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Laboratory animal allergy in a pharmaceutical company

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ABSTRACT A cross sectional survey was carried out on 138 workers exposed to laboratory animals. Sixty (44%) had symptoms in a self completed questionnaire that were consistent with laboratory animal allergy (LAA) of whom 15 (11%) had chest symptoms. There was a positive skin prick test to one or more animal urine extracts (rat, mouse, guinea pig, rabbit) in 13% and 38% had a positive radioallergosorbent test to urine extract. LAA chest symptoms were almost five times more common in atopic than non-atopic subjects (who were distinguished by skin test response to common, non-animal aeroallergens). A positive skin test to animal urine was associated with LAA chest symptoms and with atopy. Nose, eye, or skin symptoms without chest symptoms were not associated with atopy. There was an inverse relation between duration of employment at the firm and LAA chest symptoms, suggesting selection of affected people out of employment with animals.

Workers exposed to animals are at risk of occupational asthma, rhinitis, conjunctivitis, or urticaria, components of the urinary protein of rats and mice being major allergens.[1] Several surveys have described prevalence rates of laboratory animal allergy (LAA) of 15 to 30%[2-8] and a prospective study has estimated the cumulative incidence rate in the first year of employment as 15%.[9] The present survey was carried out as part of a more general assessment of occupational hazards at a pharmaceutical company. The company was aware of a few cases of LAA but it was not considered to be an important problem.

Methods

SUBJECTS

The survey took place in 1984 at a United Kingdom pharmaceutical company. The firm's laboratory safety officer identified 158 workers who came into contact with animals in their work. All workers whose current exposure was at least as great as his own were included. Of these, 138 (87%) completed a questionnaire, 133 (84%) had skin prick tests, 130 (82%) gave a blood sample, and 129 (82%) had all the tests. We understand that some of the 20 individuals we did not see had animal related symptoms and, despite reassurances, feared that information from the survey might be passed to their management.

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EXPOSURE TO ANIMALS

Visits to the animal houses and laboratories showed that the company bought or bred a wide variety of animal species. Large numbers of small mammals (rat, mouse, guinea pig, and rabbit) were kept and all subjects had some contact with them, at least indirectly, such as by working near them or near cages, bedding, or dirty laboratory coats. Other species, such as insects, were handled in separate accommodation and only a few people were exposed.

QUESTIONNAIRE

A self administered questionnaire was distributed before the survey. It was based on questionnaires we have used previously in surveys of occupational asthma[10 11] and contained questions on date of birth, sex, date of joining the company, type of current contact with animals, history of exposure to animals at the company, in previous employment, and at home, and smoking history and symptoms. The symptom questions asked if the worker had ever experienced chest, nose/eye, or skin symptoms and, if "yes," the dates of first and most recent symptoms, if the severity

changed when away from work, and if they were provoked by one or more named animal species.

An animal handler was defined as someone whose animal exposure in his present job was by "general care of animals." This group appeared to have the most frequent and intense exposure to animals. An experimental worker carried out experimental procedures on animals, their tissues or body fluids, but was not an animal handler. A worker with indirect contact was one who was neither a handler nor an experimental worker. A smoker had smoked at least one manufactured cigarette a day (or its equivalent in other tobacco products) for at least one year. An ex-smoker had not smoked for three months or more. Chest symptoms were wheezing or whistling in the chest, chest tightness, or difficulty in breathing. Nose/eye symptoms were blocked, itchy, or runny nose, sneezing, or itchy or runny eyes (excluding colds or influenza). Skin symptoms were itchy bumps on the skin (excluding insect or nettle stings). A work related symptom was defined as improving at weekends, on holiday, or after a change in work practices which reduced animal exposure, such as wearing respiratory protection or protective clothing, delegating animal work to others, or moving workplace. An animal related symptom was defined as occurring on contact with one or more animal species or their tissues or body fluids.

