

Allergy to murine antigens in a biological research institute

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Symptomatic and immunologic responses to allergens from laboratory mice were studied in a research institute. Subjects who had been exposed to mice and 50 unexposed subjects were studied by questionnaire and by prick tests with seven prevalent aeroallergens and allergens from mouse urine and pelts. Of the 121 exposed subjects, 39 (32.2%) had respiratory, ocular, or cutaneous symptoms after exposure to mice; occurrence of these symptoms correlated with positive skin tests to purified mouse urinary proteins (MUP) and pelt allergens from CBA/H mice. Serum levels of IgG antibodies correlated with the frequency of mouse exposure. In subjects with seasonal allergic rhinitis, nasal symptoms from exposure to mice, positive prick tests to MUP, and IgE antibodies to MUP were significantly more prevalent. The possibility of genetic influences on susceptibility to mouse allergy were also suggested by a negative association between the incidence of HLA-DRW6 and positive prick-test responses to urinary proteins from C57BL and BALB/c mice among the 54 subjects who were exposed to mice and tested for DR locus antigens ($p = 0.05$). However, no significant differences in any of the loci studied could be shown in subjects with and without nasal symptoms from exposure to mice. (J ALLERGY CLIN IMMUNOL 68:310, 1981.)

Allergic symptoms after exposure to rodents is a frequent problem in biological laboratories and, for the more severely affected individuals who are unable to avoid allergen exposure, a change of occupation may be needed.¹ Allergens from mice have been characterized by several investigators,²⁻⁴ but there are few published studies of the incidence of allergic symptoms from mouse allergens among laboratory workers.^{1, 5} Aside from practical considerations, investigation of the development of hyperreactivity to allergens from mice also provides an opportunity to study the determinants of an immune response to an aeroallergen not previously encountered in significant amounts, thereby helping to elucidate the interaction between environmental factors and genetic susceptibility in the etiology of allergic disease.

This report is of a survey of the majority of the staff members of the WEHI, a research center in which almost all of the experimental animals used are mice. The purpose of this study was to identify allergens important in mouse laboratories and to discover whether allergy to mice was determined mainly by the extent and duration of exposure to mouse allergens, or whether particular individuals were susceptible to the development of mouse allergy by virtue of their atopic status and by virtue of genetic factors that demonstrate association with particular HLA alleles.

MATERIALS AND METHODS

Subjects

The staff at WEHI during the study numbered 208, of whom 162, together with nine staff members and students from the adjacent hospital, participated with informed consent. For 69 of the subjects, criteria for employment as animal technicians and animal attendants had included a negative history of allergic rhinitis or asthma requiring medication or of any specific allergies (Table I). However, they were not examined for signs of rhinitis or asthma. The subjects comprised 71 men and 100 women; 56% were younger than 30 yr and 25% were older than 45 yr. They had worked at WEHI for periods ranging between 3 mo and 41 yr (median 3.0 yr). Frequency of exposure to mice among the 121 exposed subjects is shown in Table I. Animal technicians and animal attendants spent the longest pe-

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Abbreviations used

BALB/c, CBA/H, C57BL:	Inbred strains of mice
MUP:	Major urinary protein complex of mice
P4:	Low molecular weight allergen from CBA/H mouse pelt
WEHI:	Walter and Eliza Hall Institute
RAST:	Radioallergosorbent test
PRIST:	Paper radioimmunosorbent test

riods in mouse rooms, as compared with most laboratory technicians and scientific staff members. However, during their first year, all laboratory technicians spent at least 2 mo in animal rooms, where they had daily exposure to mice. Among the workers exposed to mice, a small number were also exposed to other laboratory animals. Although allergic symptoms were sometimes attributed to exposure to rats and rabbits, the major allergic problems recognized by the workers were associated with exposure to mice.

Questionnaire

All subjects were questioned for a personal and family history of seasonal rhinitis, asthma, eczema, urticaria, and allergic reactions to foods, insect stings, and drugs. All who were exposed by entering mouse rooms periodically and/or handling mice were questioned for symptoms of rhinitis, conjunctivitis, wheezing, or cough during and immediately after exposure to mice, and for wheal and flare reactions to mouse bites or scratches.

