. The tendency

Table II. *Parents and sibs, classified by age group, with at least one positive skin test*

Age range	Group RH-II		Group C	
	No.	% positive	No.	% positive
5-9	33	30.3	43	7.0
10-14	26	34.6	52	5.8
15-19	18	33.3	25	16.0
20-24	3	—	3	—
25-29	4	—	2	—
30-34	12	41.7	15	26.7
35-39	21	42.9	27	25.9
40-44	31	19.4	24	12.5
45-49	23	21.7	26	19.2
50 and over	11	18.2	7	—

In age range 25-29, 2 of the 4 in Group RH-H and 1 of the 2 in Group C were parents. Otherwise, all were sibs in the age range 5-24, and all were parents in the age range 30 and over.

Table III. *Frequency of positive skin tests to ragweed pollen extract in sibs of RH-H and control probands in various categories*

	No.	% positive
All sibs of RH-H probands	82	28.0
Sibs of probands with asthma and ragweed hay fever	43	32.5
Sibs neither of whose parents has positive skin test	49	14.3
Sibs at least one of whose parents has positive skin test	33	48.5
Control sibs	126	4.8

to a decrease in frequency of positive skin tests to allergens with increasing age has been recognized for many years,²⁰ although opinions differ as to its significance.²¹

The proportion of positive ragweed skin tests is higher in the parents of the ragweed group (26.0 per cent) than in the control parents (17.0 per cent), but not significantly so. More data are needed to decide whether the difference is real. Unfortunately, there are no data for adult sibs of RH-H probands. Thus, we cannot distinguish between two possibilities: (1) As the sibs in the ragweed hay fever group get older, the proportion of positive skin tests may increase to a value higher than that of the parents, suggesting recessive inheritance. (2) As the sibs get older, the frequency of positive skin tests may remain the same as in the parents, as in dominant or multifactorial inheritance. The familial tendency would then represent simply the capacity to become sensitized relatively early in life.

Further evidence on the familial nature of the ability to develop skin-sensitizing antibodies is found within the families of Group RH-H. When neither parent has a positive skin test the proportion of probands' sibs with positive ragweed skin tests is only 14.3 per cent (7/49), as compared to 48.5

Table IV. *Positive skin tests to ragweed and grass pollen in mothers, fathers, and sibs of probands*

	<i>Group RH-H</i>		<i>Group C</i>	
	<i>No.</i>	<i>% positive</i>	<i>No.</i>	<i>% positive</i>
<i>Ragweed pollen</i>				
Mothers	50	14.0	50	10.0
Fathers	50	18.0	50	8.0
Sibs	82	15.9	124	3.2
<i>Grass pollen</i>				
Mothers	50	2.0	50	—
Fathers	50	—	50	—
Sibs	82	2.4	124	1.6
<i>Ragweed and grass pollen</i>				
Mothers	50	10.0	50	6.0
Fathers	50	10.0	50	10.0
Sibs	82	12.2	124	3.2

Table V. *Positive skin tests to ragweed and grass in sibs of probands with ragweed hay fever, with and without positive skin tests to grass*

<i>Proband</i>	<i>Positive skin tests of sibs</i>				<i>% sibs grass positive</i>	<i>Total</i>
	<i>Ragweed only</i>	<i>Grass only</i>	<i>Both</i>	<i>Neither</i>		
Grass positive	5	3	8	37	20.8	53
Grass negative	6	0	3	20	10.3	29

per cent when at least one parent is affected (16/33) (Table III). This difference, which is highly significant ($p < 0.001$), supports the conclusion that the capacity to develop ragweed skin sensitization is familial, and strongly suggests that the intrafamily correlation has a genetic basis.

Tests with grass pollen extract

Table IV shows the number of parents and sibs in Group RH-H and Group C that reacted to skin tests with ragweed pollen, grass pollen, or both. Of the 79 individuals with positive tests, only 6.3 per cent were positive to grass alone, 51.1 per cent were positive to ragweed alone, and 40.5 per cent were positive to both. This may simply reflect the fact that ragweed pollen is a more potent allergen than grass pollen. However, 66 per cent of the probands in Group RH-H themselves had positive skin tests to grass pollen.

Table V shows that when the proband has a positive skin test for grass pollen (as well as for ragweed), the proportion of sibs positive for grass (20.8 per cent) is significantly higher ($p < 0.02$) than the proportion in the control subjects (4.8 per cent), and also higher than the proportion of grass positive reactions in the sibs of the grass negative ragweed hay fever probands (10.3 per cent), though not significantly so. The most likely interpretation is that the

familial predisposition to become sensitized to ragweed pollen also predisposes the individual to become sensitized to grass pollen, but more data are needed to clarify this point.

CONCLUSIONS

The observations presented in this study permit the following tentative conclusions:

1. The frequency of positive skin tests to ragweed pollen extract is higher in the sibs of children with positive skin tests and symptoms of ragweed hay fever (28.0 per cent) than it is in sibs of children with negative skin tests and no ragweed fever (4.8 per cent).

2. The frequency of positive skin tests to ragweed pollen extract is higher in the sibs of children with positive skin tests and symptoms of ragweed hay fever when at least one parent has a positive skin test (48.5 per cent) than it is when neither parent has a positive skin test (14.3 per cent). These findings (Table III) clearly demonstrate that the ability to form skin-sensitizing antibodies to ragweed pollen is familial and probably genetically determined.

3. The ability to develop a positive skin test to grass pollen is also familial.

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