IMMUNOLOGICAL TESTS

Skin prick tests were carried out on the flexor surface of the forearm and read at 10 to 15 minutes. The mean of two weal diameters at right angles was measured, without knowledge of exposure or symptoms. Results are presented relating to histamine, Coca's solution, B2 grass pollen mixture, *Dermatophagoides pteronyssinus*, and *Aspergillus fumigatus* (Bencard), and rat, mouse, guinea pig, and rabbit urine extracts (Beecham Pharmaceuticals). Cat and dog dander and, in selected subjects, insect antigen extracts, were also used but no results are presented. A weal diameter of 2 mm or more, after subtraction of any response to Coca's solution, was regarded as positive. Atopy was defined as a positive test to the non-animal aeroallergens grass pollen, *D pteronyssinus* or *A fumigatus*. The radioallergosorbent test (RAST) carried out without knowledge of exposure, symptoms, or skin test results, was used to measure serum specific IgE antibody to rat, mouse, guinea pig, and rabbit urine extracts, whose preparation has been described.[9] The mean counts per minute (cpm) from duplicate tests was taken and expressed as percentage binding of 125I anti-IgE tracer added (100 × cpm bound after washing/cpm added). Serum samples from 20 workers from a light engineering workshop were tested as unexposed referents in a separate assay. The *t* distributions from their results were used to derive values estimated to cut off the top 1% of binding in unexposed subjects. Binding of at least this value was regarded as positive.

Statistical analysis was aided by the software package Minitab (Pennsylvania State University) and used conventional techniques. Statistical significance was assumed when $p < 0.05$.

Results

Of the 138 subjects seen, 42 were animal handlers, 80 were experimental workers, and 16 currently had only indirect exposure (table 1). The group was young (mean age 32·3 years), contained more men than women (82:56), and its mean duration of employment at the firm was 8·8 years. The "indirect" animal contact group, which included department heads, had worked at the firm almost twice as long as the others. The 138 subjects described contact with a wide variety of animals at the firm (table 2); 45 reported previous occupational exposure to animals and 115 had, at some time, kept an animal at home. Fifty one reported symptoms provoked by at least one (usually several) species. Nose or eye symptoms were the most common symptoms provoked by animals, and rat, mouse, guinea pig, and rabbit were the group most frequently reported to provoke symptoms (table 2). The analyses were restricted to rat, mouse, guinea pig, and rabbit. They were carried out first by individual species, with similar results, so, with some exceptions, grouped data are presented.

LAA was accordingly defined as symptoms which were either provoked by rat, mouse, guinea pig, or rabbit or were work related (see Methods). Sixty (44%) had LAA and all 60 reported symptoms at some time at this firm, 46 (77%) during the six months before the survey. In 43 (72%) the symptoms had started for the first time after joining the firm. Of the 60

Table 1 *Animal contact, sex, age, and duration of employment*

Current animal contact	*Animal handlers*	*Experimental workers*	*Indirect contact*	*Total*
No	42	80	16	138
Women	55%	34%	38%	41%
Age (y)*	32·8 ± 12·2	31·2 ± 8·8	36·9 ± 9·5	32·3 ± 10·1
Employment duration (y)*	8·5 ± 7·7	7·8 ± 7·5	14·0 ± 10·1	8·8 ± 8·0

*Mean ± SD.

Table 2 *Direct exposure to, and symptoms provoked by, different animal species*

	Exposure		*Symptoms*			
Species	*This firm*	*Lifetime*	*Chest*	*Nose or eye*	*Skin*	*Any*
Rat	117	121	5	14	14	22
Mouse	89	99	3	8	6	11
Guinea pig	77	95	8	12	4	12
Rabbit	87	105	5	25	6	28
Any small animal*	124	130	10	35	17	41
Cat	56	95	10	13	4	15
Dog	81	115	5	8	5	10
Miscellaneous†	81	101	2	4	0	4
Any other animal*	117	134	12	20	6	21
Any animal	138	138	16	45	18	51

*Small animal: rat, mouse, guinea pig, or rabbit.
†Various types, including sheep, cattle, primates, birds, and insects.

with LAA, 25 (42%) had multiple symptoms (fig 1). All of the 15 with LAA chest symptoms reported additional symptoms. There were 45 with either LAA nose or eye or LAA skin symptoms only.

