Medical Surveillance of Allergy in Laboratory Animal Handlers

James P. Seward

Abstract

Allergic disease is a serious occupational health concern for individuals who have contact with laboratory animals. Principal respiratory symptoms include allergic rhinitis, conjunctivitis, and asthma. Urticaria ("hives") is the most common skin manifestation. The overall prevalence of allergic disease among laboratory animal handlers is about 23%, and respiratory allergy is much more common than skin allergy. Prevention of animal allergy depends on control of allergenic material in the work environment. Personal protective equipment such as air filtering respirators should be used in addition to the other exposure control technologies where conditions require. Preplacement evaluation and periodic medical surveillance of workers are important aspects of the overall occupational health program. The emphasis of these medical evaluations should be on counseling and early disease detection. The article provides recommendations for the content of the medical evaluations.

Key Words: animal allergy; contact dermatitis; occupational asthma; occupational health; urticaria

Introduction

Work with laboratory animals is an established risk factor for several allergic conditions. Allergic conjunctivitis, rhinitis, asthma, and dermatological symptoms may all result from contact with laboratory animals. Collectively these may be called laboratory animal allergy (LAA[1]). Although individuals with prolonged contact are more likely to have serious medical complaints and disability, even workers with intermittent or occasional contact may be affected. Animal type is a major factor, and certain species, particularly rodents, appear to be more allergenic than other species. The major objective for health and safety in these work environments should be to eliminate and reduce exposures. Primary prevention techniques include reducing the use of animals in experimentation, controlling the environment in the animal facility, and limiting the number of personnel with access. Another approach to primary prevention that has been proposed is to eliminate susceptible individuals from exposure. As discussed below, this method has both legal and technical limitations. In contrast to medical screening, medical surveillance is a secondary prevention tool to identify early signs of disease, hopefully at a stage in which intervention will improve the outcome. A surveillance program also examines the medical status of the exposed group as a whole and, whenever possible, attempts to use the tools of population analysis to improve the effectiveness of the health and safety program.

In this article, the issues involved with screening and surveillance of laboratory animal workers are reviewed. Substantial research has examined possible predictors and markers of allergic disease in working populations. In addition to reviews of these factors, this article provides a recommended approach to surveillance, which includes the essential elements of an effective program. Personal protective equipment, although not strictly a part of a surveillance program, is an important consideration for allergy prevention in laboratory animal care, and the use of the major types of protective equipment is discussed below.

Basis for a Medical Surveillance Program

No formal legal requirement specifically mandates employers to maintain an occupational health program in animal care facilities; however, the general duty clause of the Occupational Safety and Health Administration requires employers to maintain a safe and healthful workplace. It is both the duty of a responsible employer and a good management practice to provide such programs. Research institutions that receive funds from the National Institutes of Health have an additional obligation to comply with the requirements of the National Research Council (NRC[1]) *Guide for the Care and Use of Laboratory Animals*, which describes the necessity of an occupational health program. As stated in the NRC *Guide*, "The extent and level of participation of personnel in the occupational health and safety program should be based on the hazards posed by the animals and materials used; on the

James P. Seward, M.D., M.P.P., is Medical Director of Lawrence Livermore National Laboratory and Associate Clinical Professor of Public Health at the University of California, Berkeley, California.

[1]Abbreviations used in this article: IgE, immunoglobulin E; LAA, laboratory animal allergy; NIOSH, National Institute for Occupational Safety and Health; NRC, National Research Council; PPE, personal protective equipment; RAST, radioallergosorbent testing.

exposure intensity, duration, and frequency; on the susceptibility of personnel; and on the history of occupational illness and injury in the particular workplace"(NRC 1996, p. 14). In the *Guide,* medical surveillance is designated as one of the key elements of a program. The Association for Assessment and Accreditation of Laboratory Animal Care International also relies on the *Guide* for its standards in evaluating facilities that are attempting to attain accreditation status. The NRC has also published a report on occupational health and safety in the use of research animals, which identifies medical surveillance as a central element of its recommendations (NRC 1997).