Mouse facilities

A total of 135,000 mice were bred annually in an air-conditioned specific pathogen-free facility for transfer at regular intervals to an eight-floor main building, where most of the subjects worked. All mice were held in air-conditioned rooms situated on five floors of this building. Air systems in the mouse rooms were maintained at eight to 15 fresh air changes per hour, at a lower pressure than that in corridors and surrounding laboratories. Exhaust air was ducted from the mouse rooms to the outside of the building. All mouse boxes were replaced with steam-sterilized boxes containing new sawdust litter at least once per week. The strains of mice that were most frequently used were CBA/CaHWehi (designated as CBA/H), BALB/cAnBradleyWehi (designated as BALB/c), and C57BL/6JWehi (designated as C57BL).

Preparation of murine antigens

Allergens from mouse urine and pelts were prepared as previously described.¹ In brief, allergenic material was prepared by chromatography of urine collected from groups of six CBA/H, BALB/c, and C57BL male mice to isolate the MUP (mol. wt. 16,500 daltons). Allergens were also pre-

pared by extraction from CBA/H mouse pelts, and after Sephacryl chromatography, the most potent fractions were obtained from the fourth peak, which eluted at K_{av} 0.54 and had components of molecular weights ranging between 14,000 and 59,000 daltons (P4 allergens).

Skin tests

Skin testing was performed by the prick method with purified CBA/H, BALB/c, and C57BL mouse urine, crude CBA/H mouse pelt extract, and purified P4 pelt allergen preparations (1.25 mg/ml in 50% glycerol). Crude pelt extract for skin testing could not be concentrated further because of appearance of insoluble material. Other allergens tested on all subjects were 1:10 w/v extracts of perennial rye, Bermuda grass, plantain, cat and dog dander, and *Alternaria* (Hollister-Stier), and a 5000 PNU/ml extract of *Dermatophagoides pteronyssinus* allergens (Commonwealth Serum Laboratories, Melbourne, Australia). All subjects were tested with each of the five mouse allergen preparations in addition to the other allergens. Any wheal diameter of at least 4 mm (after subtraction of the control glycerol-saline wheal diameter) with a flare was read as positive, and a wheal response of 2 to 3 mm was regarded as borderline.

IgE and IgG antibodies

In the RAST for IgE antibodies to purified CBA/H MUP and P4 allergens, filter paper discs (Whatman No. 114) were activated by a cyanogen bromide method,⁶ and allergens (5 mg protein/ml) in 0.3 ml of buffer were coupled to the discs at 4° C overnight. To each tube was added 50 μ l of radiolabeled anti-IgE antibodies (Pharmacia Diagnostics, Piscataway, N.J.) giving counts from 8 to 10 \times 10⁴/4 min, and the tubes were incubated and washed as described by Ceska et al.⁶ before counting. Serum levels of IgE protein were measured by Phadebas PRIST (Pharmacia). To measure IgG antibodies to CBA/H mouse urine and pelt allergens, purified MUP and P4 allergens were radiolabeled by the chloramine T method^{7, 8} with iodine 125 at a specific activity of 10 μ Ci/ μ g. Specific IgG antibodies were measured in 1:5 dilutions of sera by coprecipitation of antibody-bound radiolabeled allergens with optimal amounts of sheep antiserum to human IgG.⁸⁻¹⁰

HLA phenotyping

Lymphocytes were separated from peripheral blood by the density centrifugation method of Boyum.¹¹ B lymphocyte separation was performed by the rabbit anti-human IgG F(ab')₂ technique previously described.¹²⁻¹⁴ A standard microlymphocytotoxicity test was used for HLA-AB phenotyping of the B cell-depleted lymphocyte population,^{15, 16} and a similar method with prolonged incubation times was performed for HLA-DR phenotyping of B lymphocytes.¹⁷ Tests were carried out for 12 A locus, 18 B locus, and seven DR locus alleles. Seventy subjects who had been exposed to mice were typed for A and B locus antigens, and 54 of these subjects were typed for DR locus antigens. In addition to comparisons between allergic and nonallergic groups of subjects, results from these subjects were compared with

