Laboratory animal allergy

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Approximately one third of laboratory animal workers have occupational allergy to animal danders, and a third of these have symptomatic asthma. Sensitization generally occurs with the first 3 years of employment, and risk factors include atopic background, as well as job description as it relates to the intensity of exposure. A symptomatic worker can reduce allergen exposure with personal protective devices. A laboratory can further reduce exposure with generally available equipment, such as laminar flow caging, and procedures, such as frequent wet washing of vivaria and careful maintenance of ventilation systems. It is advisable to institute periodic medical screening of all laboratory animal workers with questionnaires and allergy skin testing in addition to providing them with training programs to reduce personal exposure. (J Allergy Clin Immunol 1998;102:99-112.)

CLINICAL ASPECTS

Laboratory workers who are in regular contact with furred animals commonly develop sensitivity to those animals. As such, laboratory animal allergy represents a major occupational illness to the thousands of technicians, animal caretakers, physicians, and scientists whose work requires such exposure. Allergy to rats and mice is the most common clinical problem, primarily because these animals are the most widely used in medical research. Estimates of the prevalence of laboratory animal allergy have varied considerably in different studies, at least in part because of differences in the diagnostic techniques that have been used. For rats, prevalence rates have ranged from 12% to 31%.[1-5] The prevalence of mouse allergy is overall very similar, ranging from 10% to 32%.[2,4-6]

In addition to rats and mice, allergic reactions will occur upon regular exposure to virtually all furred animals. Although allergy to other animals in the workplace is less common overall than allergy to rats and mice, this is primarily because these other animals are used less often, not because they are inherently less allergenic. Allergy to guinea pigs, rabbits, hamsters, gerbils, dogs, cats, pigs, cows, horses, sheep, and monkeys will therefore occur in workers exposed to these animals. In a very large epidemiologic study involving over 5000 laboratory animal workers in Japan, symptoms were reported in 26% of workers exposed to mice compared with 25% for rats, 31% for guinea pigs, 30% for rabbits, 26% for hamsters, 25% for dogs, 30% for cats, and 24% for monkeys.[4]

The onset of symptoms after beginning to work with laboratory animals can also range widely. Cullinan et al.[3] prospectively followed a group of workers without previous rat exposure and found a range of less than 30 days to 1369 days from the time of employment to the onset of symptoms. The mean duration of employment before symptom onset was 365 days for chest symptoms, 214 days for nose and eye symptoms, and 335 days for skin symptoms.

Symptoms in laboratory animal allergy range from mild skin rashes to severe asthma. Overall, the most common symptom is allergic rhinoconjunctivitis with nasal congestion, rhinorrhea, sneezing, and itchy, watery eyes.[3,4] These symptoms have been reported to occur in up to 80% of symptomatic workers. Skin reactions, most commonly contact urticaria or pruritic maculopapular rashes, are typically the next most prevalent symptoms, occurring in about 40% of symptomatic individuals. Asthmatic symptoms are reported in 20% to 30% of symptomatic workers. It is also important to recognize, however, that the majority of symptomatic workers have more than one type of symptom. This is especially true of asthma, which rarely occurs in the absence of upper respiratory tract symptoms.

As will be discussed below, the risk of animal allergy is related in part to the type of exposure incurred by the worker. Similarly, the nature and intensity of symptoms are also due in large part to the specifics of the exposure. Handling animals can cause contact urticaria and rashes. Activities associated with high airborne allergen levels, such as cage cleaning, are therefore more likely to produce respiratory reactions than activities associated with lower airborne allergen levels. Furthermore, it has been demonstrated in patients allergic to rats that the intensity of their respiratory response to rat exposure is highly correlated with the level of airborne rat allergen.[7]

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TABLE I. Laboratory animal allergens

Animal	Allergen	MW (kd)	Source
Mouse (*Mus musculus*)	Mus m 1 (prealbumin)	19	Hair, dander, urine
	Mus m 2	16	Hair, dander
	Albumin		Serum
Rat (*Rattus norvegicus*)	Rat n 1A/Rat n 1B (α_{2u}-globulin)	16-21	Hair, dander, urine, saliva
	Albumin		Serum
Guinea pig (*Cavia porcellus*)	Cav p 1		Hair, dander, urine
	Cav p 2		Hair, dander, urine
Rabbit (*Oryctolagus cuniculus*)	Ory c 1		Hair, dander, saliva
	Ory c 2		Hair, dander, urine
Cat (*Felis domesticus*)	Fel d 1	38	Hair, dander, saliva
	Albumin		Serum
Dog (*Canis familiaris*)	Can f 1	25	Hair, dander, saliva
	Albumin		Serum

MW, Molecular weight.

THE ALLERGENS

The allergens responsible for most laboratory animal allergy have now been identified and characterized (Table I). Rodents and rodent-like animals have persistent proteinuria, and their urine is a major source of allergen production. Hair, dander, and, to a lesser extent, saliva are also important rodent allergen sources. For cats and dogs, hair, dander, and saliva are the major sources of allergen production.

