Introduction

The Science and Pervasiveness of Laboratory Animal Allergy

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Allergic reactions to animals are among the most common conditions that adversely affect the health of workers involved in the care and use of animals in research (NRC 1997). Of the 90,000 laboratory animal workers in the United States (Bland et al. 1987), up to 46% develop allergy to laboratory animals. Of those who develop symptoms, more than 10% eventually develop occupation-related asthma with symptoms that persist even after exposure ceases. A rare but life-threatening consequence of laboratory animal allergy (LAA[1]) is an anaphylactic reaction to animal bites, scratches, and needle sticks carrying the animal proteins. The manifestations of animal allergy, which range from rhinitis and itchy eyes to respiratory distress, have caused more than one third of laboratory animal workers at the National Institutes of Health to lose time from work (Bland et al. 1986).

Occupational allergy to animals is clearly an important and pervasive condition that affects workers in many countries of the world. Although first reported many years ago, LAA continues to be an important health problem for animal workers and an administrative and financial burden on research institutions due to lost productivity and health care costs. Although much is known about the etiology and prevention of LAA, there is much that is yet to be learned. Contributors to this *ILAR Journal* issue discuss many of the key issues of LAA and review what is known from the literature and what is yet to be determined.

The development of LAA commonly begins with the inhalation of allergens, such as animal dander and urinary proteins, into the lungs. If these allergens stimulate the development of immunoglobulin E (IgE[1]) antibodies, a cascade of events may follow. Antigen-presenting cells capture the antigen and stimulate complex T-cell replication and the production of cytokines leading to the well-known histamine response of allergy. An important variable in this equation is atopy, which is a genetic predisposition for production of IgE antibodies and the cascading events that lead to allergy. Once allergen-specific IgE antibodies are present, subsequent exposure to the allergen leads to an immediate response. It is thought that the intensity of the allergic reaction depends on the duration and intensity of exposure. Other risk factors for development of LAA are less certain. In the article titled Mechanism and Epidemiology of Laboratory Animal Allergy, Bush (2001b) discusses the role of coexisting allergies and tobacco smoking and provides a clear account of the mechanisms and epidemiology of LAA.

One might be able to initiate a good and effective LAA program while knowing little about the nature of the allergens involved. However, an understanding of the lipocalin group of small extracellular proteins that constitute animal allergens is revealing and provides important insights into their control. Wood's article, Laboratory Animal Allergens, provides a succinct and interesting review of this species-specific microcosm (Wood 2001). We generally think of rats and mice only in regard to allergen control; however, we make that association only because they are the most common laboratory animals and not necessarily because other species are less allergenic. All species, and employees who work with them, should be included in the allergy control program. We learn a great deal from this chapter about the science of allergy. For example, cats have 12 allergenic proteins and the most common one, Fel d 1, has been cloned and its amino acid sequence identified. Unfortunately, little is known about its biological function. Clearly, administrators, supervisors, and employees alike will benefit from an understanding of the nature and distribution of animal allergens.

The objective of responsible LAA programs is to control exposure to animal antigens in an effort to reduce the incidence of LAA and relieve the symptoms of sensitive employees. Exposure control begins with recognition of the sources of causative antigens and the species most apt to shed them. Most animals shed allergens through urine, dander, hair, serum, and saliva, but not all species or strains do so equally, and, in general, females shed fewer allergens. Allergen exposure is also related to the size of the allergen particle and environmental conditions in the cage as well as the type of bedding, job responsibility, and duration and magnitude of exposure. To address each of these issues in a

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[1]Abbreviations used in this article: IgE, immunoglobulin E; LAA, laboratory animal allergy.

logical manner, a hierarchy for exposure control consists of administrative controls, engineering controls, and personal protective equipment. Administrative controls recognize the importance of institutional commitment, employee training, and a myriad of other human elements. Engineering controls include such important aspects as facility design; heating, ventilation, and air conditioning specifications; and types of caging. Personal protective equipment is both the most burdensome for employees and the most problematic type of protection and therefore is the last strategy in the exposure control equation. It is, nevertheless, important in reducing employee exposure.

After an exposure control program has been developed and implemented, its effectiveness must be assessed. Harrison's article titled Controlling Occupational Exposure to Laboratory Animal Allergens explores a wide range of key factors including particle size (which contributes to biological response), type of animal and bedding, nature of the job, and effectiveness of control measures (Harrison 2001). Different routes of exposure (e.g., inhalation, transdermal and mucosal, and oral) elicit different symptoms, and the potential for each must be included in assessment. Particle physics and type and rate of respiration are important variables in this equation, and the nature of the job is critical. Animal handlers and cage cleaners are at a high level of risk; however, those with no direct contact, such as office workers, might also be exposed to high levels of allergens and should be included in the assessment of exposure control. For many individuals, respiratory protection is an attractive option, yet Harrison cautions that it is important to consider all options because engineering controls might be the most cost effective in the long run and should therefore be integrated into the facility design to the extent feasible. Facility managers often select the type of bedding for rodents based on cost, absorbency, and likelihood of inducing liver enzymes. It would be a mistake to give minimal consideration to the role of bedding in reducing allergen exposure because, as Harrison describes, noncontact pads, wood shavings, and corncob bedding vary greatly in this aspect. It is important to consider many other variables in regard to exposure control, such as cleaning methods, type of caging, ventilation design and efficiency, administrative controls, facility zoning, animal density, job rotation, equipment maintenance, housekeeping, personal hygiene, handling of waste and contaminated clothing, and perhaps most important, training and education. Harrison discusses each of these issues and puts them in proper perspective.