TABLE I. Relationship between occupation and symptoms, mouse exposure, and pre-employment selection of subjects

	Animal technicians and attendants	Laboratory technicians	Scientific staff*	Other staff†	Personnel from other buildings	Total
Total staff numbers	33	59	75	28	13	208
Number of subjects	33	40	58	20	20‡	171
Subjects with symptoms§	12	14	11	2		39
Exposure to mice 5 days/wk	25	15	16	1		57
Exposure to mice 10 days/yr to 4 days/wk	8	21	32	3		64
Unexposed or rarely exposed	0	4	10	16	20	50
Subjects selected before employment	29	32	3	5		69

*Excludes those who had never handled mice.

†Workers including scientific staff in buildings where mice were kept but who either never entered mouse rooms or did so only briefly and rarely.

‡Includes nine subjects from staff of adjacent hospital.

§Subjects who had any symptoms from exposure to mice.

TABLE II. Relationships between prick test responses to CBA/H MUP* and symptoms from exposure to mice

Prick test responses (wheal diameters)	Nasal symptoms		Eye symptoms		Chest symptoms		Wheal from mouse bites or scratches		Any symptoms	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
	4 mm and larger	7	2	4	5	4	5	4	5	8
<4 mm	6	6	4	8	0	12	5	7	7	5
Negative	16	84	6	94	1	99	6	94	24	76
P value (rows 1 and 2 combined)	10 ⁻⁵		10 ⁻⁵		0.003†		10 ⁻⁶		10 ⁻⁵	
χ ²	20.1		17.5				21.7		17.9	

*Correlation also found between skin tests to P4 allergens and either nasal symptoms, eye symptoms, or wheals from bites or scratches (p < 0.001).

†Fisher's exact test.

results from HLA phenotyping of an unselected reference panel of 748 blood donors and other volunteers who, although healthy, had not been screened for allergic disorders. In preliminary testing of the validity of comparisons with the reference panel, there were no significant differences between the incidence of HLA antigens in the whole group of subjects and that in the reference panel, except for HLA-A28, HLA-B15, and HLA-B18, which were increased significantly in the group of 70 subjects. Therefore, the incidence of these three antigens in subgroups of allergic subjects were not compared with that in the reference panel.

Statistical analysis of data

History information from questionnaires and the results of skin tests, antibody studies, and HLA typing were coded and analyzed by a Cyber 175 computer. In cross-tabulations of variables, significances of any differences between

groups were tested by Fisher exact probability testing or by application of Chi-square analysis according to the suggestions of Cochran.¹⁸ Cells in columns and rows of contingency tables were combined as needed to ensure validity of significance testing. HLA data were analyzed by Fisher's exact testing if an expected value in any cell of a table was less than 5.

RESULTS

Symptomatic and immunologic responses to mouse allergens

Thirty-nine of the 121 exposed subjects had symptoms during and immediately after exposure to mice; 16 had multiple symptoms. Twenty-nine subjects had symptoms of rhinitis, 16 had wheal and flare reactions to mouse bites or scratches, 14 had conjunctivitis, and

TABLE III. Relationships between nasal symptoms from exposure to mice and serum antibodies to CBA/H MUP and P4 allergens

Nasal symptoms	MUP RAST		P4 RAST		IgG antibodies to MUP†	
	<2.0%	2.0% and greater*	<2.75%	2.75% and greater*	<10%	10% and greater
Moderate or severe	1	8	1	8	3	6
Mild	15	4	13	6	11	8
None	80	14	76	18	76	18
P value	<0.0001‡		<0.0001		0.0019	
χ^2			21.0		12.5	

*Percent radiolabeled anti-IgE bound.

†Percent radiolabeled CBA/H MUP at 1.5 ng/ml bound by 1:5 dilutions of sera.

‡Fisher's exact test; rows 2 and 3 combined.

5 had wheezing episodes. Slightly less than one third of symptomatic individuals assessed their symptoms as moderate or severe, and the remainder complained only of mild symptoms.