Prevalence and Incidence of Allergic Diseases

The incidence and prevalence of LAA in the laboratory animal handler population are important considerations in the design of an occupational health program. These factors affect the types of tests, their frequency, and the overall medical surveillance strategy. The species to which a group of workers is exposed will be the most important determinant of disease frequency. The incidence and prevalence of allergy to a given species also depend on the intensity and duration of exposures to the laboratory animals. Research on these disease indicators has resulted in a wide range of findings.

Prevalence measures the number of cases of allergic disease in a population at a particular time. Studies among animal handlers have revealed a range of prevalence from 11 to 44% in various populations. Although variables such as the type, intensity, and duration of animal exposure affect prevalence, efforts to understand it are hindered by other factors. These factors include lack of a standard definition of allergy, systematic self-selection of highly allergic individuals from the workplace, and difficulty in controlling for pre-existing allergic disease.

Aoyama and colleagues performed the largest study of LAA prevalence in animal handlers, a cross-sectional survey of 5641 laboratory animal workers in Japan, in which they demonstrated an overall prevalence of 23.1% (Aoyama et al. 1992). Hunskaar and Fosse's meta-analysis of 19 different studies of animal allergy revealed an average prevalence of 20.9%. Thus, on average, one fifth of the laboratory animal exposed population will report an allergic symptom as a result of exposure (Hunskaar and Fosse 1990).

Different studies have also shown a wide range of estimated prevalence for asthma, an often disabling respiratory allergic condition. Estimates range from a low of 4% (Beeson et al. 1983) to a high of 22% (Bryant et al. 1995) of the exposed population. Aoyama's survey indicated that 9% of the occupationally exposed individuals report asthma, Venables and colleagues reported 11% prevalence (Venables et al. 1988), and Cockcroft and coworkers found 12% (Cockcroft et al. 1981)

The incidence of disease is the number of new cases occurring in a population during a defined time period. Because the study of incidence requires a prospective study and an assessment of pre-existing disease, our knowledge of incidence comes from the few studies of allergy to laboratory animals that meet these criteria. The existing studies of incidence, including all respiratory manifestations of allergy, reveal a range of approximately 2 to 12% of the population with new onset symptoms over 1 yr (Botham et al. 1987, 1995; Davies 1983; Kibbe et al. 1989). These studies indicate that intensity of exposure, exposure controls, and self-selection in the working population all affect the incidence of disease.

Skin manifestations of allergy are also a concern for laboratory animal workers. The most common problem is contact urticaria, although contact dermatitis may also occur. Unfortunately, there are only sparse data on the incidence or prevalence of skin conditions. A study performed in Sweden by Agrup and Sjöstedt (1985) revealed a 14% prevalence of contact urticaria to rats, but this appears to be an unusually high rate. Another study of pharmaceutical industry and university laboratory workers found no increase in urticaria (Davies and McArdle 1981). Evidence from the study of Aoyama and coworkers (1992) indicates that skin allergy tends to be accompanied by respiratory allergy symptoms.

Preplacement Medical Examination

In accordance with the Americans with Disabilities Act (PL 101-336 1990), employers are permitted to require preplacement examinations after an offer to hire has been made as long as the examination is given to all individuals hired for the same type of work. In some circumstances, findings on the preplacement examination may lead to the withdrawal of a job offer if the individual is not able to perform the essential functions of the job. In most cases, it is difficult to predict that an individual's allergy risk presents an imminent and severe health risk or that an individual would not be able to perform the work as a result. Most situations in which a new employee has risk factors for LAA would probably not meet the legal requirements of the Americans with Disabilities Act for withdrawal of a job offer. However, the preplacement examination is still a valuable and useful procedure for individuals who will have animal exposures. It provides an opportunity for employees to learn about their personal health risks in relation to the work with animals and to receive counseling about the advisability of assuming those risks. The clinician can also educate the employee about the signs and symptoms of allergic disease. Finally, the examination process also establishes a baseline against which future changes in health status can be measured.

Possible Predictors of Allergic Disease

Various risk factors or predictors for allergic disease have been proposed for assessment in a preplacement or baseline

medical evaluation. A personal or family history of atopy is one frequently cited predictor. Skin testing for allergy and in vitro radioallergosorbent testing (RAST[1]) testing have also been proposed. Unfortunately, the predictive value of all of these approaches is limited (see below).

