Mechanism and Epidemiology of Laboratory Animal Allergy

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Abstract

Laboratory animal allergy (LAA) is a form of occupational allergic disease. The development of LAA is due to the presence of immunoglobulin E antibodies directed against animal proteins. The process of sensitization (development of immunoglobulin E antibodies) is a complex process that involves interaction of antigen-presenting cells and lymphocytes of the Th-2 cell type. These cells generate a host of cytokines and other factors that lead to immediate hypersensitivity reactions and the generation of allergic inflammation. Typical symptoms of LAA include nasal symptoms (e.g., sneezing, watery discharge, and congestion) and skin rashes. Asthma, which produces symptoms of cough, wheezing, and shortness of breath, may affect 20 to 38% of workers who are sensitized to laboratory animal allergens. Rarely, a generalized, life-threatening allergic reaction (anaphylaxis) may occur. The estimated prevalence of LAA is variable, depending on the method used for diagnosis, but nonetheless may affect exposed workers. The presence of pre-existing allergies to nonworkplace allergens (e.g., dust mite, pollens, molds), exposure to laboratory animal allergens, and possibly tobacco smoking are risk factors for the development of LAA. Progress in the understanding of the mechanism and epidemiology of LAA will lead to improved methods for its prevention.

Key Words: allergic conjunctivitis; allergic inflammation; allergic rhinitis; anaphylaxis; angioedema; atopy; IgE antibodies; urticaria

Mechanism of Laboratory Animal Allergy

Laboratory animal allergy (LAA[1]) is a form of occupational allergic disease. Such allergic diseases are classified as immediate hypersensitivity reactions, or type 1 according to Gell and Combs (Shearer and Fleischer 1998). Immediate hypersensitivity reactions involve the production of immunoglobulin E (IgE[1]) antibodies, which are formed in response to a variety of protein or glycoprotein antigens of which LAA is a typical example. Generation of IgE antibodies requires the central role of CD4+ T-helper lymphocytes. In the development of LAA, exposure to the allergens (antigens capable of eliciting any IgE antibody responses), such as mouse or rat urinary proteins, largely occurs through inhalation of these proteins into the lung. Some exposure may also occur through skin contact.

Development of IgE Antibodies

The first step in the process of the development of LAA consists of the production of IgE antibodies to the animal proteins or glycoproteins. This initial step is termed "sensitization." The allergens are taken up by antigen-presenting cells in the lung, which include monocytes, alveolar macrophages, and dendritic cells (Kiekhaefer et al. 2000). Dendritic cells and Langerhans cells in the skin serve a similar function and possess the properties necessary for the presentation of antigens to T-lymphocytes. For the antigen to be recognized by the T-cell, it must first be processed into small peptide fragments and presented on the surface of the antigen-presenting cell in association with major histocompatibility (MHC[1]) class II proteins (Whitton 1998). Antigen-presenting cells capture and internalize the protein. They migrate to draining lymph nodes where the processed peptides are presented on the surface of the cell in association with the MHC class II molecules. Naive T-cells, through a T-cell receptor that has specificity for a particular antigenic peptide, recognize the complex of the antigen and the MHC class II molecules. For the naive T-cell to become activated, certain costimulatory signals are also necessary. The most common of these interactions is between the B7 molecule (B7.1 or B7.2) on the antigen-presenting cell and its counter ligand, CD28, on the T-cell (Figure 1) (Whitton 1998). The activated T-cell can then undergo multiple rounds of replication, which requires autologous production of the cytokine, interleukin (IL[1])-2, and the surface expression of the IL-2 receptor, CD25. Initially, a multipotential population of T-cells (Th0) are produced. There are two types of effector cells, each with the potential to generate a selective and mutually exclusive array of cytokines, which dictate the type of immune response that may occur. The Th1-type lymphocytes preferentially secrete IL-2, interferon-gamma (IFNγ[1]), and tumor necrosis factor-α;