At least three relevant mouse allergens have been identified.[8-10] The major allergen, Mus m 1, which was previously designated MUP (major urinary protein) or Ag 1, is a prealbumin with a molecular weight of 19 kd as determined by sodium dodecylsulfate–polyacrylamide gel electrophoresis. The gene for the protein has been molecularly cloned, and its amino acid sequence has been deduced.[11] It is found in urine and in hair follicles and dander. Mus m 1 is produced in liver cells, and levels in serum and urine are about four times higher in male mice as compared with female mice because of the fact that the gene expression is testosterone dependent. A second mouse allergen, Mus m 2, is a glycoprotein with a molecular weight of 16 kd. This allergen originates from hair follicles and dander but is not found in urine. A final mouse allergen is albumin, which has been shown to be allergenic in about 30% of patients allergic to mice.

Two allergens have been identified in rat urine, saliva, and pelt.[12-14] One, designated Rat n 1A, was thought to be a prealbumin with an apparent molecular weight of 20 to 21 kd. The other, designated Rat n 1B, was believed to be an α_{2u}-globulin of molecular weight 16 to 17 kd. More recent data comparing nucleotide and amino acid sequences now have demonstrated that both allergens are variants of the same protein, α_{2u}-globulin. This 16 kd protein is produced in the liver, where it is androgen dependent, as well in a number of exocrine glands (salivary, mammary, preputial, and meibomian), where the production is not androgen dependent.[15-17] As is the case in mice, rat albumin has also been shown to have some antigenic activity, with 24% of patients allergic to rats exhibiting sensitivity to albumin.

Allergens from guinea pigs have not been extensively characterized, although two antigenic fragments, Cav p 1 and Cav p 2, have been identified.[18,19] Both of these allergens are found in urine, hair, and dander. Rabbit allergens have also not been well characterized, although two have been identified.[20] Ory c 1 is found in the hair, dander, and saliva, whereas Ory c 2 is found in the hair, dander, and urine.

Although cats and dogs are much more common as domestic pets than as laboratory animals, they are nevertheless important laboratory animals whose allergens have been well characterized. At least twelve proteins of cat origin have been found to be allergenic, with one major cat allergen, Fel d 1, being by far the most important.[21-25] It is a tetrameric polypeptide with a molecular weight of 38 kd. It has been molecularly cloned, its amino acid sequences have been established, and its allergenic structure has been analyzed.[26] Fel d 1 is produced in hair follicles and, to a lesser extent, in salivary glands. Male cats produce more Fel d 1 than female cats.

Several dog-specific proteins have also been shown to possess antigenic activity.[27-29] The most important of these is Can f 1, which is produced in hair, dander, and saliva. It is a polypeptide with a molecular weight of 25 kd. Dog albumin is a minor allergen, and another immunologically distinct allergen with a molecular weight of 19 kd was also recently described.[30,31]

Other animals used in laboratories may on occasion cause allergic reactions. Despite exposure to primates in research facilities, few cases of sensitivity to primates have been documented. Cases of allergy to lesser bush baby (galogo) and cottontop tamarin monkey have been identified.[32] The allergens were found in the dander of these animals.

ENVIRONMENTAL DISTRIBUTION

Many of these allergens have also been characterized with regard to their environmental distribution

and aerodynamic properties. Although rodent allergens can certainly be present in household environments, they have been studied primarily in laboratory settings. Cat and dog allergens, on the other hand, have been characterized best in home environments. Information on total airborne allergen levels and particle size distribution are available for most of the allergens, although variations in sampling devices and assay methods make data from different centers difficult to compare. In addition, the clinical relevance of these levels has only been explored in detail for rat and cat allergens. These factors make the interpretation of airborne levels quite difficult, especially when making decisions about occupational risk and the efficacy of various interventions.

In general, animal allergens tend to be carried on relatively small particles. These particles can remain airborne for extended periods and are easily respirable. Airborne mouse allergen has been shown to reside on particles ranging from 3.3 to 10 μm in one study[33] and from 6 to 18 μm in another study.[8] Ohman et al.[33] also found a particle size distribution ranging from 0.43 to 3.3 μm in rooms that did not contain mice.

Airborne mouse allergen levels in the Ohman study ranged from 16.6 to 563 ng/m^3 in rooms with mice and from 1.2 to 2.7 ng/m^3 in rooms without mice, with the highest levels being associated with direct mouse contact. In another study levels ranged from 1.8 to 825 ng/m^3 and varied with both the number of mice and the degree of work activity in the rooms.[34] An additional study demonstrated higher allergen levels in rooms with male mice compared with rooms with female mice (Mus m 1, 13,050 pg/m^3 versus 317 pg/m^3, respectively).[35]

Airborne rat allergens are carried on particles ranging from less than 1 μm to more than 20 μm, with the majority of allergen on particles less than 7 μm in diameter.[36,37] It has been shown that a significant proportion of the airborne allergen remains airborne 15 to 35 minutes after disturbance. Levels of airborne rat allergen have been studied in a variety of settings, and it is clear that exposure is highly dependent on the type of activity being performed, with cleaning and feeding being associated with the highest levels of exposure (Fig. 1).[38,39]

Studies have also been performed in individuals allergic to rats to determine the levels of exposure that would be expected to induce symptoms. In one study of 12 volunteers allergic to rats, all subjects experienced nasal symptoms, and five experienced a decrease in FEV_1 of greater than 10% during a 1-hour exposure with airborne Rat n 1 levels ranging from less than 1.5 to 310 ng/m^3.[39] In a follow-up study exposures to high allergen levels (cage cleaning, mean Rat n 1 = 166 ng/m^3) were compared with exposures to low allergen levels (quiet sitting in a rat vivarium, mean Rat n 1 = 9.6 ng/m^3) in 17 subjects.[6] A clear dose response was demonstrated, with both upper and lower airway responses being dependent on airborne allergen levels.