History of Atopy

Atopy is the tendency, presumably inherited, to develop allergic reactions such as hay fever and dermatitis. The association between family history of atopy and the development of allergic symptoms has been demonstrated in some studies but is not a consistent finding in the research (Aoyama et al. 1992; Slovak and Hill 1987). In contrast, many studies indicate a relation between a personal history of atopy and LAA. One study by Kruize and colleagues (1997) demonstrated that atopic individuals have a relative risk for LAA 4.2 times that of nonatopic individuals. Bland and coworkers (1986) documented a history of atopy in 51.2% of LAA cases as opposed to 20.8% of controls. Although there have also been some studies that have demonstrated no association, the weight of the evidence is that personal history of atopy to some degree predicts subsequent allergy to laboratory animals.

Skin Prick Testing

The assessment of allergic predisposition by skin prick testing is another approach that has been considered for risk prediction. A distinction must be made between testing with general environmental allergens (e.g., ragweed, grasses, and dust mites) and testing with animal allergens. Numerous investigators have evaluated this issue in cross-sectional studies, but there have been few prospective efforts. Cross-sectional studies by Bryant et al. (1995) and Slovak and Hill (1981) indicate that there is a relation between positive skin tests to environmental allergens and asthmatic responses to laboratory animals. The research of Fuortes and colleagues (1996) extends the association to upper respiratory allergy. There are contradictory prospective studies on the issue of environmental allergen skin prick tests. Slovak and Hill (1987) demonstrated that individuals with positive tests were more likely to develop asthma, but Renström and coworkers (1994) found no significant association.

The use of animal-specific allergens in skin prick testing offers a more specific method of identifying the population at greatest risk. A drawback to the use of animal allergens in skin testing has been the historically poor quality of the reagents. However, there has been significant progress in identifying and purifying the major allergens for the commonly encountered laboratory animals. The skin prick tests have consequently improved. Hunskaar and Fosse (1990) reviewed the data from seven different studies of skin testing with animal allergens and found that 51 to 69% of individuals with laboratory animal allergy had positive skin prick tests to animal allergen. In general, the skin tests with animal allergens tend to be better predictors of asthma than of allergic rhinitis.

Other Laboratory Tests

Another possible approach to identification of individuals with a predisposition to LAA is the measurement of immunoglobulin E (IgE[1]) in the blood. Indeed, cross-sectional studies do indicate an association with total IgE. There does not appear to be prospective evidence on this issue. However, Davies (1983) examined immunoglobulin G prospectively and did not find it to be a useful predictor.

RAST is an in vitro technique used to test for the presence of IgE antibody to a specific animal antigen. In a prospective analysis over 3 yr, Botham and colleagues (1987) found that only 40 to 64% of symptomatic laboratory animal workers had positive RAST tests. In this study, there was also an apparent lack of specificity, inasmuch as some asymptomatic workers were positive to antibodies for the animals to which they were exposed. As with skin tests, the accuracy and efficiency of the test may be affected by the quality of the reagents in addition to other factors.

Genetic Testing

As with some other types of occupational disease, there is interest in the possibility of predicting laboratory animal allergy through genetic tests. Genetics tests, as well as the other types of testing described above, raise significant ethical and legal issues in their application. Based on research by Sjösted and coworkers (1996), there appears to be an elevated risk for animal allergy in individuals lacking HLA-B16. There appears to be a positive association with the HLA-DR4 antigens (Oxelius et al. 1996).

Summary of Issues Related to Predictive Factors and Preplacement Examinations

Existing research indicates a significant association between personal history of atopy and laboratory animal allergy. Skin prick testing with animal allergens appears to have modest predictive value for an individual's subsequent development of LAA. The practical limitation in the use of these tests is that for most populations of prospective workers, these tests would lead to more false than true positives. If the tests were used as a basis for exclusion from employment, they would incorrectly identify two or three individuals as an allergic risk for each correct one. At this time, the preplacement history, physical examination, and any ancillary tests (e.g., skin prick tests) should be used primarily to identify individuals at potential risk for counseling and close medical surveillance. When alternative job placements exist, it would make sense to direct an individual with an elevated probability

of allergic disease into a position with minimal or no exposure.

