

Skin tests and blood leukocyte histamine release of patients with allergies to laboratory animals

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Skin tests and in vitro histamine-release reactions were used to evaluate 130 patients observed in an employee allergy clinic at a biomedical research facility. The allergens used included extracts from pollens (ragweed, grasses, trees, weeds), molds, mixed feathers, house dust, cat, dog, mouse, rat, rabbit, guinea pig, and hamster. Of all patients, 66% complained of allergic symptoms on laboratory animal exposure, although only 52% worked directly with animals. Among patients with symptoms, 91% were positive by skin test to at least one laboratory animal, and 46% had asthma. The median length of exposure to laboratory animals before onset of symptoms was 2.8 yr with 60% of the patients developing their symptoms within 3 yr. Among patients who had allergic symptoms before exposure to laboratory animals, 79% were skin test positive to laboratory animals when they were evaluated in this study. There was a close association found between the skin test and histamine-release results with the laboratory animal allergens: 91% of the 4+ skin reactors had leukocytes positive for histamine release versus 5% of the leukocyte donors with <1+ skin reactions. A close relationship in positive reactions to different laboratory animal allergens was also found. For example, individuals positive to mouse were positive also to rat (95%), rabbit (79%), guinea pig (83%), and hamster (88%). Patients who reacted to laboratory animals also reacted to some extent to house dust and cat and dog allergens, and about one half of the animal-allergic individuals reacted to pollens. Although nonpollen-allergic individuals can develop sensitivity to laboratory animals, the group at higher risk are allergic individuals, especially those sensitive to house dust, cats, or dogs. (J ALLERGY CLIN IMMUNOL 73:457-465, 1984.)

Allergy to common laboratory animals is an established occupational disease of many laboratory workers.¹⁻⁹ Symptoms usually follow within minutes after exposure to allergen, and they commonly include rhinitis, conjunctivitis, contact sensitivity, and asthma. Patients are frequently sensitive to more than one species of animal; among the most common are rats followed by rabbits, mice, guinea pigs, and hamsters. Individuals with this disorder can be identified by a history of clinical symptoms, positive skin tests, and in vitro tests including RAST or leukocyte-histamine release reactions with allergen from the sus-

pected animals. The mouse allergens appear to include the mouse urinary protein and serum albumin.^{7, 10} Recently a technique has been developed to quantitate the amount of airborne allergens.⁶

In this study skin tests and in vitro IgE-mediated histamine release reactions were compared in a large group of subjects suspected of having allergies to laboratory animals. Statistical correlations between histamine-release reactions to a variety of pollen and animal allergens were also calculated, and conclusions were drawn concerning the frequency of occurrence of positive reactions to different allergens. By use of these data, associations were found between allergic responses to different laboratory animals as well as between responses to these animals and nonlaboratory-related allergens.

MATERIAL AND METHODS

Solutions

A PIPES-buffered (pH 7.4) medium was used containing 120 mM NaCl, 5 mM KCl, 40 mM NaOH, 25 mM PIPES

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Abbreviations used

PIPES ACM: Piperazine-N,N'-bis[2-ethanesulfonic acid] buffered saline containing 120 mM NaCl, 5 mM KCl, 40 mM NaOH, 25 mM PIPES, 2 mM calcium chloride, 0.5 mM magnesium chloride, and human serum albumin 0.3 gm/1

HSA: Human serum albumin

(piperazine-N,N'-bis[2-ethanesulfonic acid]) 0.03% human serum albumin, 2 mM Ca^{2+} , and 0.5 mM Mg^{2+} (PIPES ACM).