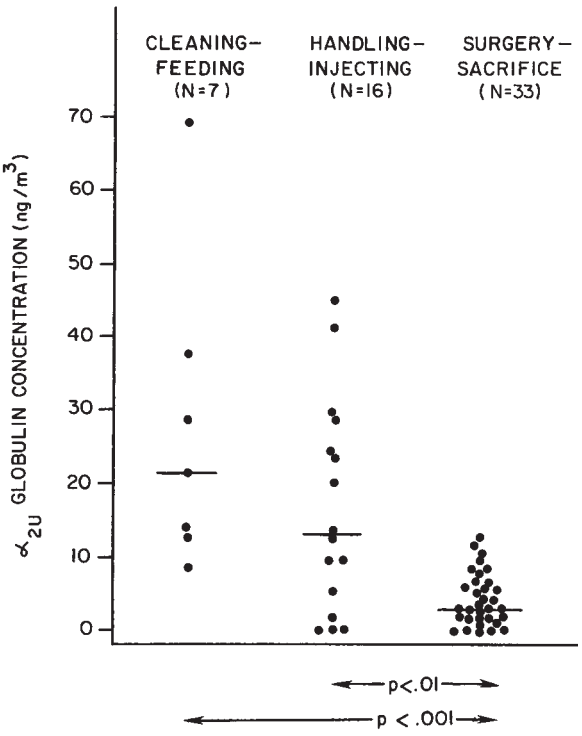

FIG. 1. Task-related airborne rat allergen (Rat n 1) concentrations in a laboratory facility. (From Eggleston PA, Newill CA, Ansari AA, Pustelnik A, Lou SR, Marsh DG, et al. Task related variation in airborne concentrations of laboratory animal allergens: studies with Rat n 1. J Allergy Clin Immunol 1989;184:L347-52).

However, because of variations in response, it was not possible to determine a threshold or *safe* allergy level for an asthmatic response.[6]

Much less information is available about other laboratory animal allergens. Airborne guinea pig allergens have been measured with RAST inhibition that demonstrated urine and pelt allergen levels of 17 and 90 ng/m^3, respectively.[19] Forty percent of the guinea pig allergen was found on particles less than 0.8 μm in diameter, which remain airborne for long periods and are capable of depositing in small airways.

Cat and dog allergens have been best studied in nonlaboratory settings. Cat allergen has been shown to be carried on particles that range from less than 1 μm to greater than 20 μm in diameter. Although estimates have varied, it is clear that at least 15% of airborne cat allergen is carried on particles less than 5 μm in diameter.[40,41] Less data are available on dog allergen, but preliminary evidence suggests that it is distributed very much like cat allergen, with about 20% of airborne allergen being carried on particles less than 5 μm in diameter.[42]

RISK FACTORS

The risk factors for laboratory animal allergy relate to individual susceptibility and environmental expo-

TABLE II. Relationship of skin tests and RAST to laboratory animal allergens to work-related symptoms

	Skin Test	+	−	−	+		RAST	+	−	−	+	
Author	Symptoms	+	−	+	−	*n*	Symptoms	+	−	+	−	*n*
Slovak and Hill[44]		22	98	0	98	218		—	—	—	—	
Beeson et al.[45]		5	247	10	10	272		8	251	7	6	
Venables et al.[46]		3	31	0	5	39		—	—	—	—	
Renstrom et al.[47]		2	31	0	5	38		—	—	—	—	
Schumacher et al.[6]		24	125	25	5	179						
Platts-Mills et al.[48]		19	134	11	1	165		15	133	15	2	165
Agrup et al.[49]		19	30	11	0	60		—	—	—	—	
Total (%)		94 (10)	696 (71)	57(6)	124 (13)	971		23 (5)	384 (88)	22 (5)	8 (2)	437

TABLE III. Relationship of atopic status to reported work-related symptoms, skin tests, and serologic tests to laboratory animal allergens

