Laboratory animal allergy: a clinical survey of an exposed population

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ABSTRACT A clinical survey of workers exposed to laboratory animals in a pharmaceutical company was designed to discover the prevalence and severity of symptoms of laboratory animal allergy (LAA). The overall prevalence of the condition was 30%, and two distinguishable LAA syndromes, termed regional and progressive LAA, were found. The first is characterised by rhinitis with negative skin prick tests. The second consists of rhinitis leading progressively to asthma with positive prick tests. Prick tests were useful diagnostically only in the latter. Atopics were shown not to be at special risk of developing LAA, but if they did so were more likely to progress to asthma. The implications for selection and management policy are outlined and specific measures for the further study of LAA are proposed.

The development and safety evaluation of new therapeutic agents has resulted in the exposure of human populations in industry to experimental animals and the consequent possibility of developing allergy during the course of work. Lincoln et al and Lutsky and Neuman in the United States have reviewed large populations handling laboratory animals and have described the associated symptoms. Perception of the true nature of allergens in laboratory animal allergy (LAA) has been refined by the observation of Newman-Taylor et al of the sensitising potential of low molecular weight urinary proteins in the rat. Our survey, which was carried out in a pharmaceutical company in the summer and autumn of 1978, was designed to discover the prevalence and the clinical characteristics of LAA in a population exposed to laboratory animals in Britain.

Methods
The population studied was located at two sites and was engaged in animal husbandry and experimental studies. Working conditions were similar to those obtaining in animal-handling facilities in other companies in Britain. The total exposed population was identified by reference to job descriptions and subdivided into work categories.

The MRC respiratory questionnaire, an in-house LAA questionnaire designed specifically for this study, and lung function and prick tests were all administered on the same occasion. The LAA questionnaire examined family and personal histories of atopy and pre-employment exposure to animals, and then sought information on symptoms due to allergy. The possibility of symptoms being work-related was then explored. Questions about correlation to animal exposure were left to last. Details of time sequence and progression of symptoms were also recorded. All procedures were performed on a Friday, thus allowing lung function tests to act as possible indicators of work-week effect. The entire population of 146 people currently exposed to animals took part in the survey voluntarily.

Standard skin prick tests were performed using commercially available preparations of common environmental allergens and dander extracts of animals used in research (Bencard for guinea pig, mouse, and rat extracts). Dome Labs for remainder). One person from the index population refused prick tests. Lung function tests were performed on the Vitalograph spirometer according to standard techniques. Records were made of FEV1, FVC, and FEV1/FVC ratio. One trained operator performed all the tests, and there were no refusals of lung function tests.

Atopy was defined according to Pepsy's criteria as any skin-positive reaction with wheal and flare to one or more of the following—grass mixture, house-dust extract or house-dust mite, or Aspergillus
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fumigatus. Asthma due to LAA was understood, in terms of the in-house questionnaire, as a positive subjective correlation between work, exposure to certain specific animal species, and chest wheezing. Conjunctivitis and rhinitis were defined in similar terms.

Results

PREVALENCE
Table 1 shows the number of cases of LAA and its prevalence in each work category. These results show asthma to have been confined to experimental workers but indicate that those engaged in animal husbandry include an appreciable proportion of people with rhinitis.

DISTRIBUTION OF ATOPY
Tables 2a and 2b show the distribution of atopy within the exposed population and the number of atopes with asthma contrasted with atopy in those with rhinitis only.

LATENCY
Table 3 compares the latency of onset of symptoms in rhinitis-only and in asthmatic (progressive) cases. There is little difference in time to onset of first symptoms, but 66% of those with progression to asthma who responded positively to the question developed their asthma within three years of their first symptom. This rapid acquisition of further symptoms, however, is not pronounced enough to be useful in setting a cut-off point for predicting who will or will not develop asthma.

SKIN PRICK TESTS TO ANIMAL ALLERGENS
The distribution of positive prick tests within the total animal-exposed population (table 4a) shows that positive prick tests are confined to the population with LAA. This result may be refined by comparison of syndrome subgroups within the LAA population (table 4b). There is a strong correlation between positive prick tests and asthma (progressive) disease but poor correlation for rhinitis-only LAA.

