

EDITORIAL

Occupational sensitization to laboratory animals

Laboratory animal allergy (LAA) is a common occupational health problem affecting those working with rats (*Rattus norvegicus*), mice (*Mus musculus*) and other small animals. Approximately one-third of those who encounter these animals in their work will develop allergic symptoms such as rhinitis, conjunctivitis, contact urticaria and asthma [1,2]. Symptom severity can vary from mild upper respiratory tract symptoms to severe, life-threatening asthma; in rare cases anaphylactic episodes can follow animal bites. Laboratory animals are consistently reported by the SWORD (surveillance of work-related and occupational respiratory disease) project as one of the three most common causes of occupational asthma [3]. Asthma may develop in one in 10 people with animal exposure and may increase in severity should they remain exposed. Changes in airway responsiveness have been reported in subjects who have mild LAA without chest symptoms after relatively short periods of working with animals [4]. A history of atopy and current exposure are consistently identified as risk factors for LAA symptoms but do not have enough discriminatory power to enable their use for effective pre-employment screening [2,5].

Since there is still a need for animals in medical research and close animal contact is difficult to avoid, recent research has focused on understanding the aetiology of the disease and the influence of allergen exposure on disease incidence. In this issue, Hollander *et al.* [6] report a detailed study describing the exposure of Dutch research workers to rat and mouse urinary aeroallergens.

Allergen characterization

In 1977, the urine of rats and mice was first identified as an important source of allergen [7]. Urine has therefore been employed frequently as a standard for the quantification of airborne rat and mouse allergens. Immunoblotting studies have identified the major urinary allergens [6,8] and have demonstrated how the age and sex of the animal, particularly in rats, can influence the allergenic composition of the urine; adult male rats and mice are important sources of the major allergens Rat n 1.02 (17 kDa, also called α_{2u} -globulin) and Mus m 1 (18 kDa, also called major urinary protein [MUP]). The sequence homology between Rat n 1.02 and Mus m 1 is high (66%) [9]. Both are globular proteins with pheromonal properties [10,11] whose production are under complex hormonal control [12,13]. Rat n 1 is very effective at binding toxins which results in a progressive renal nephropathy [14] and the ultimate excretion of increasing amounts of serum

proteins in the urine of rats [8]. Female rats, and mice are less prone to these effects.

Gordon *et al.* have examined the allergenic composition of rat dust [15] and identified the presence of Rat n 1 in airborne dust. A recent study by Bayard *et al.* [16] reported the amino acid sequence of Rat n 1 and prealbumin (21 kDa) and found that they constitute different forms of the same parent protein. These observations identify Rat n 1 as a suitable marker protein for the development of monoclonal antibody based assays. Little is known about the allergenic composition of mouse dust.

Quantification of aeroallergen exposure

Measurement of occupational exposure to rat and mouse proteins has only recently been undertaken. The many different immunological methods used have probably contributed to variations in the exposure values reported for rat (range 10^{-10} g/m³– 10^{-4} g/m³) [6,17,18]; when the RUA content of the same air samples was quantified by two assays employing Rat n 1 monoclonal antibodies and specific IgE (RAST inhibition), up to 2700-fold differences in the reported values were observed [19]. Measurements made within the breathing zone of those working with animals show that the exposure to rat allergens within any job category is very heterogeneous. Tasks involving direct contact with animals or soiled litter are associated with particularly high levels of exposure. Hollander *et al.* have confirmed these observations in personnel working with rats in the Netherlands and have reported one of the first detailed studies of the occupational exposure to mouse aeroallergens [6]. Although the quantification of mouse aeroallergens is less well documented, qualitatively the exposure to both species appears to be similar probably reflecting the similar nature of the allergens and the analogous working practices adopted [20,21]. The factors which contribute to the heterogeneity of the exposure are poorly understood although the variation in site (ventilation, etc.) and procedures undertaken may account for up to 73% of the variation [22].

These methods have been used to investigate the effect of exposure on disease development. Cullinan *et al.* [23] have described a trend for the increasing prevalence of sensitization and symptoms with increasing exposure intensity; the odds of having skin symptoms were increased 10-fold in animal technicians and individuals handling soiled litter, and fivefold in those less frequently or indirectly exposed, such as scientists. These observations imply that a reduction of exposure to laboratory animal allergens would be associated with a reduction in the risk of developing the disease.

This hypothesis is supported by Botham *et al.* who observed a decrease in the incidence of LAA symptoms when more stringent procedures, including changed work practices and the mandatory use of respiratory protection (e.g. disposable mask or ventilated helmet), was adopted [24]. The prevalence of sensitization was, however, unaffected suggesting that, in common with immediate hypersensitivity to other environmental allergens, the threshold of exposure for sensitization may be lower than that to provoke symptoms. Eggleston *et al.* [25] have challenged rat allergic individuals within rat rooms under controlled conditions and have found evidence for an apparent threshold for both nasal and respiratory symptoms. Repeated challenges with the same individuals suggested a dose–response effect between intensity of exposure and the severity of nasal and bronchial symptoms [26].

Control of exposure

It is clear from the continuing high prevalence of LAA worldwide [27–29] that individuals with animal contact remain exposed to sufficient allergen to become sensitized and develop symptoms. Even when rigorous safety procedures were enforced in a pharmaceutical company, although the reporting of symptoms was apparently improved, the numbers becoming sensitized were not [24]. Highly effective and practicable methods are needed to reduce animal allergen exposure sufficiently to prevent sensitization.

The development of methods to quantify aeroallergen exposure have allowed the objective assessment of interventions designed to reduce exposure to rat and mouse allergens. Litter has been shown to be an important vehicle for allergen dissemination [30] and the use of non-contact absorbent litters is a very effective way of reducing animal aeroallergen. The number of animals (stock density) and cage design may also directly influence aeroallergen concentrations; the use of positive individually ventilated cage systems is, although expensive, an excellent way of housing large numbers of animals whilst maintaining background levels of allergen at almost undetectable levels [31]. Exposure associated with the handling of animals may be reduced $\approx$ 20-fold when the procedure is undertaken in a ventilated safety cabinet as compared with on an open bench [31]. The same study was, however, unable to show the efficacy of vacuum systems to reduce aeroallergen exposure when removing soiled litter from cages.

Future trends

Laboratory animal allergy is a well researched cause of occupational asthma and is an excellent model for future investigations of disease aetiology (such as the interaction of immunogenetic factors and environmental exposure).

Such studies will be of fundamental importance in understanding the aetiology of allergy in general.

Rat and mouse urine (and the resulting dust within the animal environment) are complex sources of allergen exposure, and the standardization of immunological assays to quantify aeroallergen may be difficult; assays employing monoclonal antibodies for Rat n 1 will not accurately quantify all relevant allergen exposure, but polyclonal antisera will be more difficult to standardize. Standardization of assays will facilitate the comparisons of exposure data in epidemiological studies and enable scientifically based threshold values for the sensitization and elicitation of symptoms to be determined. As general measures to reduce airborne allergen (such as the use of absorbent litter, minimal stock density and individually ventilated cages) appear insufficient to reduce the risk of sensitization, future safety recommendations (in the absence of threshold values) should probably focus on the increased use of safety equipment for certain procedures. Better control of exposure during high risk procedures such as animal handling and cleaning out (including the use of ventilated work stations and respiratory protection) should assist in reducing the incidence and prevalence of this important occupational disease.

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