Author	Atopic*	*n*	Symptoms (%)	Number skin tested	Positive skin test response to animal allergens (%)	Symptoms and skin tests	RAST tested	Positive RAST result (%)
Cockcroft et al.[51]	Yes	70	21 (30)	70	21 (30)	17	—	—
	No	109	4 (4)	109	8 (7)	4	—	—
Platts-Mills et al.[48]	Yes	71	17 (24)	71	32 (45)	—	71	30 (42)
	No	108	14 (13)	108	10 (9)	—	108	10 (9)
Beeson et al.[45]	Yes	110	10 (9)	—	—	—	—	—
	No	202	3 (1)	—	—	—	—	—
Slovak and Hill[44]	Yes	35	20 (57)	35	13 (37)	—	—	—
	No	111	28 (25)	111	6 (5)	—	—	—
Venables et al.[46]	Yes	56	27 (48)	56	13 (23)	19	56	17 (30)
	No	73	29 (40)	73	4 (5)	12	73	14 (19)
Agrup et al.[49]	Yes	22	16 (73)	22	13 (59)	—	—	—
	No	38	14 (37)	38	6 (16)	—	—	—
Cullinan et al.[3]	Yes	88	36 (41)	88	19 (22)	—	—	—
	No	150	34 (23)	150	2 (1)	—	—	—
Aoyama et al.[4]	Yes	2090	772 (37)	—	—	—	—	—
	No	3551	532 (15)	—	—	—	—	—
Gross[50]	Yes	86	34 (40)	—	—	—	—	—
	No	313	25 (8)	—	—	—	—	—
Total	Yes	2628	953 (36)	342	111 (32)		127	47 (37)
	No	4655	683 (15)	589	36 (6)		181	24 (13)

*Defined as a history of seasonal symptoms plus one or more positive skin prick test responses to inhalant allergens.

sure. Individual susceptibility has been examined carefully in multiple epidemiologic studies. At this time, methods to predict risk are well established and can be easily applied in workplace settings. Environmental exposure assessment, on the other hand, is more difficult, and the techniques are both less widely available and less clearly supported by research data.

Individual susceptibility

Individual susceptibility has a genetic basis. The term *atopy* was coined in 1923 by Coca and Cooke[43] to describe the combination of a genetic predisposition to produce a prolonged IgE antibody response to environmental allergens and the resulting chronic conditions of allergic rhinitis, asthma, and eczema. The atopic status of a worker may be determined by asking for a history of allergic rhinitis, asthma, or atopic eczema either as chronic conditions that are not related to work or that have been related to previous jobs with animal exposure. Because atopy is familial, a family history of similar diseases in first-order relatives (parents, siblings, and children) also indicates an increased predisposition to atopy. Detection of IgE antibody to environmental allergens, either by using immediate wheal and flare skin tests or serologic tests for specific IgE, is a strong indicator of atopy; however, this may or may not be associated with an elevated total IgE.

What of the relationship of work-related symptoms and the presence of positive skin test or in vitro test responses for specific IgE antibodies? As shown in Table II, the relationship is relatively close. In seven studies[6,44-49] the concordance between skin tests and symptoms was 81% (790 of 971). However, 57% of persons with positive skin test responses did not report symptoms, whereas 62% of persons with symptoms had positive skin test responses. Thus the positive pre-

TABLE IV. Relationship of job description to symptoms of lab animal allergy, skin test responses, and RAST results

Author	Type of exposure	*n*	Symptoms (%)	Positive skin test responses (%)	Positive IgE (%)	Positive IgG (%)
Platts-Mills et al.[48]	Handlers	54	—	7 (13)	9 (19)	31 (58)
	Users	125	—	15 (12)	8 (6)	37 (30)
	Unexposed	34	—	0 (0)	0 (0)	6 (18)
Cockcroft et al.[51]	Handlers	52	17 (33)	—	—	—
	Users	127	32 (25)	—	—	—
	Unexposed	29	0 (0)	—	—	—
Schumacher et al.[6]	Handlers	33	12 (36)	—	—	—
	Users	98	25 (26)	—	—	—
	Unexposed	40	2 (5)	—	—	—
Venables et al.[46]	Handlers	42	19 (45)	—	—	—
	Users	80	32 (40)	—	—	—
	Unexposed	16	9 (56)	—	—	—
Slovak and Hill[44]	Handlers	19	8 (42)	—	—	—
	Users	101	34 (34)	—	—	—
	Unexposed	26	6 (23)		—	—
Total	Handlers	148	56 (38)	7 (13)	9 (19)	31 (58)
	Users	404	123 (30)	15 (12)	8 (6)	37 (30)
	Unexposed	116	17 (15)	0 (0)	0 (0)	6 (18)

TABLE V. Relationship of duration of exposure and presence of IgE- and IgG-specific antibodies to murine antigens

Author	Exposure (days)	*n*	Positive IgE (%)	Positive IgG (%)
Schumacher et al.[6]	5	47	1 (2)	0 (0)
	16	63	14 (22)	55 (87)
	30	50	12 (24)	45 (90)

dictive accuracy of a positive skin test response was 43%. Ninety-two percent of workers with a negative skin test response reported no symptoms, giving a negative predictive accuracy of 92%. RAST and symptoms agreed in 93% of cases. The frequency of positive skin test responses varies widely among these reports, and it can be questioned whether each investigator used an active allergen extract for testing. For example, compare Beeson et al.,[45] who found that only 6% of workers had a positive skin test response, with Slovak and Hill,[44] who found a rate of 55%.