LUNG FUNCTION TESTS
Table 5 shows the significant findings from these tests. The asthmatic cases show a decrease in FEV1/FVC ratio, which may be a work-week effect; there is no such decrease in controls or in cases with rhinitis-only.

AGE, SEX, ETHNIC GROUPING, SMOKING, AND OWNING OF PETS
The data were analysed for the effect of these factors on all results, but no significant differences were noted within the LAA groups or in controls.

Table 2a Distribution of atopy in the exposed population

<table>
<thead>
<tr>
<th>Subjects with LAA</th>
<th>Asymptomatic subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atopes</td>
<td>20</td>
</tr>
<tr>
<td>Non-atopes</td>
<td>28</td>
</tr>
</tbody>
</table>

x² = 2-00. Not significant.

Table 2b Distribution of atopy within the LAA group. Rhinitis v progressive disease

<table>
<thead>
<tr>
<th>Rhinitics</th>
<th>Asthmatics (progressives)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atopes</td>
<td>8</td>
</tr>
<tr>
<td>Non-atopes</td>
<td>25</td>
</tr>
</tbody>
</table>

x² = 14-7. Significant at p = 0-001.

Table 3 Latency from first exposure to first and subsequent symptoms, rhinitis v progressive cases

<table>
<thead>
<tr>
<th>&lt;1 year</th>
<th>1-3 years</th>
<th>&gt;3 years</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhinitics</td>
<td>9%</td>
<td>39%</td>
<td>36%</td>
</tr>
<tr>
<td>Asthmatics (progressive)</td>
<td>20%</td>
<td>27%</td>
<td>40%</td>
</tr>
</tbody>
</table>

Time from first exposure to onset of first symptom

Time from first to subsequent symptoms

Table 4a Distribution of positive prick tests to animals in the exposed population

<table>
<thead>
<tr>
<th>Prick tests</th>
<th>Subjects with LAA</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive (1 or more)</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td>Negative</td>
<td>26</td>
<td>98</td>
</tr>
</tbody>
</table>

x² = 15-64. Significant at p = 0-001.
Table 5  Student t test on FEV₁/FVC ratio

<table>
<thead>
<tr>
<th>FEV₁/FVC ratio</th>
<th>Mean ± SE</th>
<th>Predicted ratio</th>
<th>t value</th>
<th>2-tail significance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Actual ratio</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthma cases vs rhinitic cases</td>
<td>77.1 ± 2.39</td>
<td>82.3 ± 1.20</td>
<td>-2.194</td>
<td>p = &lt;0.05</td>
</tr>
<tr>
<td>Asthma cases vs controls</td>
<td>77.1 ± 2.39</td>
<td>83.3 ± 0.90</td>
<td>-2.800</td>
<td>p = &lt;0.01</td>
</tr>
</tbody>
</table>

Discussion

Previous surveys have shown the prevalence of LAA to be between 11.3%¹ and 14.7%² in laboratory animal-exposed populations. The prevalence in this study was 30%. Previous studies, like the one described here, have been cross-sectional and therefore, by their nature, deal with survivor populations. An entire working population were traced the prevalence might be over 50% (A Newman-Taylor, personal communication). The under-reporting of prevalence in earlier surveys may be due to differences in working conditions in laboratories in the United States and Britain but is more possibly due to variations in method. Thus one study² relied on obtaining prevalence rates by sending a questionnaire to many institutions handling laboratory animals, and it is unlikely that the respondents from these institutions would all use the same criteria for the definition of LAA or the same energy in seeking out cases. Also the amount and type of animal exposure was relatively imprecisely quantified, so that the populations were likely to show dilution by including those administratively ascribed to a particular department but not actually having contact with animals. This survey has attempted to define its animal-exposed population much more closely. The definition, however, of an animal-exposed population in absolute terms can only be consequent on a properly constituted occupational hygiene survey correlated to work patterns and clinical manifestations of illness.