The subset of individuals who are at greatest risk from LAA are those with established asthma who have had prior severe allergic responses to animals. These individuals face a serious long-term risk from exposure to the animals to which they are allergic. Research with other causes of occupational asthma indicates that there is increasing likelihood of irreversible disease with longer duration of exposure and particularly with continued exposure after symptoms develop (Paggiaro et al. 1994). Strong consideration should be given to finding alternatives to placing such individuals in continued exposure situations.

Recommendations for a Medical Surveillance Program for Allergic Disease

An appropriate medical surveillance program for LAA operates on both individual and population levels. The medical surveillance program should promote an early diagnosis of allergy so that appropriate interventions can be made with individual workers to prevent the development of serious disease. Analysis of the data collected on the population of workers provides an opportunity to improve preventive measures and exposure controls in the workplace. Medical surveillance programs usually include baseline (preplacement) medical evaluation and testing, periodic follow-up questionnaires and interval medical examinations as symptoms or exposure risks warrant, and selective use of tests focused on early detection of disease. Education of workers about medical risks, including the symptoms and signs of allergy, is another important objective. An often neglected role of these programs is the communication of medical findings back to individual workers. Population data should be used to evaluate patterns of risk across various work areas and over time. These patterns can be correlated with actual exposure data and information about working conditions in an effort to evaluate potential work place improvements.

There should be a medical review of each employee on a regular basis. Most programs perform examinations annually, although the value of the annual examination should be evaluated in terms of its yield in any given work environment. Some institutions perform periodic examinations only for indications, such as symptoms, on an annual questionnaire. Individuals at high risk for allergy based on medical history or prior medical findings should receive follow-up at more frequent intervals.

Medical Questionnaire

It is valuable to collect both a baseline medical history and a periodic update that includes any work-related symptom changes. A suggested list of the minimal items for inclusion in a baseline questionnaire appears in Table 1. A more comprehensive questionnaire can be found elsewhere in this volume (Bush 2001). Important issues include personal and family history of allergy, specifics of any allergic diseases, prior allergic reactions to animals, results of any prior skin testing or other allergy tests, and history of any treatments received.

Periodic Medical Examination

The medical examination should focus on the respiratory system and the skin. Concerns are any indications of allergic rhinitis, conjunctivitis, or asthma. Dermatological conditions of concern include eczema and urticaria.

Pulmonary Function Testing

Administration of a preplacement spirometry and peak flow test provides a baseline against which changes can be assessed. In the symptom-free individual, the routine readministration of these tests for screening has a relatively low yield, although it may be considered in the periodic examination. However, when laboratory animal care workers develop respiratory symptoms, the value of screening pulmonary function tests is enhanced. The preferred test is composed of sequential measurements of peak flow over time. The intensive monitoring of pulmonary function is a secondary screening test in symptomatic individuals. A patient may be given a disposable peak flow meter and a recording chart with instructions to record the peak flows every 2 hr throughout the day. The patient records the best of three successive measurements on a recording form. Ideally, measurements should span 2 wk and cover both work and rest days. The evaluation of the results involves assessing variation between peak flows while at work and away from work. Generally, a variation of peak flow while at work of more than 15% from daily mean values is indicative of an asthmatic response. This test is relatively specific but not very sensitive; many cases of occupational asthma require confirmation by other diagnostic tests such as bronchial challenge. More information on the interpretation of peak flows is available elsewhere (Burge 1993).

Cross-shift spirometry can also be a useful technique. The forced expiratory volume over 1 sec and the forced vital capacity are taken before and after work. A significant difference with a pattern typical of obstructive disease indicates the possibility that the individual is developing occupational asthma. Use of cross-shift spirometry technique includes the following disadvantages: It is often logistically difficult to administer, given the need for two trips to the medical department; and it can result in false-negative responses when the allergic reactions are delayed.