The importance of a history of atopy as a risk factor for laboratory animal allergy has been examined in nine studies (see Table III). In these reports atopy is defined either by a positive skin prick test response to at least one of a panel of common inhalant allergens other than laboratory animal allergen,[3,44-46] by a history of allergic rhinitis or asthma,[4,50] or by a combination of history and skin test responses.[48,49,51] Despite different criteria for atopy and the fact that several of the studies[4,48,49,51] evaluated had selected populations, the frequency of atopy averaged 36% in agreement with that found in the general population.[52,55] A history of work-related symptoms and objective evidence (positive skin test responses and RAST results) were equally useful in predicting symptoms reported by 36% of atopic workers and 15% of nonatopic workers (odds ratio, 3.35). The relationship of atopy to positive skin test responses and RAST results to laboratory animal allergens was similar, with odds ratios of 6.86 and 3.93, respectively. It is also obvious that both the frequency of laboratory animal allergy, whether defined by symptoms, skin tests, or RAST, varied widely between the various studies. For example, Venables et al.[46] found a high prevalence (48%) and a marginal relationship to atopy, whereas Cockcroft et al.[51] found a prevalence of 30% and a strong relationship to atopy. These variations were likely due to differently worded questions and different skin testing and RAST techniques, but the variability of the findings together with the modest association between atopy and laboratory animal allergy has led some to conclude that preemployment screening for individual susceptibility is of limited value. Alternatively, a study by Rothman et al.[54] suggests that atopic workers are at increased risk for laboratory animal allergy. Screening for atopy is helpful in alerting potential workers to the risk of animal exposure and educating them to take protective measures to prevent the development of laboratory animal allergy.

Environmental exposure

Environmental animal allergen exposure may be assessed by job description, by the percentage of time with direct exposure to animals, and by the specific tasks performed with the animals.

A useful categorization of job description, which was proposed by Cockcroft et al.,[51] is shown in Table IV. Handlers include workers who are responsible for cage cleaning and for the feeding and care of the animals. Users include persons involved in experimental use of the animals, such as technicians, students, and

TABLE VI. Preventative measures and interventions

Method	Use	Advantage	Disadvantage
I. Screening and surveillance programs			
1. Questionnaires	Determine presence of nonwork-related allergic disease; determine existence of prior laboratory animal sensitization; assist in task assignment	Inexpensive	Accuracy of self-reporting
2. Skin testing or serologic assays for specific IgE antibodies to laboratory animal and other allergens	Determine presence of preexisting nonwork-related sensitization; determine baseline existence (or lack thereof) of sensitization to laboratory animals	Ability to determine occupational relationship of sensitization or symptoms; early detection of sensitization	Cost and availability; invasive
3. Pulmonary function tests (PEFR, spirometry)	Assess airway function; detect presence of reversible airway obstruction (asthma); required if patient is using effective respiratory protective gear	Early detection of asthma	Cost and availability
II. Facility design and equipment			
1. Ventilation systems (HEPA filters)[56,63]	Decrease airborne allergen levels	Effective but not proven to prevent or reduce symptoms	Very expensive
2. Ventilated cage/rack systems[57,58]	Decrease airborne allergen levels	Effective but not proven to prevent or reduce symptoms	Expensive
3. Increase humidity in facility[61,62]	Decrease airborne allergen levels	Inexpensive; not proven to reduce or prevent symptoms	May not be tolerated by animals or humans
4. Work stations for cage emptying/cleaning[64,65]	Decrease airborne allergen exposure	Relatively inexpensive	May not totally eliminate high level exposure
III. Work practices			
1. Education programs[65,66]	Increase employee awareness of risks	Inexpensive	Time consuming
2. Job assignment	Reduce exposure in individuals at risk	Inexpensive	Validity not proven
3. Use of noncontract bedding pads[59]	Reduce airborne allergen exposure	Inexpensive	Validity not proven
IV. Personal protective respiratory equipment			
1. Respiratory protective gear[64,68,71]	Reduce airborne allergen exposure	Efficient respirators effective in reducing symptoms	Requires motivated employee, medical supervision
V. Evaluation of the worker allergic to animals			
1. Referral to physician	Properly diagnose and treat affected individual	Improve employee health	Requires knowledgeable physician
VI. Emergency procedures			
1. Self-administered epinephrine[79,80]	Prevent severe allergic reactions	Potentially live-saving	

HEPA, High efficiency particulate air cleaner; *PEFR*, peak expiratory flow rate.

investigators; these are persons who are in contact with the animals on a more intermittent basis. Unexposed workers include secretaries and administrators who have no direct contact with the animals but who have an office in the same building.

This classification predicts that those with the greatest exposure to the animals will be the most likely to become sensitized and to have symptoms related to work exposure. As seen in Table IV, this prediction is generally supported by epidemiologic studies. Compared with the rate of symptoms in unexposed workers, handlers (odds ratio, 3.56) and users (odds ratio, 2.31) have an increased frequency of symptoms. On the other hand, it is also important to note that many people who are not exposed have symptoms. Work-related symptoms were reported by up to 56% of workers with no direct contact with the animals.[46] A recent epidemiologic study of Dutch laboratory workers used a combination of area allergen assays and workers diaries of activities in these rooms to classify exposure. Statistical modeling allowed the investigators to demonstrate a clear relationship between sensitization to rat aller-

gens and exposure. In addition, they found an interaction between this relationship and atopy, such that heavily exposed atopic persons had a 42-fold higher prevalence of symptomatic rat allergy.[55] In the only report that described immunologic changes, Platts-Mills et al.[48] found that 18% of unexposed workers had IgG antibody to rat allergens. This suggests that sensitization through indirect exposure may be possible. Schumacher et al.[6] studied workers exposed only to mice. They measured work exposure as the total number of days each month that the workers reported exposure to the animals. Serologic changes were used to indicate the effect of exposure, and as seen in Table V, exposure for more than 5 days per month was associated with an increased frequency of detectable specific IgE, as well as IgG, antibody.