Wheal and flare reactivity after skin testing to at least one of the purified MUP and P4 allergen preparations was seen in 40 subjects, only one of whom had never entered mouse rooms (but worked for many years in the building where mice were kept). The remainder of the subjects with no exposure to laboratory mice in mouse rooms had negative responses to skin testing with murine allergens. Among the 14 subjects with positive responses to tests with P4 pelt allergens, six had borderline or negative responses to crude pelt extract even though this contained components with the molecular weight of mouse serum albumin. No subject with a positive response to crude pelt extract had a negative or borderline response to P4 allergen. Therefore results of tests with P4 allergens instead of crude pelt allergens were used for subsequent analysis. Of the 31 subjects who reacted to purified urine allergens, 18 reacted to urine allergens from all three strains of mice. Highly significant correlations were found between nasal symptoms on exposure to mice and positive skin-test responses to all three of the purified MUP and P4 allergen preparations (Table II). Similar correlations were also found between positive skin-test responses to all of the MUP and P4 preparations and eye symptoms and between mouse allergen skin-test responses and cutaneous reactions to mouse bites or scratches.* Wheezing reactions from exposure to mice also correlated with positive skin-test responses to MUP from the three mouse strains and P4 allergens of CBA/H mouse pelt.

Although some individuals with IgE antibodies specific for MUP and P4 allergens from CBA/H mice had no nasal symptoms from exposure to mice, serum levels of these antibodies were significantly higher in

*Data available as tables on application to M. J. S.

TABLE IV. Relationships between serum levels of IgE antibodies to CBA/H MUP allergen and exposure to mice

Binding in RAST*	Daily exposure	Exposed less often	Unexposed or rarely exposed
<1.5	20	29	35
1.5-2.0	18	20	11
2.0-2.5	4	5	1
>2.5	8	9	0

Column 1 added to column 2 vs column 3: $p = 0.003$, $\chi^2 = 16.2$.

*Percent radiolabeled anti-IgE bound by discs coupled with MUP.

subjects who did have nasal symptoms on exposure to mice (Table III). High levels of IgG antibodies to MUP tended to be more prevalent in those with nasal symptoms from exposure to mice, but correlations between IgG antibodies and nasal symptoms were not as strong as correlations between IgE antibodies and nasal symptoms. There was a significant correlation on a per-subject basis between the incidence of RAST binding with MUP and P4 and positive skin tests with MUP ($p < 0.001$ for all correlations, data not shown).*

Effects of frequent exposure to allergens from mice

In a study of the effect of the extent of exposure to mouse allergens on the development of allergy to mice, it was found that the frequency of exposure to mice in mouse rooms beyond 10 days per year did not significantly influence either the incidence of symptoms of allergy to mice or the incidence of positive skin-test responses to MUP. There was also no correlation between the number of years exposed to mice and the incidence of respiratory symptoms from mice

*Data available as tables on application to M. J. S.

TABLE V. Relationships between IgG antibodies to CBA/H MUP allergen and exposure to mice

Binding*	Numbers of subjects exposed to mice (days per mo)				Number of unexposed or rarely exposed subjects
	Daily	17-20	4-16	<4	
<2	1	4	5	3	14
2-10	2	20	25	21	33
10-20	2	5	3	1	0
>20	9	7	4	1	0

*Percent radiolabeled MUP added at 1.5 ng/ml bound by 1:5 dilutions of sera; rows 1 and 2 vs rows 3 and 4: $p < 0.001$, $\chi^2 = 24.9$.

or incidence of positive prick-test responses to mouse allergens. Although 26 of the 27 subjects with greater than 2% binding in a RAST assay specific for MUP had been exposed to mice, there was no correlation between the frequency of exposure to mice and the level of RAST binding above 2% (Table IV). However, serum levels of IgG antibodies to MUP did correlate with the frequency of exposure to mice, with a greater proportion of the more heavily exposed persons having higher levels of IgG antibodies (Table V). This relationship between frequency of exposure and serum levels of IgG antibodies was also reflected by analysis of groups of workers, among whom the animal technicians had the highest levels of IgG antibodies.