RAST binding is compared with skin weal diameter for rat urine extract in fig 2; plots for mouse, guinea pig, and rabbit were similar. RAST binding and skin weal diameter were correlated, even when the strong effect of the large number of people in whom both tests were negative was removed by restricting the calculation to those with detectable skin weals. In these, Spearman's rank correlation coefficient was significant at the 1% level for all four animal species (rat 0·73, mouse 0·74, guinea pig 0·69, rabbit 0·63). RAST binding in the unexposed referent sera is also shown in fig 2. The positive RAST definitions obtained from these sera were at least 1·2% for rat, 0·9% for mouse, 1·1% for guinea pig, and 1·0% for rabbit.

Subjects tended to be positive, in both RASTs and skin tests, to several species or to be negative to all. There were 49 with at least one positive RAST (rat 24, mouse 40, guinea pig 23, rabbit 20) and 17 with at least one positive skin test (rat 13, mouse 7, guinea pig 10, rabbit 6). All 17 with at least one positive skin test also had at least one positive RAST (table 3) and in comparisons for individual urine extracts all subjects with a positive skin test except one had a positive RAST against the corresponding animal. Thirty one had negative skin test results but at least one positive RAST. Comparing those with a positive RAST, binding was significantly higher in those with a positive than a negative skin test for all four species, as

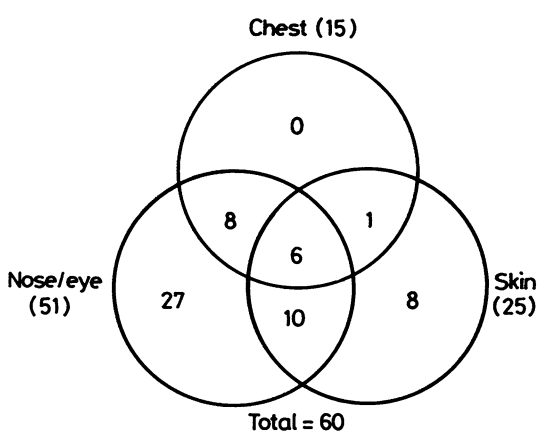

Fig 1 *Overlap of symptoms of LAA.*

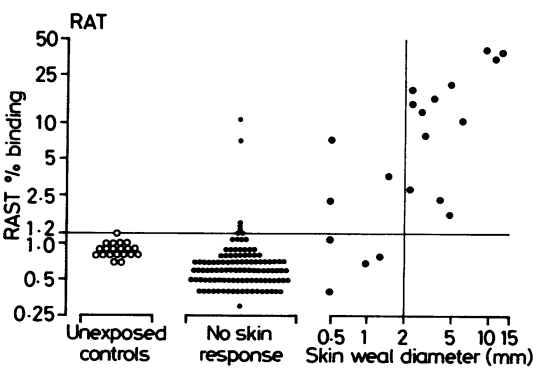

Fig 2 *Relation between serological and skin response to rat urine extract. A total of 129 had skin tests and gave a blood sample. Horizontal line at 1·2% is a positive rat urine extract RAST and vertical line at 2 mm is a positive skin test. For those with detectable skin weals, Spearman's rank correlation coefficient was 0·73 ($p < 0·01$).*

Table 3 *Skin tests and RASTs with small animal urine extract*

	Skin test	
	*At least one positive**	*All four negative*
RAST:		
At least one positive*	17	31
All four negative	0	81

*Definitions in methods section. One person declined skin tests but had positive RASTs, four declined a blood sample and had negative skin test results, and four declined skin tests and giving a blood sample.