Finally, the specific tasks performed while working with animals carry different exposure risks. Measurements of airborne rat allergen were made with personal monitors worn during work. It can be seen in Fig. 1 that cleaning cages or manipulating active animals is associated with significantly higher levels of airborne rat allergen exposure. In the study from which Fig. 1 is derived,[38] symptomatic or serologic responses to these exposures were not studied. The significance of these different exposures was explored in subsequent studies.[6] Symptomatic and inflammatory responses of sensitized workers were studied while they stood in a rat vivarium or were present during cage cleaning. The measured airborne concentrations during these operations were comparable with those in Fig. 1. All of the sensitized subjects had symptoms during cage cleaning, as did half of them during quiet activity. The symptomatic and inflammatory response correlated with the airborne allergen concentration. However, workers also responded to conditions in which allergen levels were close to measurement threshold (1.5 to 5 ng/m^3).[6] These data not only support the idea that allergen control measures may reduce illness in sensitized workers, but also suggest that any exposure to environments where animals are present can induce disease.

PREVENTIVE MEASURES AND INTERVENTIONS

Efforts to minimize exposure to animal allergens should result in a reduction in the frequency of sensitization in laboratory animal workers and a reduction in symptoms in those who are sensitive. Unfortunately, there are little data to support those hypotheses. In spite of a number of approaches to reduce or minimize exposure, laboratory animal allergy remains a significant problem. Further research is needed to determine which measures are most cost effective in preventing and controlling symptoms of laboratory animal allergy. Table VI provides a summary of preventive and interventional methods that may be useful in reducing rates of sensitization and symptoms in individuals with laboratory animal allergy.[56-59,63-68,70,71]

Screening and surveillance programs

As discussed above, preplacement screening evaluations may be helpful in identifying individuals who might be at risk for having laboratory animal allergy or asthma and educating them to take protective measures. Screening programs can also identify individuals with preexisting allergies and asthma unrelated to laboratory animal exposure. The extent of the evaluations will depend on the resources of the facility, and a simple questionnaire (see Appendix) has been provided as a starting point. The presence of allergy to domestic pets (cats and dogs) has been identified as a risk factor for laboratory animal allergy.[70] Such assessments should not and cannot legally be used to preclude employment but rather are useful to the employee to assign tasks that substantially reduce the level of exposure to laboratory animal allergens. The questionnaire may be supplemented by skin testing or in vitro tests to detect specific IgE antibodies to animal and other allergens. Positive results can be used to place the employee with preexisting sensitivity to laboratory animals in low-risk assignments. The tests can also be used as a baseline to identify sensitization in people who might later become symptomatic. In addition to the questionnaire, objective measurement of pulmonary function by peak expiratory flow rate or spirometry is encouraged for employees with a history of asthma or chest symptoms. The use of methacholine bronchial hyporesponsiveness as a predictor of subsequent laboratory animal allergy–induced asthma has not been established. Therefore the use of methacholine challenge as a screening procedure to assign work tasks is, at present, of uncertain value.

Clearly, individuals with known laboratory animal sensitivity should avoid repetitive exposure. Sensitized individuals who have had 2 or more years experience working with laboratory animals are at risk for asthma.[5] Such employees need to be closely monitored for the presence of chest symptoms.

For individuals who are chronically exposed to laboratory animals, annual surveillance programs should be implemented to detect those who have symptoms so that appropriate measures can be taken to prevent long-term sequelae. Such surveillance programs should consist of a questionnaire regarding allergy and asthma symptoms. It may also include skin testing or an in vitro test for specific IgE antibodies. Periodic monitoring of pulmonary function and possibly methacholine challenge testing should be considered, especially if asthma symptoms develop. Such programs may be of value in reducing permanent disability from asthma.

Facility design and equipment

Attention to facility design and equipment may be helpful in reducing the incidence of laboratory animal allergy, although these measures have not been fully validated. The airborne allergen load in animal rooms

is dependent on the rate of allergen production, which is a function of animal density (numbers of animals present), and the rate of allergen removal from the air, which is a function of ventilation. To achieve a substantial reduction in allergen exposure in an area heavily populated with laboratory animals, frequent contact with the animals by laboratory workers should be reduced (e.g., no cage cleaning or surgery). Employees using effective respiratory protection (respirators) will need fit-testing of the equipment and medical clearance.[71]

Evaluation of the worker allergic to animals

When individuals have allergic symptoms related to laboratory animal exposure, consultation with appropriate physicians should be considered so that an accurate diagnosis and effective management can be achieved. For animal facility personnel suspected of having allergic problems, the diagnosis of animal sensitivity is largely made on the basis of the history of symptoms in conjunction with exposure. The diagnosis is confirmed by the demonstration of specific IgE antibodies to the allergen in question.