While our LAA questionnaire was specifically designed to avoid leading questions whenever possible, our acceptance of patients’ correlation between symptoms and work-exposure is clearly subjective and cannot avoid memory bias. We consider, however, that our reliance on this method is vindicated by the high level of agreement between the results of the prick test and the subjective finding of symptoms in the asthmatic group with LAA. We did not perform any type of challenge test as we were not satisfied that any set of standardised conditions could evoke the true range of responses in the population studied.

There appear to be two syndromes associated with LAA. The first, which includes most cases, comprises patients who have rhinitis with or without skin sensitivity. In terms of the results of the prick test and prevalence of atopy this group cannot be separated from a positive control group (the animal-exposed population without LAA) except by the manifestation of their symptoms. The minority group contains those who develop asthma due to LAA. They are characterised by an illness that usually begins as rhinitis and progresses to asthma, usually over a period of a year or two. This group may be clearly differentiated from the exposed population without LAA and from the rhinitis-only group in terms of prevalence of atopy (80%), and prick and lung function test results. Possibly, therefore, two separate groups with LAA can be defined on clinical grounds. For these groups we propose the terms regional and progressive LAA.

This differentiation improves our perception of LAA, particularly with regard to the prognosis of case. The minority group consists of people who are unlikely to progress to asthma. They may therefore be allowed, if they wish, to continue working with animals. In the reasonable belief that there is a low risk of serious consequences. A few of the group will progress to asthma, but these can easily be identified at an early stage by follow-up, which is clearly an important part of their health supervision.

The survey results indicate that atopy by itself is not associated with a higher prevalence of LAA but that the distribution of atopes is concentrated among those with progression to asthma. It appears, therefore, that while atopes are no more likely than others to get LAA, if they do it tends to be progressive. This has clear implications for employment selection policies. The distribution of atopy in the population under study was 33%, which is similar to that of the general population,² suggesting that our data are not biased by the loss of atopes from work involving exposure to animals.

It has been suggested that LAA is a disease of animal experimenters and not of animal handlers,² but this is refuted by the results presented in table 1. The absence of progressive cases in animal handlers in this study is noteworthy but, bearing in mind the small numbers surveyed, could also be due to job transfer or to chance. The fact remains that LAA clearly occurs among animal handlers, as indeed it does in those supposedly more casually concerned with animals in auxiliary jobs and maintenance.
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Prick test results to animal dander extracts showed a good correlation with symptoms in the progressive LAA group. Moreover, the people in this group were able to identify accurately those animals to which they were allergic, and their prediction was confirmed by subsequent prick testing. This was in direct contrast to the regional LAA group, where positive prick tests to animals were relatively uncommon and correlated poorly with patient claimed allergy. The prick test is therefore a useful tool in diagnosing established, progressive LAA. It appears to be of no value in rhinitis, however, and its usefulness in predicting progression from rhinitis to asthma awaits a larger scale prospective study.

Our knowledge of the antigens in LAA is sketchy. Most studies have examined allergy to the Wistar rat, and work is currently under way to identify the antigenic role of animal hair and scales. Although the rat poses the largest problem of LAA since so many are used in laboratories, other animals may be more efficient sensitisers. Rudolph6 has noted the high antigenicity of the guinea pig and we have also observed this to be the case. The rabbit is also a highly antigenic animal. To gain a better understanding of LAA, it is important that this area of comparative antigenicity be explored further.

We have touched on the difficulties inherent in using a cross-sectional survey to establish “true” incidence and prevalence of an occupational disease. There is a clear need for a prospective study of recent entrants to laboratory animal work to establish the incidence and prevalence of LAA and to chart its development. Such a study could be definitive, especially if it were designed to run alongside a properly constituted occupational hygiene survey, so that some quantitative correlation could be made with incidence and prevalence. Only then would it be possible to offer an opinion on the establishment of hygiene standards. Meanwhile we consider it premature to make any other than the most general recommendations about the protective efficacy of specific designs for cages, animal rooms, experimental rooms, ventilation systems, and other protective equipment.

We thank Sister L A Hyde, SRN, for her clinical work and her resolution in achieving 100% compliance within the survey.

References