Gordon's discussion of laboratory animal allergy in the United Kingdom is a valuable contribution to this issue (Gordon 2001). She provides a detailed review of UK research in LAA and details the more than 20 yr of attention that have been devoted to this occupational disease. It is interesting to note, however, that in spite of this extensive literature, Gordon concludes that "the introduction of health and safety legislation . . . and an increasing knowledge of the factors that contribute to the etiology of this disease have had surprisingly little impact on the prevalence and incidence of LAA over the last 10 to 20 yr. Attitudes toward LAA have changed more quickly in large institutions and the pharmaceutical industry than in academia. If a casual attitude toward LAA still persists at the 'user' level, it is most likely because of lack of education and/or lack of support from higher management." She concludes, "Prevention of LAA in the future will probably be driven by the needs of the industry and will most likely rely on the adoption of guidelines describing 'best practise,' which incorporate sophisticated engineering methods of controlling exposure to animal allergens." She continues, "Only when it becomes unacceptable to enter an animal unit, even briefly, without following current best practice (as it now is to handle radioactive chemicals without appropriate protection), will the incidence rate of LAA reach its lowest level." Stated differently, Gordon is calling for the adoption of performance standards that will specify the important elements of that portion of the occupational health and safety program dealing with laboratory animal allergy. Her statements are in harmony with a similar call for the professional use of scientifically based performance standards, in lieu of inflexible engineering approaches, as espoused in the *Guide for the Care and Use of Laboratory Animals* (NRC 1996).

This issue of *ILAR Journal* is intended to complement and update *Occupational Health and Safety in the Care and Use of Research Animals* (NRC 1997) with information related to the topic of laboratory animal allergy. In an ever-increasing climate in which research and use practices are compared and scrutinized globally, it is important to know not only the practices but also the basis on which those practices are developed. In the United Kingdom, there is a hierarchy of criminal, social, and civil laws through which the government or injured party can seek relief and restitution. As US institutions seek to develop and implement LAA programs, it is important to know the strengths and weaknesses of other countries' approaches.

It is obvious that simply doing the "right thing" is not sufficient for the consequences of some employee's mistake or equipment failure that can be significant in terms of employee health and medical costs. Controlling and assessing the exposure are important lines of defense, but equally important is the medical surveillance of the workers. The *Guide for the Care and Use of Laboratory Animals* (NRC 1996) provides guidance for developing an occupational health and safety program, and *Occupational Health and Safety in the Care and Use of Research Animals* (NRC 1997) stresses that the population at risk must be defined quite broadly and include more that those employed to work with animals. Students and maintenance personnel, for example, are also exposed and included in the medical surveillance program.

New employees offer a unique challenge to employers, and consideration of LAA is often disregarded. How does one handle a situation in which a preplacement examination, after an offer to hire has been made, reveals that the employee has a nonoccupational allergy, such as hay fever? What is the health risk to this person if placed in an animal facility?

In the Americans with Disabilities Act (ADA 1990), it is stated that an offer to hire may be withdrawn if an individual is not able to perform the essential functions of the job. Does LAA qualify under this legal clause of the act? In Medical Surveillance of Allergy in Laboratory Animal Handlers, Seward (2001) states that it might not qualify, yet he argues that preplacement examinations are valuable for employees who will have animal exposure. Such data, collected on all at-risk employees, serve to provide an early warning and opportunity to improve preventive measures and exposure controls. Seward provides guidance for what to include in both the preplacement examination and periodic medical questionnaire and examinations. Because many animal research facilities do not have ready access to informed medical allergy information, screening and testing for LAA become insurmountable tasks. Seward's discussion of the strengths and weaknesses of the many laboratory tests and examinations provides important guidance in this regard.

It is, of course, important to take the next step and understand how to assess and treat workers with LAA. Bush's article titled Assessment and Treatment of Laboratory Animal Allergy informs us that this process begins for the research institution with a comprehensive medical history of each employee at risk (Bush 2001a). Seemingly straightforward, this assessment is complicated by the lack of standardized questionnaires; however, he provides a list of key questions and a sample questionnaire. Interestingly, one important and highly suggestive indicator of LAA is the improvement of employees' symptoms while they are away from the work environment, although this measure becomes less reliable the longer cases of LAA persist. The questionnaire provides an important baseline and, in some cases, might indicate alteration of work assignments. The assessment also provides an opportunity to educate the employee about LAA, the risks of the environment, and preventive measures that can be utilized to protect employees and their families.

Nevertheless, diagnosis of LAA relies on the presence of allergy symptoms concurrent with in vivo skin tests and in vitro measures (e.g., the radioallergosorbent test and the enzyme-linked immunoassay test) that demonstrate IgE antibodies specific to laboratory animal antigens. Measurement of lung function is also important because respiratory decompensation may not be apparent in individuals with only rhinitis and conjunctivitis. Although tests such as spirometry are well-standardized and widely accepted measures of lung function, they must be conducted appropriately for meaningful interpretation. Bush discusses the ramifications of several such important tests. As soon as a patient has been diagnosed with LAA, the single best administrative practice is to remove the worker from further exposure. It is especially important for patients with asthma to be protected from further exposure because the longer they are exposed to animal allergens, the more deterioration of the lung occurs, which places the employee at the risk of lifetime medication. Prevention, however, is much better than treatment and consists of preplacement history, education and training of the employee, administrative commitment to a safe and healthy workplace that may facilitate changes to provide appropriate engineering controls, and personal protective equipment. Each aspect of prevention has its place and each has strengths and weaknesses, which are discussed in subsequent articles of this issue.

Allergy is as common as the common cold but often has consequences that go far beyond the runny nose and itchy eyes of those affected. Rats and mice are common shedders of allergens, but most animals, including invertebrates, also shed and should not be excluded from consideration. This issue of *ILAR Journal* places LAA in proper perspective as a major health hazard and provides essential guidance for adding allergy control and assessment to an institution's overall occupational health and safety program.

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