To obtain a history of asthma, the examiner should ask about wheezing, cough, chest tightness, or difficulty breathing that is episodic (see Appendix). Symptoms are typically increased with exercise; colds; irritants such as cigarette smoke, odors and cold air; and allergen exposure. If asthma medications have been used, symptoms should be clearly improved. The worker should also be asked if a physician has made a diagnosis of asthma. A history of allergic rhinitis should include chronic congestion and rhinorrhea accompanied by sneezing, itchy nose or throat, and itchy eyes. A typical history of eczema describes a chronic, intensely pruritic, scaly red rash typically found in the flexural areas of the arms and legs.

The most widely used tests for specific IgE-mediated allergy are the skin test and RASTs. Skin testing is typically done with the prick-puncture technique.[72] In this procedure a drop of an extract of an allergen, such as animal pelt, is placed on the surface of the skin, and the underlying skin is lightly pricked with a small lancet. The diameter of the surrounding wheal and flare is measured at 15 minutes and is compared with a positive (histamine) and a negative control. In the RAST the allergen extract is covalently bound to a solid-phase support (paper disc, microcrystalline cellulose, or sepharose beads). Patient serum is incubated with the solid-phase support, allowing specific IgE antibodies to bind to the allergen. Bound IgE is then detected with a second antibody. The RAST generally correlates well with skin tests. It has the practical advantage that it can be performed on stored sera from epidemiologic studies and is not affected by medications; increased expense and lower sensitivity are disadvantages.

An important variable in the accuracy of either test is the composition of the allergenic extract used. These extracts are made from a source of allergenic material such as pollens, fungal cultures, or animal epithelium. Allergenic proteins generally constitute a small fraction (1% or less) of the total protein in these extracts, and this fraction may vary as much as 1000-fold between different lots of extracts. Furthermore, the concentration of allergenic proteins tends to decrease gradually, in part because of proteases that are frequently found in the extracts. Loss of activity can be decreased by storage at 5° C or less or by adding 50% glycerin. Standardized, stable extracts have now become available for many allergens,[73] but at this time, the only standardized animal extract is from cats. Animal allergen extracts are marked either as *epithelium*, indicating that they are made by washing an animal, or as *pelt* extracts, which are made of animal hides. Epithelium extracts are preferable because they contain a higher proportion of appropriate allergens.

For RAST or skin testing, diagnosis and screening typically are performed with a panel of common allergens, including house dust mite, fungi (*Alternaria*, *Aspergillus*, *Helminthosporium*, and *Penicillium* species), cat, dog, cockroach, tree pollen (oak, maple, birch, and alder), grass pollen, and ragweed pollen. When testing for laboratory animal allergens, it is reasonable to include tests with epithelial extracts of several different animals whether or not the person is aware that they are exposed to these animals at work. These include rat, mouse, guinea pig, hamster, gerbil, and rabbit.

Exposure reduction and avoidance measures should be undertaken when individuals become sensitized and have symptoms resulting from their exposure as discussed above. Appropriate medications to control allergy and asthma symptoms should be administered. Nonetheless, many highly sensitized individuals will continue to have symptoms in spite of exposure reduction and are compelled to avoid animal allergen exposure completely.

In a few individuals immunotherapy to cats and dogs has been undertaken with some degree of success.[74-77] However, these results are most applicable to individuals with intermittent exposure and have not been applied to chronically exposed laboratory workers. Uncontrolled studies of immunotherapy to laboratory animals (mice, rats, and rabbits) have also demonstrated some improvement.[78] However, the use of immunotherapy as a means to protect workers from further symptoms has not been fully established.

Emergency procedures

On rare occasion, an allergic worker may experience an anaphylactic reaction from an animal bite[79] or from needle punctures contaminated with laboratory animal allergens.[80] Because these reactions can progress rapidly and become potentially fatal, physicians may recommend that the worker carry a self-administered form of epinephrine (e.g., Epi-Pen or Ana-Kit). In appropriate circumstances it may be helpful to instruct coworkers in emergency procedures such as cardiopulmonary resuscitation.

SUMMARY

Laboratory animal allergy is a common occupational hazard. Symptoms range from mild skin irritation to severe asthma. Many of the important allergens causing sensitivity have been identified and purified. The allergens are often carried on small airborne particles that remain suspended for extended periods, which makes them easily respirable. Methods to quantitate exposure have been developed, and certain tasks such as cage cleaning or surgery are associated with higher exposure levels. Preplacement evaluations of employees may reduce the presence of laboratory animal allergies in individuals at risk. Constant surveillance of exposed employees may identify the early onset of laboratory animal allergy and prevent long-term disability. Exposure reduction and avoidance are the mainstay of protection and therapy, although many of the available methods, such as air filtration systems and personal protective gear, have not been validated. Removal of the affected individual from all exposure may be necessary in some cases.

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APPENDIX.