Allergens

Allergenic extracts were purchased as aqueous solutions in 50% glycerine from Hollister-Stier, Spokane, Wash. Mixed ragweed pollen contained equal amounts of tall and short ragweed pollen; mixed grasses contained equal amounts of timothy, orchard, June, red top, and sweet vernal pollen; mixed trees consisted of ash, beech, birch, elm, hickory, maple, oak, and poplar pollens. The mixed molds consisted of equal amounts of *Alternaria*, *Hormodendrum* (four varieties), *Aspergillus*, and two varieties of *Penicillium*. The mixed weeds were from lambs quarters, cocklebur, marsh elder, and English plantain pollens. The mixed-feathers allergen contained equal amounts of chicken, duck, and goose feathers. Cat dander, dog dander, and house dust were also used. The mixed ragweed, grasses, trees, molds, and weeds were obtained at a concentration of 40,000 PNU/ml; the mixed feathers, the cat and dog dander, and house dust were at a concentration of 20,000 PNU/ml. All the allergens were diluted in sterile commercial diluent, (NaCl, 0.5%; potassium phosphate monobasic, 0.036%; sodium phosphate dibasic, 0.143%; and phenol, 0.4%) to a concentration of 10,000 PNU/ml. HSA was added to a final concentration of 0.03%, and the allergens were kept refrigerated (4° C). For histamine-release experiments, extracts were dialyzed against phosphate-buffered saline (NaCl 150 mM, PO_4 20 mM, pH 7.4) to remove substances that might interfere with the fluorometric assay.

Clinical evaluation

Skin tests were performed with the same lot of allergens used for the in vitro studies but were diluted in commercial diluent (without HSA). For skin tests, 0.02 ml of allergen at 100 PNU/ml was injected at each site on the upper arm, and the reactions were read at 15 min. Skin test grading was based on measurements of the wheal by use of the following criteria: negative, site no different from a diluent control; 1+, <5 mm wheal; 2+, 5 to 10 mm; 3+, 10 to 15 mm without pseudopods; 4+, >15 mm wheal with or without pseudopods or >10 mm wheal with pseudopods.

Histamine release from whole blood

Venous blood (25 ml) was drawn before skin testing into a plastic syringe and transferred into a 30 by 115 mm plastic

TABLE I. Characteristics of patient population

Characteristic*	% Of total patients†
Allergic symptoms on laboratory animal exposure	66
% of this group with asthma (46)	
% positive skin test to laboratory animals (91)	
Allergic symptoms before working in a laboratory environment	43
Allergic symptoms, work and nonwork related:	
Both work and nonwork related	45
Only from work environment	22
Only from nonwork environment	24
Skin test positive ($\geq 2+$) to at least one laboratory-animal allergen	68
Skin test positive ($\geq 2+$) to at least one pollen allergen	62
Relationship of family history of any allergy vs. skin test positivity with laboratory animals:	
Family history Lab animal skin test	
+ +	50
+ -	19
- +	18
- -	13
Relationship of family history of any allergy vs. skin test positivity with pollen allergens:	
Family history Pollen skin test	
+ +	47
+ -	22
- +	15
- -	16

*Allergic symptoms refer to hay fever and asthma only. Positive skin test $>2+$. Laboratory animal allergens were mouse, rat, rabbit, guinea pig, and hamster. Pollen allergens were ragweed, grasses, trees, molds, and weeds.

†130 patients were studied.

tube containing 0.7 ml of 1000 U/ml heparin. The blood was kept at 4° C until used (usually within 4 hr after collection). Just before the blood was used, 5 ml of PIPES-ACM medium was added. Allergens (2, 20, and 200 PNU/ml) were combined with an equal volume (0.5 ml) of diluted, heparinized blood, and mixtures were incubated at 37° C for 60 min to release histamine as described previously.¹¹ Histamine was assayed by use of an automated fluorometric method with dialysis of the sample.^{12, 13} Calculations were as described previously.¹³

Statistical methods

Means and standard deviations were calculated by use of a Hewlett-Packard 65 calculator (Hewlett-Packard, Palo Alto, Calif.). Correlation coefficients, percentages, gamma values, chi square and chi square significance were determined from data encoded on punched cards by use of the

SPSS statistical package for computers.¹⁴ For each pair of allergens a 2 by 2 contingency table (cross-tabulation) compared the skin test results with the two allergens ($\geq 2+$). A corrected chi square and the gamma values were calculated from these tables. The absolute gamma has a numerical value between 0 and 1.0; the higher the value the stronger the relationship between the two pairs. Thus the gamma value is the probability of a positive skin test with the second allergen when the first skin test is positive.