Atopy and symptoms of allergy to mice

Of the 131 subjects exposed to mice, 40 had histories of seasonal rhinitis. There was a statistically significant positive correlation between a history of seasonal allergic rhinitis and nasal symptoms from mice and between seasonal rhinitis and reactions to mouse bites and scratches ($p = 0.002$ and 0.01 , respectively; data not shown). Relationships between a history of seasonal rhinitis and either eye symptoms or chest symptoms on exposure to mice were not statistically significant.

Subjects with a history of seasonal rhinitis also tended to have higher serum levels of IgE antibodies to mouse urinary protein and to purified mouse pelt allergens ($p = 0.0005$ and 0.002 , respectively; data not shown). There was also an association between seasonal rhinitis and positive prick-test responses to purified allergens from CBA/H mouse urine and pelt ($p < 0.002$, data not shown). This was supported by the finding that positive prick-test responses to three pollen allergens important in the area—perennial rye

grass, Bermuda grass, and plantain extracts—each correlated with positive prick-test responses to purified mouse urine allergens. Positive prick-test responses to perennial rye, Bermuda grass, and plantain pollen were all significantly more frequent in subjects with symptoms of rhinitis on exposure to mice (Table VI). Eye symptoms from exposure to mice were also more prevalent in subjects with positive prick-test responses to rye grass, Bermuda grass, or plantain extracts (Table VII). Skin-test responses to purified allergens from both CBA/H mouse urine and CBA/H pelt also correlated with positive skin test responses to rye grass extract. Positive skin-test responses to the pollen allergens and a history of seasonal rhinitis were equivalent in their association with the occurrence of nasal symptoms from exposure to mice, and a combination of positive skin-test responses to pollen allergens and a history of seasonal rhinitis did not show a stronger association with symptoms of allergy to mice.

Symptoms from mice or positive skin tests to mouse allergens did not correlate significantly with a family history of allergic rhinitis, asthma, or eczema or with the albeit infrequent positive skin-test responses to allergens from cat and dog dander, *Alternaria*, or *D. pteronyssinus*.

HLA antigens

HLA-DRW6 occurred significantly less frequently in subjects with positive skin-test responses to BALB/c MUP than in the panel ($p = 0.05$) and occurred insignificantly less frequently in comparison with its incidence in the BALB/c skin test-negative subjects (Table VIII). Similarly, the incidence of HLA-DRW6 was significantly decreased in subjects with positive skin-test responses to C57BL MUP in comparison with the panel ($p < 0.05$) and was insignificantly decreased in comparison with subjects with negative skin-test responses to this protein. HLA-B5 occurred more frequently in subjects with positive skin-test responses to C57BL MUP than in the reference panel ($p < 0.05$) or in the skin test-negative subjects, although the latter difference was not significant. HLA typing did not reveal statistically significant differences between subjects with and without nasal symptoms from exposure to mice in any of the loci studied.

IgE levels

Among the 25 subjects with positive prick-test responses to CBA/H mouse urinary protein, 23 (92%) had total IgE levels of 25 U/ml or greater and 10 (40%) had levels over 200 U/ml, whereas 61% and 18% of the 106 subjects with negative mouse urinary

*Data available as tables on application to M. J. S.

TABLE VI. Incidence of positive skin-test responses to pollen allergens in subjects with nasal symptoms from mouse exposure

Nasal symptoms from mice	Perennial rye wheal diameter		Bermuda grass wheal diameter		Plantain wheal diameter	
	4 mm or larger	<4 mm	4 mm or larger	<4 mm	4 mm or larger	<4 mm
Moderate or severe	6	3	5	4	3	6
None or mild	15	106	3	118	3	118
P value	0.0001		2×10^{-5} *		0.0041 [†]	
χ^2	18.1		—		—	

*Fisher's exact test.