Sample questionnaire for the evaluation of laboratory animal allergy

LABORATORY ANIMAL ALLERGY QUESTIONNAIRE

Date_____

Name:_____

Supervisor:_____

Department:_____

Age:_____ Sex: ☐ Male ☐ Female

OCCUPATIONAL HISTORY Answer these questions about your present job:

1. Job title:_____
2. Number of years employed at this facility:_____ years
3. How many months/years at your present position?_____
4. Description of duties (briefly):_____

_____

_____

5. Do you work with laboratory animals? ☐ Yes ☐ No If yes, complete the following?

Animal	Yes	No	Approximate Contact Hours/Day
Rats	☐	☐	_____
Mice	☐	☐	_____
Rabbits	☐	☐	_____
Guinea Pigs	☐	☐	_____
Monkeys	☐	☐	_____
Cattle	☐	☐	_____
Dogs	☐	☐	_____
Cats	☐	☐	_____
Other	☐	☐	_____

6. Do you feel that you are allergic to any of these animals? ☐ Yes ☐ No

☐ Rats ☐ Mice ☐ Rabbits ☐ Dogs ☐ Other

☐ Cats ☐ Monkeys ☐ Cattle ☐ Guinea Pigs

7. Did you work with laboratory animals prior to employment at this facility? ☐ Yes ☐ No

   If yes, how long?_____ years What type of animals?_____

8. Do you use or wear any of the following items when working with animals?

Protective Eye Glasses	☐ Yes	☐ No
Mask/Respirator	☐ Yes	☐ No
Lab Coat	☐ Yes	☐ No
Gloves	☐ Yes	☐ No

HOME ENVIRONMENT INFORMATION

9. Do you have any indoor pets? ☐ Yes ☐ No If yes, which animals and for how long?

Animal	1-2 Years	2-3 Years	3-4 Years	over 4 Years
Dogs	☐	☐	☐	☐
Cats	☐	☐	☐	☐
Other (Type)_____	☐	☐	☐	☐
_____	☐	☐	☐	☐

10. Do you regularly have any of the following symptoms? ☐ Yes ☐ No Please indicate if the symptom is present and the year of onset. Also check in what location or time "period" the symptom(s) is/are present.

Symptom	Yes/No Present	Year of Onset	Symptoms Are Present			
			At Work	At Home	On Vacation	No Difference
Cough	☐	_____	☐	☐	☐	☐
Sputum Production	☐	_____	☐	☐	☐	☐
Shortness of Breath	☐	_____	☐	☐	☐	☐
Wheezing	☐	_____	☐	☐	☐	☐
Chest Tightness	☐	_____	☐	☐	☐	☐
Asthma	☐	_____	☐	☐	☐	☐
Nose Congestion	☐	_____	☐	☐	☐	☐
Runny Nose	☐	_____	☐	☐	☐	☐
Sneezing	☐	_____	☐	☐	☐	☐

Itchy Eyes	☐	_____	☐	☐	☐	☐
Sinus Problems	☐	_____	☐	☐	☐	☐
Hay Fever	☐	_____	☐	☐	☐	☐
Frequent Colds	☐	_____	☐	☐	☐	☐
Hives	☐	_____	☐	☐	☐	☐
Skin Rash	☐	_____	☐	☐	☐	☐
Swelling of Eyes or Lips	☐	_____	☐	☐	☐	☐
Eczema	☐	_____	☐	☐	☐	☐
Difficulty in Swallowing	☐	_____	☐	☐	☐	☐

11. Were you ever told by a doctor that you had allergies? ☐ Yes ☐ No

12. Have you ever been skin tested for allergies? ☐ Yes ☐ No If yes, what substances were you found to be allergic to or sensitized to?

☐ Ragweed ☐ Grass ☐ Trees ☐ Mold

☐ Dust ☐ Cat ☐ Dog ☐ Mice

☐ Other_____

13. Have you ever received allergy (desensitization/immunotherapy) shots? ☐ Yes ☐ No

14. Has a doctor ever said you have asthma? ☐ Yes ☐ No

If yes, when did your asthma start? _____ (year)

Are you currently taking medication (either over the counter or by prescription) to control your asthma? ☐ Yes ☐ No

15. Has a doctor ever told you that you have a medical condition caused by your working conditions? ☐ Yes ☐ No

16. Do any of your blood relatives (grandparents, parents, brothers/sisters) have allergies or asthma? ☐ Yes ☐ No

17. Are you under a doctors care for any other illnesses? ☐ Yes ☐ No

If yes, please list illnesses:_____

_____

18. Do you take blood pressure medication(s)? ☐ Yes ☐ No

19. Do you regularly use "over the counter" (non-prescription) nose drops or nose sprays, e.g. Afrin, Neosynephrine? ☐ Yes ☐ No

20. Do you smoke cigarettes? ☐ Yes ☐ No If yes, how many cigarettes per day?_____
How many years?_____

If not presently smoking, did you ever smoke? ☐ Yes ☐ No

If yes, when did you stop smoking cigarettes? _____ (year)

How many years did you smoke? _____ years

Comments:_____

_____

_____

_____

Reviewed By:_____ Date:_____