RESULTS

Description of patient population

The patients in this study were 130 adults observed in the Allergy Clinic of the Occupational Health Service at the National Institutes of Health. Their mean age was 32.9 yr (SD $\pm$ 8.5), and the ratio of male patients to female patients studied was 2:1. Most had reported symptoms after exposure to laboratory animals. The mean interval between their first exposure to laboratory animals and evaluation in this study was 6.1 yr (SD $\pm$ 5.1). Of the 130 subjects, 66% claimed hay fever or asthma on laboratory-animal exposure, and 69% had symptoms from nonwork-related environment exposure (Table I). Forty-five percent of all patients had both work- and nonwork-related symptoms with 22% only work-related and 24% only nonwork-related complaints. Among the patients with symptoms from laboratory-animal exposure, about half complained of asthma (46%), and 91% were positive by skin test ($\geq 2+$) to at least one laboratory-animal allergen (Table I). All patients with asthmatic symptoms from laboratory animals also had hay fever-type symptoms. A family history of allergy was equally present among the pollen- or laboratory animal-reacting patients. Among the 130 patients, 43% had a history of allergic symptoms before exposure to laboratory animals; 79% of these patients were positive by skin tests ($\geq 2+$) to laboratory-animal allergens when they were evaluated for this study. Among the patients without previous allergic symptoms, 28% developed symptoms after 1 yr of laboratory-animal exposure (Fig. 1). About 60% of patients developed symptoms within the first 3 yr after exposure to laboratory animals. However, the mean length of time between exposure to laboratory animals before subsequent onset of symptoms was 4.6 yr (SD $\pm$ 4.3) with a median of 2.8 yr.

Comparison of skin test and in vitro histamine-release reactions

Individual histamine-release results with three concentrations of laboratory-animal dander allergen were compared with the intradermal skin test reactivity (Figs. 2 to 6). In all cases the greatest histamine release occurred with use of antigen concentrations of

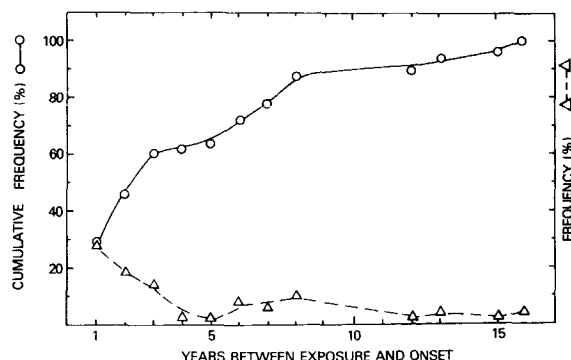


FIG. 1. Time between first exposure to laboratory animals and first appearance of hay fever or asthmatic symptoms caused by animals. Data are based on 50 subjects who had no allergic history or symptoms before exposure to laboratory animals.

10 or 100 PNU/ml, and in all groups the greatest histamine release was associated with maximum skin test reactivity. In general, when the skin test was 1+ or less, the leukocytes did not release histamine when they were incubated with the same allergen. For example, in the group with negative (0 to 1+) skin tests with mouse allergens, there were only two patients who had more than 10% histamine release (Fig. 2). With rat allergen there were no histamine-release positive results from the donors with negative skin tests (Fig. 3), and with guinea pig or rabbit allergen the histamine release was positive in only 3% to 8% of the tests (Figs. 4 and 5). However, with the hamster allergen, histamine release correlated less well with the skin test, that is, among the 0 to 1+ skin reactions, the leukocytes from eight of 70 donors released histamine to a significant degree at 100 PNU (Fig. 6.)

All the individuals with strongly positive (4+) skin reactions to mouse and rabbit allergens were also positive by histamine release (Figs. 2 and 4); 92% of the leukocyte donors with the 4+ rat skin reactions were histamine-release positive (Fig. 3); 79% of the guinea pig 4+ reactors were positive by histamine release (Fig. 5); 89% of those giving 4+ reactions with hamster allergen gave histamine release of 40% or greater (Fig. 6). However, the results demonstrate that with these allergens there were a number of patients who had sizeable skin test reactions but whose basophils were not triggered by the same allergen for histamine release. For example, among the 21 subjects with 3+ skin reactions to rat allergen, the basophils from five failed to release histamine with allergen concentrations as high as 100 PNU/ml (Fig. 3).