Table 1 Information to include in questionnaire for initial allergy medical surveillance

Name: _____

Date: _____

Age: _____

Sex: _____

Position: _____

Brief description of duties: _____
- Species used: _____
- Exposure controls (ventilation, special caging systems, etc.): _____
_____

Personal protective equipment used: _____
_____

Past occupational history, including animal care: _____
_____

Personal medical history including symptoms and treatment for
- Allergic rhinitis/conjunctivitis/hay fever: _____
- Anaphylaxis: _____
- Asthma: _____
- Chronic cough: _____
- Eczema/urticaria/hives: _____
- Family history of allergic disease: _____
_____
- Prior history of allergic symptoms with animal exposure
  - Itching, tearing, or swelling of eyes: _____
  - Nasal discharge: _____
  - Coughing: _____
  - Chest tightness or wheezing: _____
  - Skin rash or itching: _____

Additional questions for periodic questionnaire

Description and time course of current symptoms in relation to animal exposure: _____
Species involved: _____
Activities involved: _____
Diagnostic measures (including skin prick tests) and results: _____
Treatment received: _____

Other Laboratory Tests and Special Examinations

Skin Tests

Routine skin tests for individuals with regular laboratory animal exposure are of questionable value. As discussed above, the predictive value of these tests is not high, and their interpretation in the preplacement or periodic screening context should be correspondingly limited. Skin prick tests may provide a basis on which to counsel a worker regarding potentially increased risk and perhaps to increase the level of medical surveillance. Both false-positive and false-negative skin tests result, and the quality of reagents varies both with species and supplier. On the whole, skin prick tests are most cost-effective in the symptomatic individual for identification or confirmation of the species to which the individual is reactive.

RAST

Similar constraints are recommended regarding the use of RAST. At least one study has documented a close associa-

tion between positive RAST results and the presence of LAA (Venable et al. 1988). However, RAST results are not specific and have relatively low predictive value for routine surveillance (Lutsky et al. 1986). Two factors limiting the clinical effectiveness of RAST are variability of reagents and uncertainty that the antibodies detected are actually involved in the pathogenesis of allergic disease.

Challenge Testing

Although provocation or challenge testing is definitely not a surveillance procedure, it is an important clinical tool that can be used to assist in difficult diagnostic situations. The test involves inhalation exposure by the individual to material from the suspected allergenic source. Pulmonary function is monitored before and after the exposure. Challenge testing should be done in appropriately controlled circumstances by an experienced clinician because it entails the risk of potentially serious allergic reactions.

Serum Banking

Collection and retention of serum samples from laboratory animal workers has relatively limited application, particularly for animal allergy. Many programs involve routinely collecting such blood samples for storage and are based on the rationale that samples will provide a baseline for evaluation of subsequent infectious disease. Medicolegal protection is often cited as a basis for serum banking, although the value of this practice for allergy has never been rigorously demonstrated for a population of workers. Although analysis of pre- and postexposure serum samples by RAST or other techniques could theoretically help in determining the time course of allergy development, the predictive value and practical application of such testing are very limited. However, comparison of pre- and postexposure RAST tests has been useful in helping to establish the likely time course for onset of allergic disease in some instances. It would be difficult to justify the establishment of such a program for routine surveillance of LAA alone, although decisions on the utility of serum banking also should be based on consideration of the range of infectious disease issues.

Serum banking programs require clear policies and significant resources. The understanding and informed consent of the employee, proper collection and storage of the specimens, and guidelines regarding use of the stored sera are important issues. Specimens deteriorate with time and are best stored at subzero (preferably –70°C) temperatures.

Medical Surveillance as a Population-based Program

Although medical programs in the workplace tend to focus on the health on individuals, the tracking and analysis of group data are important functions for occupational health professionals. To facilitate such analysis, it is preferable for patient data to be stored in a secure electronic format. The information derived from group data may assist in evaluating the preventive measures and controls in the animal care facility. Information on the prevalence of allergic symptoms, changes in spirometry and peak flow, and results of other medical tests can be used to assess trends, compare different facilities, and monitor the effectiveness of interventions. The availability of individuals with experience in the application of epidemiological techniques and statistical tests is an important asset for a medical surveillance program.

Medical surveillance is ideally a quality improvement process; resulting information is used by occupational health professionals to improve the health and safety of the work environment continuously. In addition to the physicians, nurses, and other medical personnel, the occupational health team may include industrial hygienists, safety engineers, health physicists, and other technical experts. Feedback from the medical staff to the rest of the occupational health team is essential. Such feedback must preserve medical confidentiality; however, the surveillance process is not complete unless there is two-way exchange of information. Ideally, the medical staff visits the workplace and has both a full understanding of the work environment and interactive relationships with the field-based occupational health team, employees, and supervisors.