Table 5 *Different symptom patterns related to RAST results*

Small animal related	*Work related*		*Positive RAST*	
		No	*No*	*%*
Yes	Yes	27	14	52%
Yes	No	9	6	67%
No	Yes	21	12	57%
No	No	40	11	28%

No = 97 symptomatic workers who gave blood samples.
Six of 33 (18%) asymptomatic workers had a positive RAST. Proportion positive in rows 1–3 significantly greater than in row 4 ($p < 0.01$).

would be expected from the positive correlation between RAST binding and weal diameter.

Table 4 compares symptom categories on several variables. There were significant differences ($p < 0.001$) in the frequency of atopy, a positive skin test to urine extracts and a positive RAST, which were most common in those with LAA chest symptoms and least common in those with no symptoms. There was a suggestion of a similar pattern for current smoking, which was most frequently reported by those with LAA chest symptoms. A slight excess of workers had only indirect current exposure in the group with LAA chest symptoms.

The symptom patterns making up the definition of LAA were compared individually with RAST results (table 5). In the 97 workers with symptoms who gave a blood sample the prevalence of a positive RAST was similar in those with both small animal related and work related symptoms (52%) to that in workers with only small animal related (67%) or only work related symptoms (57%). The prevalence of a positive RAST in workers whose symptoms were related neither to small animals nor to work (28%) was lower ($p < 0.01$) and not significantly different from that in asymptomatic workers (18%).

Atopy was associated with LAA chest symptoms, which were five times more common in atopic than non-atopic subjects (20% compared with 4%, table 6). A positive urine extract skin test was also more common in atopic (23%) than non-atopic subjects (5%). The combination of atopy and positive animal skin test was particularly associated with LAA chest symptoms, which were reported by 54% of this group of 13. Atopy was not associated with LAA nose or eye or skin symptoms, when present without chest symptoms, and only weakly associated with a positive RAST when present without a positive skin test.

The effect of duration of employment was examined by grouping subjects into quartiles of employment (table 7). Although not statistically significant, there was clearly an inverse trend by duration of employment for the prevalence of LAA chest symptoms and of a positive urine extract skin test. The three with LAA chest symptoms in the indirect animal contact

Table 4 *Characteristics of workers with different types of symptoms*

	Symptom group			
	LAA chest symptoms (n = 15)	*LAA other symptoms (n = 45)*	*Symptoms not related to animals or work (n = 42)*	*No symptoms (n = 36)*
Age (y)†	31·8 ± 10·3	31·2 ± 9·4	33·6 ± 10·9	32·5 ± 10·1
Employment duration (y)†	8·5 ± 11·8	8·4 ± 6·9	10·8 ± 9·2	6·9 ± 5·4
Women	9 60%‡	17 38%	19 45%	11 31%
Work:				
Handlers	4 27%	15 33%	12 29%	11 31%
Experimental	8 53%	24 53%	27 64%	21 58%
Indirect	3 20%	6 13%	3 7%	4 11%
Smoking:				
Current	5 33%	9 20%	9 21%	6 17%
Former	1 7%	4 9%	7 17%	8 22%
Never	9 60%	32 71%	26 62%	22 61%
Atopy*	11 79%	17 39%	24 59%	6 18%
Positive skin test to urine extract*	7 50%	6 14%	3 7%	1 3%
Positive RAST to urine extract*	12 80%	20 48%	11 28%	6 18%

*$p < 0.001$.
†Mean ± SD.
‡Percentage of column total, except for atopy and skin tests, where denominators were, from left to right, 14, 44, 41, 34 and for RASTs, where they were 15, 42, 40, 33.