The association of the skin test with histamine release for animal as well as environmental allergens is

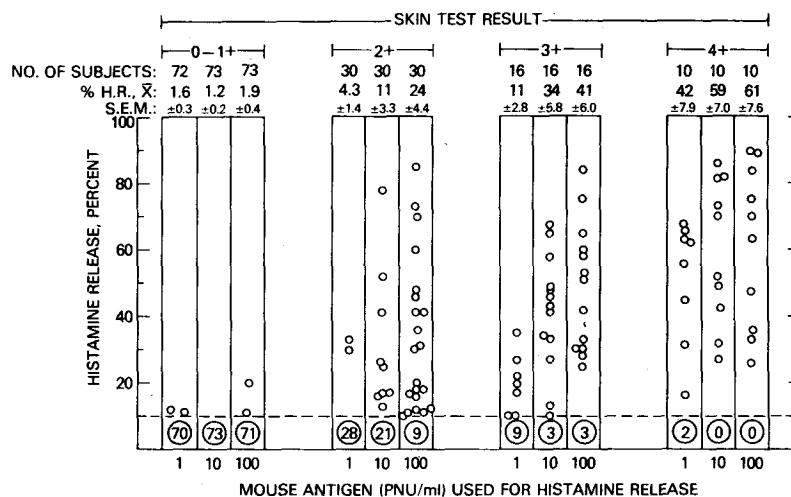


FIG. 2. Mouse-dander histamine release and skin test data. Intradermal skin tests were performed with 100 PNU/ml. Histamine release with whole blood was tested with 1, 10, and 100 PNU/ml. Number appearing in the large circles refer to number of subjects giving less than 10% histamine release. Each small circle is histamine-release value for cells of one individual at indicated allergen concentration. Example: in first column 72 subjects had skin test result of 1+ or less, and of these, 70 subjects gave less than 10% histamine release. Mean histamine release for this group was $1.6 \pm 0.3\%$.

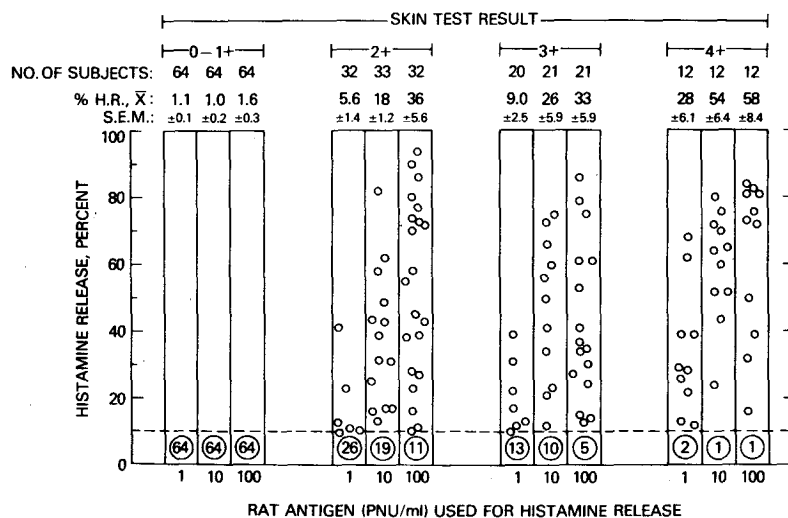


FIG. 3. Rat-dander histamine release and skin test results. Conditions are identical to those described in Fig. 2.

given in Table II. Subjects with strongly positive skin tests also gave positive results by histamine-release determinations. For example, when the skin test with laboratory-animal allergen was 3+, positive leukocyte histamine release occurred in 75% of the cases, whereas when the skin test was 4+, the leukocyte histamine release was positive in 91% of those tested. Similar results were obtained with the pollen and other environmental allergens. The washed leukocytes of some of these strongly skin test positive but whole blood negative patients also failed to release

histamine. Therefore the lack of histamine release from whole blood is not likely to be due to IgG antibodies. When skin tests were 1+ or less, positive histamine release occurred in only 6% or fewer of the cases.