Training

Any activity involving repeated exposure to laboratory animals should include a training requirement. Clearly, the range of training issues will depend on the activities and the risks entailed. From the perspective of reducing the risk of allergy and improving the early detection of disease, training should include information on the allergic diseases, the symptoms, the preventive controls and procedures, and the medical surveillance program. It is important for workers to know proper techniques for working with animals or their waste to reduce exposures. Supervisors must be particularly well informed on these issues and provide continuous assistance and feedback to workers on safety. Medical personnel should assist with training programs, and any group results or "lessons learned" from the medical surveillance effort should be incorporated into these training sessions.

Personal Protective Equipment

There are many approaches to reducing exposure to animal allergens in the workplace. These preventive measures are classified according to one of the following four categories: (1) substitution, (2) engineering controls, (3) administrative controls, and (4) personal protective equipment. Substitution involves using fewer allergenic species (e.g., female rats excrete less protein in their urine) or avoiding the use of

animals through in vitro techniques or computer modeling. Engineering controls include improvements in ventilation, caging systems, and equipment for handling animals. Examples of administrative controls include work rules and procedures, such as limiting access to animal care areas and required handling methods. These topics are covered in more detail elsewhere in this volume (Harrison 2001).

Personal protective equipment (PPE[1]) encompasses respirators, eye protectors, gloves, coveralls, laboratory coats, footwear, or other clothing used to reduce exposure. Although these devices have an important role in most prevention programs, it is important to recognize that their effectiveness is often dependent on the user. Because the use of respirators, gloves, and other PPE can be uncomfortable during extended periods, the actual protection they provide in practice can be limited. It is extremely useful for an organization that uses animals to have access to an industrial hygienist for advice on the use of PPE and compliance with federal or state regulations on its use.

Employers who require employees to use respirators must have a fully developed respiratory protection program, including quality controls, medical approval for use, and fit testing. Only respirators approved by the US National Institute for Occupational Safety and Health should be used (USHHS 1998). Because there are no clear regulatory standards for exposure to animal allergens, the choice of respirator must be based on an understanding of the work environment and the activities to be performed, including an assessment of the intensity of exposure.

Because "safe" levels of exposure to animal allergens have not been established, there is no clear guidance regarding the level of respiratory protection required in an animal care environment. Theoretically, minimization of exposure is the desired goal. Although there is some evidence that less exposure reduces the prevalence of allergy in the workforce, this has not been clearly established. Thus, it is not possible to state categorically that a rigorous program of respiratory protection will reduce the prevalence or incidence of allergy. Nevertheless, it is clear that respiratory protective devices can reduce the severity/frequency of symptoms in allergic individuals. However, the best approach for individuals with severe manifestations of allergy, including asthma, is to avoid exposure altogether.

As a practical matter, most animal care facilities rely on dust masks approved by the National Institute for Occupational Safety and Health for nonsymptomatic workers because they are relatively comfortable and readily used by workers. Research has shown that these types of respirators can remove up to 98% of rodent urinary allergens from the inhaled air (Sakaguchi et al. 1990). Individuals who have established allergic symptoms should be fitted for a negative pressure "half-mask" filtering respirator, an air filtering hood, or another respirator that offers a better protection factor than a dust mask. The use of such respirators has not been shown to reduce the progression of disease and is not a substitute for removing severely allergic individuals from exposure.

Gloves, gowns, head coverings, and other protective clothing are important to keep allergenic material off the skin and for infection control. It is crucial to remove these garments at the end of a shift so that material from the animal colony is not carried home and exposure is confined. Although the use of gloves will reduce contact allergy and the likelihood of sensitization, the choice of gloves is significant. If latex gloves are used, there is a risk of latex allergy. However, latex gloves also offer the best protection against infectious agents. Vinyl gloves are an alternative in situations in which infectious concerns are not a significant issue.

Summary

The medical surveillance program can be an effective means for tracking the development of allergic disease both in individuals and in an exposed population. Periodic medical evaluation of individuals, as described, can be used to improve individual health management, for counseling, and to avoid disease progression. Analysis of population level results can help guide systematic efforts to control exposure and to identify other measures to prevent LAA.

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