Table 6 *LAA symptoms, atopy, and immunological response to small animal urine extracts*

Immunological group	*Symptoms*	*Atopic*		*Not atopic*		*Total*	
Positive skin test and RAST	LAA chest	7	54%	0	0%	7	41%
	LAA other	3	23%	3	75%	6	35%
	No LAA	3	23%	1	25%	4	24%
		13	100%	4	100%	17	100%
Negative skin tests but positive RAST	LAA chest	3	18%	1	7%	4	13%
	LAA other	6	35%	8	57%	14	45%
	No LAA	8	47%	5	36%	13	42%
		17	100%	14	100%	31	100%
Negative skin tests and RASTs	LAA chest	1	4%	2	4%	3	4%
	LAA other	7	27%	15	27%	22	27%
	No LAA	18	69%	38	69%	56	69%
		26	100%	55	100%	81	100%
Total	LAA chest	11	20%	3	4%	14	11%
	LAA other	16	29%	26	36%	43	33%
	No LAA	29	52%	44	60%	72	56%
		56	100%	73	100%	129	100%

No = 129 who had skin tests and gave a blood sample.

Table 7 *Duration of employment at the firm and LAA*

	Employment quartiles							
	First		*Second*		*Third*		*Fourth*	
Range of duration of employment (y)	0·24–2·68		2·70–5·92		6·15–11·80		11·86–41·76	
Symptoms:								
LAA chest	6	18%	5	14%	1	3%	3	9%
LAA other	10	29%	13	37%	11	31%	11	32%
Other	8	24%	7	20%	12	34%	15	44%
None	10	29%	10	29%	11	31%	5	15%
	34	100%	35	100%	35	100%	34	100%
Immunology:								
+ Skin test	8	24%	5	16%	3	9%	1	3%
+ RAST only	9	27%	9	29%	9	27%	4	13%
Neither	16	49%	17	55%	21	64%	27	84%
	33	100%	31	100%	33	100%	32	100%

group (table 4) had been employed for longer (mean 22·3 y) at the firm than experimental workers (5·8 y) or handlers (3·8 y) with LAA chest symptoms.

Discussion

There was a high prevalence of LAA at this firm:44% of the subjects had symptoms consistent with LAA and 38% had serological evidence of specific IgE antibody against animal urine extract. It is unlikely that the high prevalence is due to selection bias. Firstly, the group was assembled by the safety officer who used his own intermittent contact with animals as the criterion for inclusion. Secondly, the response rate was 87% and we understand that an important reason for not participating was fear of disclosure of animal related symptoms to the employer. Therefore, by including subjects with minimal animal contact and excluding some who probably had LAA our estimated prevalence of LAA is likely to be conservative. Prevalence will also be an underestimate if affected people had left because of symptoms: there is indirect evidence that this had happened. There were more subjects with indirect animal exposure among those with LAA chest symptoms than in other symptom groups (table 4). Also, the prevalence of LAA chest symptoms and of a positive skin test to animal urine was inversely related to duration of employment (table 7). These paradoxical relations between LAA and indices of exposure to animals suggest that workers with LAA, particularly with chest symptoms, avoided animal exposure, either by leaving or by taking a job at the firm with less animal contact. Such selection is often assumed to occur in populations at risk of occupational asthma[12 13] but we believe these are the first data which support this assumption.

The high prevalence at this firm may be, in part, due to study methodology. Our definition of LAA symptoms was broader than in some other studies. For example, a similar study in a different pharmaceutical company defined LAA as symptoms which were both work related and animal related and reported a

prevalence of LAA of 30%.[3] Had we used this definition our prevalence estimate would have been lower (table 5). The proportion with positive RAST(s), however, was similar in people with only work related or only animal related symptoms compared with those with both symptom patterns so our definition of LAA does not appear too broad. The RAST binding values we regarded as positive were lower than, for example, those of Davies *et al*,[9] who took binding of 3% or more as positive. But fig 2 shows that the control blood samples, which were tested in a separate assay, gave relatively high binding compared with most of the survey samples and thus conservative cut off values for positive. Taking a weal of at least 2 mm diameter as a positive skin test was also conservative, for even those with skin weals of less than 2 mm had higher RAST binding than those with no detectable weal (fig 2). Lastly, if we had also measured antibody in other classes, included other antigens, such as animal dander or saliva,[14] or studied allergy to additional species used at the firm, the prevalence of an immunological response to animals would probably have been higher.