Significance of positive skin test reactions to different antigens

Among the 130 subjects studied, significant associations were found among the skin tests with different laboratory-animal allergens (Table III). For each

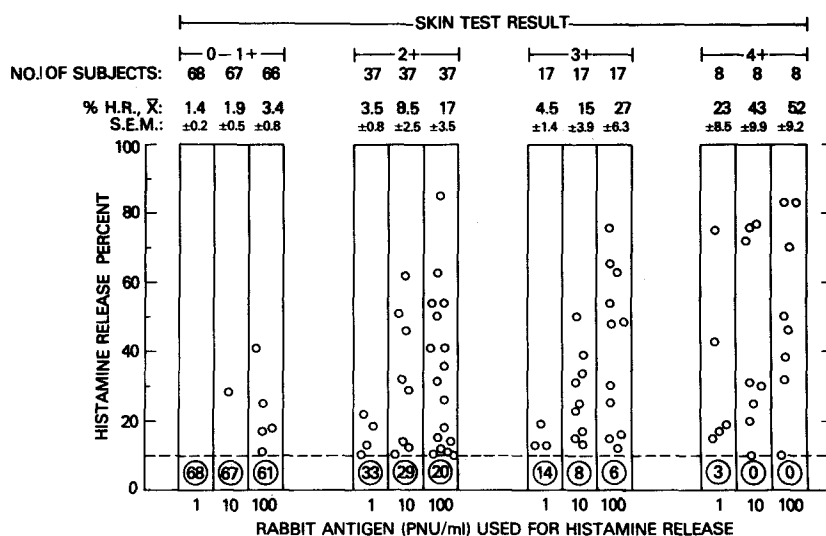


FIG. 4. Rabbit-dander histamine release and skin test results. Conditions are identical to those described in Fig. 2.

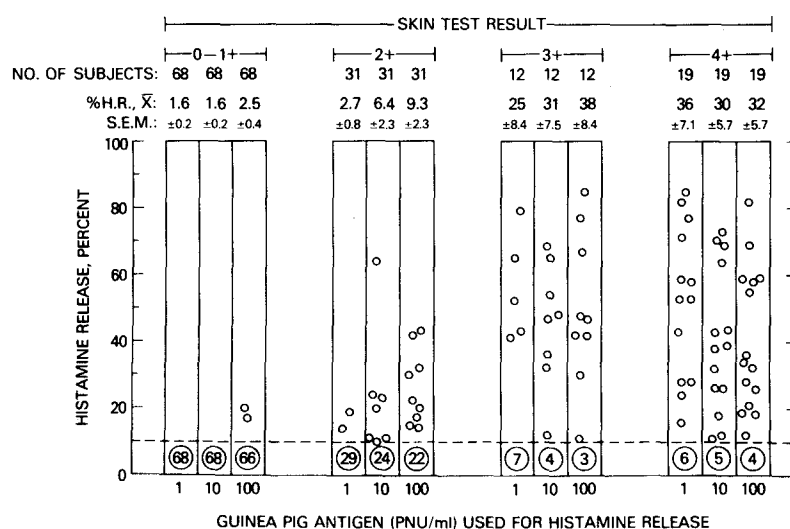


FIG. 5. Guinea pig-dander histamine release and skin test results. Conditions are identical to those described in Fig. 2.

pair of allergens, a 2 by 2 contingency table (cross-tabulation) was prepared to compare the positive and negative skin tests. Although only 43% of all subjects were positive to mouse allergens, 79% to 95% ($\gamma = 0.85$ to 0.98) of these were also positive to rat, rabbit, guinea pig, or hamster allergens. Similar associations were noted with the patients reactive with the other laboratory animal allergens. The chi-square values in all cases were highly significant indicating an association between reactions to laboratory-animal allergens. This is quite different when reactivity to the laboratory animal allergens is compared with reactivity to pollens and other environmental allergens

(Table IV). For example, among all the mouse-reactive individual, only 54% ($\gamma = 0.19$) reacted also to ragweed, and 39% to 55% ($\gamma = 0.04$ to 0.24) reacted to trees, grasses, or weeds. This value is not significantly different from the 38% to 49% positive reactions to ragweed, trees, grasses, or weeds in the entire group of patients (Table IV). Therefore there is no statistical association between reactivity to pollens and laboratory-animal allergens. However, 39% to 55% of the laboratory animals-reactive patients are skin test positive to pollens (data not shown), and this is higher than would be seen in the general population. In contrast to results with pollens, there is some