TABLE VII. Relationships between prick-test responses to perennial rye pollen extract and eye symptoms from mouse exposure and prick-test responses to CBA/H MUP and P4 allergens

Wheal response to perennial rye*	Eye symptoms		Wheal response to MUP allergen		Wheal response to P4 allergen	
	Yes	No	4 mm or larger	<4 mm	4 mm or larger	<4 mm
4 mm or larger	6	15	5	15	6	14
<4 mm	8	86	4	97	7	94
P value	0.004		0.001		0.0023	
χ^2	8.26		10.7		9.26	

*Correlations were also found between eye symptoms and responses to Bermuda grass ($\chi^2 = 13.7$) and to plantain ($\chi^2 = 10.1$).

TABLE VIII. Incidence of HLA-B5, HLA-B15, and HLA-DRW6 in subjects with positive prick-test responses to urinary proteins from CBA/H, BALB/c, and C57BL mice

	Prick-test response						Normal panel
	CBA/H		BALB/c		C57BL		
	Positive	Negative	Positive	Negative	Positive	Negative	
HLA-B5	4 (19.1%)	6	4 (21.0%)	6	5 (26.3%)	5	74 (9.9%)
n	21	48	19	50	19	50	748
p value*	NS		NS		NS(0.03)		
HLA-DRW6	1 (6.7%)	6	0	7	0	7	28 (20.0%)
n	15	39	14	40	15	39	140
p value*	NS		NS(0.05)		NS(0.04)		

n = number of subjects; NS = not significant.

*Significance of differences between incidences of HLA antigens in the positive and negative skin-test groups. Significance of differences between the positive skin test group and the normal panel are in parentheses.

protein skin tests had levels of total IgE above 25 and 200 U/ml, respectively ($\chi^2 = 10.6$, $p = 0.005$).

DISCUSSION

Symptoms of rhinitis, conjunctivitis, and asthma occurring after exposure to mouse rooms and wheal reactions to mouse bites and scratches were frequent among workers who were periodically exposed to mice, affecting 32% of those exposed. One third of

symptomatic subjects assessed their symptoms to be moderate or severe, and nearly all in this group had positive responses to prick tests with purified mouse allergens. Symptoms in subjects with negative skin tests to mouse allergens were usually mild, suggesting that allergens of murine origin were the main cause of symptoms in the mouse laboratories. As further evidence of the importance of type I hypersensitivity to mouse allergens, symptoms and positive skin tests

correlated significantly with the presence in sera of IgE antibodies to purified mouse allergens.

Although all exposed subjects were skin tested with crude pelt extract as well as with purified urine and pelt components in the expectation that more subjects would respond to the crude extract, it was found that the incidence of positive responses to crude allergens was lower than that of responses to purified materials. Since this was probably a reflection of increased potency of purified materials without loss of major allergens, many analyses presented in this article were of data from testing with purified urine allergens, which were more frequently positive than were tests with both crude and purified pelt extract. Minor pelt allergens could have been lost in purification of the crude pelt extract, but it was not possible to support this hypothesis from the available data. Although RAST with MUP or P4 allergens probably did not recognize antibodies to all mouse allergens, skin testing and RAST data in this article complement the previous findings⁴ of the importance of urine components as allergens in mouse laboratories.

Several subjects reacted to only one or two MUP preparations from the three strains of mice, suggesting the possibility of strain-specific allergens. These data alone were inconclusive, but differences in the MUP from the three strains shown by isoelectric focusing in another study⁴, do support this possibility. Previous findings of cross-antigenicity among MUP from the three strains⁴ do not exclude the possibility that some individuals could have acquired allergic reactivity to minor noncrossreactive antigens.

The development of symptoms of mouse allergy usually began in the first year of employment, and subjects who had been exposed to mice for 2 yr or longer did not have a greater incidence of symptoms than those exposed for briefer periods. There was also no demonstrable effect of extent of heavy exposure on the occurrence of symptoms, since employees who visited mouse rooms infrequently had a risk of becoming allergic to mice similar to that of employees heavily exposed on a daily basis. These findings suggested that development of allergy to mice was determined by constitutional predisposing factors affecting a proportion of the population regardless of the frequency of exposure to airborne mouse allergens in mouse rooms beyond 10 days per year.