The evidence suggests, therefore, that LAA was common in this firm even though it was not regarded as a problem. Commercial, governmental, and academic institutions conduct research with animals and there may be similar, unsuspected, high rates of LAA elsewhere. One problem with the high prevalence of LAA is that it may become a familiar and accepted occupational hazard and, as in this firm, rarely present for medical attention. Most of the LAA symptoms reported by subjects were mild but nevertheless probably reduced well being and the long term effects of exposure to animals are unknown. In a follow up of occupational asthma due to Western red cedar wood those with a poor outcome after avoiding exposure had been exposed for longer after developing symptoms than those with a good outcome,[15] leading Chan-Yeung to suggest that delay in diagnosis and in avoiding exposure adversely affected prognosis.[16] Continued exposure may, by analogy, adversely influence prognosis in LAA. Although anecdotally LAA has a good prognosis when exposure is avoided, no formal follow up studies have been carried out.

Primary control of any occupational hazard is achieved by reducing exposure. Interested organisations such as the Association of the British Pharmaceutical Industry are aware of LAA and offer advice on control measures[17] but there is no consensus as to the best method of reducing exposure to animals. The concentration of rat urine allergen in animal house dust samples is greater than that of house dust mite allergen in house dust samples,[18] which may explain the higher frequency of LAA than house dust allergy. Airborne animal allergen concentration varies with spontaneous activity of the animals and with type of experimental procedure.[19] Experimental work has suggested that modifying the humidity or ventilation in animal houses can reduce the environmental allergen load[20] but no controlled study of these or other measures under normal working conditions has been done to evaluate their effectiveness in reducing the incidence of LAA or severity of symptoms. The absence of definitive intervention studies, however, should not preclude attempts at environmental control.

Secondary control measures include excluding those thought to be at increased risk of occupational disease from exposure and detecting disease at an early stage. The survey confirmed that atopy is associated with LAA and that this is explained by a strong association with chest, rather than other, symptoms.[3 5 7] It is unclear why only some people develop chest symptoms or why atopy is particularly associated with chest symptoms. Both atopy and an immunological response to urine extract were associated with chest symptoms, so that over half the atopics with a positive skin test to urine extract (who also had the highest RAST binding to urine extract) had LAA chest symptoms (table 6). As atopy is common in the general population, it is difficult to justify excluding atopic subjects from employment with animals,[21] but atopic subjects who develop a positive skin test to animal allergens may be at particular risk of chest symptoms and could be identified during employment and advised of this risk. Screening by skin testing and questionnaire is carried out in some large institutions and, it could be argued, should be practised more widely. But the translation of these results to screening assumes that the results of a cross sectional study are applicable to follow up of exposed workers. Only one longitudinal study has been reported,[9] and this presented no data on atopic status at the time of joining the firm. Nevertheless, regular screening at least provides useful information on the scale of the LAA problem within an organisation and, in conjunction with occupational histories, may point to particular working areas or practices which should be modified. For routine screening of large numbers, skin tests appear preferable to RASTs as they are less invasive, inexpensive, give results in a few minutes, and there is broad agreement that a weal of at least 2–3 mm diameter is of clinical relevance. Furthermore, high serum levels of specific IgG antibody to animal antigens, and of total IgE antibody, are potential sources of error in the RAST.[22]

There is evidence that smoking increases the risk of developing specific IgE antibody to occupational allergens and of developing symptoms of asthma.[23] There was a suggestion in these results of an association between LAA chest symptoms and current smoking and the role of smoking as a risk factor for

LAA is examined further in a companion paper.[24] No previous study of LAA has suggested an association with smoking, but if present, there would clearly be potential for prevention and many firms already discourage smoking because of its established health risks.

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