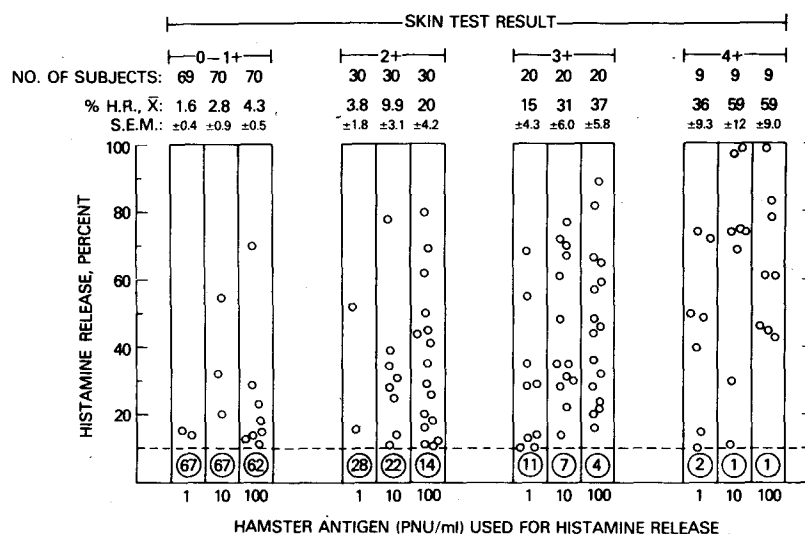


FIG. 6. Hamster-dander histamine release and skin test results. Conditions are identical to those described in Fig. 2.

TABLE II. Relationship of skin test to histamine-release results (130 patients)

Skin test response*	Histamine release†								
	Laboratory animal dander‡			Pollens§			Other environmental allergens		
	No. of tests	No. positive¶	% Of tests positive	No. of tests	No. positive	% Of tests positive	No. of tests	No. positive	% Of tests positive
≤1+	343	17	5	380	22	6	396	18	5
2+	162	82	51	126	55	44	163	80	49
3+	87	65	75	71	56	79	66	57	86
4+	58	53	91	66	50	76	20	18	90

*Intradermal skin test with 100 PNU/ml.

†Histamine release from whole blood was tested with 1, 10, and 100 PNU/ml of each allergen.

‡Mouse, rat, rabbit, guinea pig, and hamster dander were tested separately; data were pooled.

§Ragweed, trees, grasses, and weeds were tested separately; data were pooled.

||Molds, mixed feathers, house dust, and cat and dog dander were tested separately; data were pooled.

¶Histamine release $\geq 10\%$ at 100 PNU/ml.

association between the laboratory-animal reactivity and positive skin reactions to dust, cat dander, and dog dander (Table V). The χ^2 tests are generally less significant than those seen in Table III when laboratory-animal reactivities are compared to each other. Interestingly, in this group the reactivity to dust is associated with reactivity to both pollens and animals (Table V). Reactivity to cat allergen was significantly associated with positive skin tests to dog antigen, that is, 79% of those who were reactive to dog antigen also were reactive to cat allergen. Similarly, 94% ($\gamma = 0.85$) of the cat allergen-positive subjects reacted also to dust. The widespread reactivity with dust allergen could be due to the presence of multiple antigens in the dust preparation. Therefore those patients who react to one laboratory animal tend to be

also positive with other laboratory-animal allergens. These individuals are also more reactive to cat, dog, and dust allergen.

The skin test results of the 130 patients were also compared to detect relationships among their responses to pollens (Table VI). Although only 48% of all patients were positive to ragweed, 65% ($\gamma = 0.84$), 63% ($\gamma = 0.81$), and 81% ($\gamma = 0.89$) of these also reacted to grasses, trees, or weeds (χ^2 very significant). Similar associations were observed with reactivity to the different tree, grass, and weed pollens.