Predisposition to mouse allergy was related to the coexistence of atopic disease. Thus symptoms of mouse allergy and positive skin-test responses to mouse allergens were significantly correlated with a personal history of seasonal rhinitis and positive prick-test responses to perennial rye, Bermuda grass, and plantain pollen extracts. The tendency for high

serum levels of IgE to be associated with mouse allergy may be explained by the association of high IgE levels with the presence in serum of mouse allergen-specific IgE antibodies; this tendency is also consistent with an atopic defect as an explanation for susceptibility to sensitization by mouse allergens. The relationship between mouse allergy and atopic disease confirms the suggestive findings of Rajka¹⁹ and Newman-Taylor et al.² and may be similar to the association between atopy and other occupational respiratory allergies, including sensitivity to proteolytic enzyme detergents,²⁰⁻²² green coffee beans,²³ and locust antigens.²⁴ Gross²⁵ has also shown positive correlations between hypersensitivity to laboratory animals and allergy to common airborne allergens in Chicago. In contrast to the results of Gross, our findings showed a low incidence of sensitivity to cat and dog dander and no correlations between sensitivity to household pets and sensitivity to laboratory animals; this may have been because of pre-employment exclusion of pet-sensitive applicants for technical positions at our institute or because pets in Chicago may be kept indoors more frequently than those in Melbourne, where the climate is more temperate. In another study of allergy to laboratory animals, Slovak and Hill²⁶ could not correlate the prevalence of symptomatic allergy to one of several laboratory animals with prevalence of atopy, as defined by a positive prick test to at least one of several aeroallergens, including housedust.

Although seasonal rhinitis and positive skin tests to pollen allergens correlated equally well with mouse allergy, screening of prospective employees in mouse laboratories by questionnaire methods could be improved by use of pollen skin tests in their pre-employment assessments to minimize need for compensation for occupational disability. This is suggested because employees who had been screened for atopy before employment by questionnaire only were found during the survey to have an incidence of atopic disease similar to that in the unscreened employees. Some individuals may have developed atopy since their commencement of employment, but this suggests the postulate that atopy developed preferentially in subjects allergic to mice. It is more likely that many atopic individuals may have failed to recollect atopic symptoms at the pre-employment interview. On the other hand, although correlation between pollen skin-test responses and symptoms of mouse allergy was statistically significant, many pollen test-positive individuals did not develop symptoms, indicating that pollen skin testing for screening purposes could preclude employment of a person who could work among mice without becoming sensitized. Furthermore, many

subjects who developed positive responses to mouse allergen skin tests did not have seasonal rhinitis.

Population studies of associations between allergic diseases and HLA antigens have revealed associations with several antigens,²⁷ particularly HLA-B8.²⁸⁻³² Lack of agreement between results from the present study and previous reports could be due to the small sample size of this study, hence our findings would need to be confirmed by larger surveys of allergy in mouse laboratories. Nevertheless, the negative association between HLA-DRW6 and positive skin tests to mouse allergens is of interest. Genes with a suppressive immunoregulatory function (*Is* genes) have been demonstrated in animals³³ and have been postulated as a suppressive regulator of IgE antibody function in man.³¹ If negative associations between DRW6 and allergy can be confirmed by other studies, this allele may provide a marker of linkage with *Is* genes.

The occurrence of high serum levels of IgG antibodies to mouse allergens was more directly related to levels of exposure to mice than was occurrence of high serum levels of IgE antibodies. In comparison with IgE antibodies, levels of IgG antibodies were less well related to symptoms of mouse allergy, and increased levels of IgG antibodies were found in most of the heavily exposed individuals. This suggests that production of allergen-specific IgG antibodies may not be controlled by the same constitutional factors that influence mouse allergen-specific IgE antibodies. There was no evidence to suggest that any of the subjects developed hypersensitivity pneumonitis, and on epidemiologic grounds, the levels of IgG antibodies observed did not appear to be pathogenic. Conversely, there was no evidence that high levels of IgG antibodies were negatively associated with allergy to mice, so that these naturally acquired antibodies could not be shown to be protective against sensitization to mouse allergens.

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