DISCUSSION

Among the 130 subjects studied, 66% complained of hay fever or asthmatic symptoms after laboratory-animal exposure. Most of these patients (91%) were

TABLE III. Comparison of positive skin tests with different laboratory animal allergens*

Second allergen	Positive with first allergen			
	Mouse	Rat	Rabbit	Guinea pig
	43	50	47	47
Gamma values and χ^2 significance†				
Rat	0.98***‡			
Rabbit	0.85***	0.78***		
Guinea pig)	0.89***	0.78***	0.83***	
Hamster	0.96***	0.91***	0.81***	0.92***

*Intradermal skin tests of 130 patients were analyzed. Positive skin test = $\geq 2+$.

†Gamma and χ^2 significance values were calculated for each pair of allergens from a 2×2 contingency table. Gamma is defined as the probability of a positive skin test with the second allergen when the first skin test is positive.

‡ χ^2 significance at: * $p \leq 0.01$; ** $p \leq 0.001$; *** $p \leq 0.0001$.

positive by skin tests to laboratory-animal allergens, and two thirds also had symptoms caused by non-work-related exposure to pollens or animals. Therefore multiple allergies are a frequent problem among these subjects.

The length of exposure to laboratory animals is associated with the development of allergic symptoms (Fig. 1). In the subgroup of patients who had no other allergies, the mean exposure to laboratory animals before onset of symptoms was 4.6 yr ($\bar{x} 4.6 \pm 0.6$, range 1 to 15 yr). More than half the patients developed symptoms within 3 yr of exposure to laboratory animals with 28% of the symptoms occurring during the first year. In other studies the average length of exposure before development of symptoms has been reported to be 2 to 4 yr.^{2, 3} The information for Fig. 1 was obtained retrospectively, and only data from those subjects without previous allergies were used for the calculations. These patients might form a subgroup who develop allergies at a different rate than the overall group, and therefore the results should be interpreted cautiously.

There are a number of inherent problems in the study of a population observed in a clinic. The subjects are self-referred and may therefore be representative of a group with more serious problems. The 46% incidence of asthmatic symptoms in the animal-allergic patients in this study is much higher than the rate reported by other investigators. Thus the patients with more severe symptoms might be those seeking medical help. The information on exposure is historical and relies on the subjects' ability to recall. It is also difficult to quantitate the level of exposure to

TABLE IV. Comparison of positive skin tests to laboratory-animal allergens to reactivity with pollens

Second allergen	Positive with first allergen				
	Ragweed	Trees	Grasses	Weeds	Molds
	48	38	38	49	18
Gamma values and χ^2 significance					
Mouse	0.19	0.24	0.05	0.23	0.22
Rat	0.29	0.28	0.09	0.32	0.35
Rabbit	0.02	0.37	0.05	0.26	0.01
Guinea pig	0.08	0.25	0.25	0.20	0.51
Hamster	0.04	0.36	0.23	0.32	0.16

See footnotes of Table III; all values $p > 0.05$.

laboratory animals that tends to be variable, especially in the case of scientists with changing experimental programs.

Allergic reactions of research workers to experimental animals can be a serious occupational health problem. The reported incidence for the occurrence of hypersensitivity to those animals has been variable. Lutsky and Neuman¹ surveyed 39 animal facilities in the United States by questionnaire and found that 15% of the individuals with direct animal contact developed symptoms of laboratory-animal allergy. In another study about 11% of all individuals with animal contact were symptomatic.² In several other studies the frequency of symptoms was 23% to 32% of the exposed population.^{3, 4} Interestingly, some studies have suggested that the problem occurs more frequently among those individuals exposed intermittently (i.e., scientists) than those exposed on a continuous basis (e.g., animal handlers).²

Three different allergen concentrations were used in the present study for in vitro histamine release (1, 10, and 100 PNU/ml). The 1 PNU/ml allergen dose gave a lower percentage of positives and less histamine release than the 10 or 100 PNU/ml concentrations. Thus testing with 1 PNU/ml appears to be unnecessary. The histamine-release results with 10 and 100 PNU were similar. With the cells of some patients, the histamine release was greater with 10 PNU/ml than with the 100 PNU/ml concentration. However, some allergens at 100 PNU/ml had a higher frequency of positive histamine release ($\geq 10\%$) but with negative skin tests (0 to 1+). Because of the possibility of inhibition of histamine release by excess antigen, it was deemed worthwhile to use both 10 and 100 PNU concentrations for the day-to-day testing.

There is close correlation between the skin test and

TABLE V. Comparison of positive skin tests to feathers, dust, and cat and dog allergens with all other allergens tested

Second allergen	Positive with first allergen			
	Feathers	Dust	Cat	Dog
	% Of all patients tested			
	33	70	38	33
Gamma values and χ^2 significance				
Ragweed	0.23	0.48	0.16	0.09
Trees	0.26	0.67**	0.36	0.45
Grasses	0.32	0.67**	0.36	0.19
Weeds	0.21	0.72***	0.55*	0.46
Molds	0.36	0.40	0.43	0.61*
Feathers		0.74**	0.45	0.58*
Dust	0.74**		0.85***	0.59*
Cat	0.45	0.85***		0.89***
Dog	0.58*	0.59*	0.89***	
Mouse	0.12	0.63*	0.58**	0.54*
Rat	0.11	0.33	0.51*	0.54*
Rabbit	0.40	0.75***	0.63**	0.56*
Guinea pig	0.14	0.64**	0.43	0.32
Hamster	0.02	0.72***	0.67***	0.54*

See footnotes of Table III.

histamine-release results with these laboratory-animal allergens. When the skin test was strongly positive (4+), 91% of the histamine-release results were also positive. With 3+ skin reactions this dropped to 75%, and 51% were histamine positive when the skin tests were 2+ (Table II). Therefore the skin test detected more positives than did leukocyte-histamine release. There were a number of patients with strongly positive skin tests, convincing histories of laboratory-animal allergy, but with negative leukocyte histamine release with use of both whole blood and washed leukocytes. Similar observations have been made in previous studies with other allergens, and possible reasons for this phenomenon have been suggested.¹³

In the population studied, the incidence of positive skin tests to different allergens varied between 18% and 70%. There were strong associations among positive skin reactions to different laboratory-animal allergens (Table III). For example, 95% ($\gamma = 0.98$) of those who were positive to mouse were also positive to rat allergen. A possible explanation could be the presence of contaminants in the allergen preparations. This appears unlikely because multiple cross-reactivities were observed with different lots of allergens. Another possibility is the presence of cross-reactive allergens in the different preparations. Previously, it had been observed that mouse and rat albumin have such cross-reactive determinants.^{7, 15, 16} A third expla-

TABLE VI. Comparison of positive skin tests with different pollen and mold allergens

Second allergen	Positive with first allergen			
	Ragweed	Trees	Grasses	Weeds
	% Of all patients tested			
	48	38	38	49
Gamma values and χ^2 significance				
Trees	0.84***			
Grasses	0.81***	0.84***		
Weeds	0.89***	0.89***	0.80***	
Molds	0.59	0.43	0.24	0.66*

See footnotes of Table III.

nation could be the increased responsiveness, probably on a genetic basis, of the same allergic individual to different laboratory-animal allergens. It is in fact rare for subjects to be exposed to only one animal species. Therefore patients who react to one laboratory animal tend to react with other animal allergens. Interestingly, only about half the number of the animal-allergic individuals react to pollens (Table IV). This is higher than the percentage of the general population reactive to pollens. All subjects are exposed to pollens; therefore the lack of reactivity to these environmental allergens by half of the subjects is significant. Thus there is a group of individuals who do not have pollen allergy but who are at risk for developing laboratory-animal allergy. It has been suggested that persons who have allergies should not work with laboratory animals; this study indicates that this would not eliminate the problem. However, allergic individuals are clearly at greater risk in developing laboratory-animal allergy. In contrast to the above results, there were relationships observed between reactivity to laboratory animals and positive reactions to dust, cat, or dog allergens (Table V). Thus genetic susceptibility for sensitivity to laboratory and domestic animals appears to be similar.

In summary, in vitro histamine release with laboratory-animal allergens is associated with skin test reactivity and can be a valuable research tool for studies of this allergic problem. Those patients who react to one laboratory animal also tend to be positive to other animals. Further studies to define the incidence of this problem are clearly indicated.

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