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[1]Abbreviations used in this article: IFNg[1], interferon-gamma; IgE, immunoglobulin E; IL, interleukin; LAA, laboratory animal allergy; MHC, major histocompatibility.
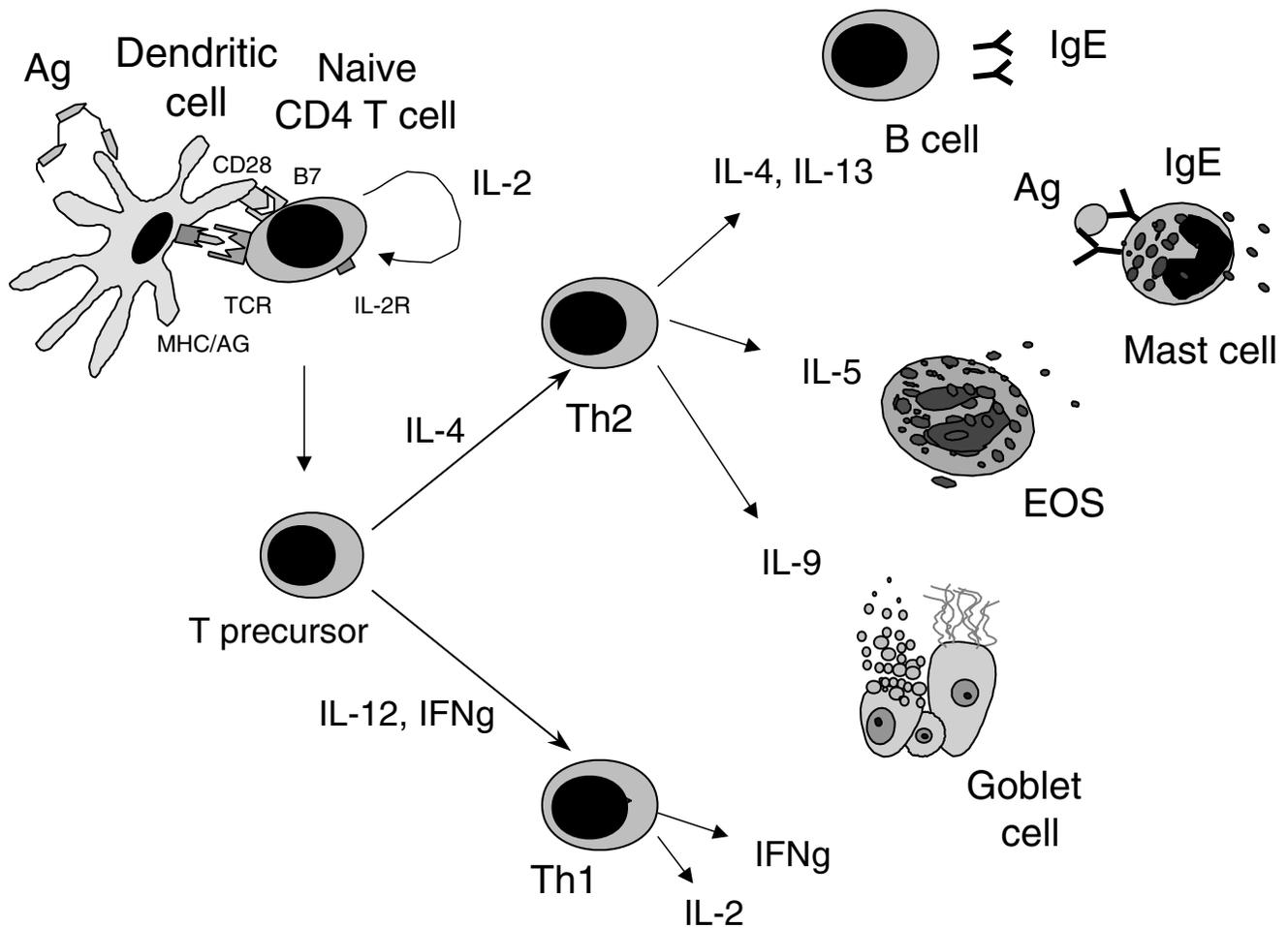
Figure 1 Antigen presentation to naive T-cells requires (1) recognition of antigen (AG)/major histocompatibility (MHC) complex by T-cell receptor (TCR), and (2) costimulatory signals provided through the interaction of CD28 and B7. Differentiation of T-precursor cells into Th1 or Th2 effector cells is influenced by the presence of interleukin (IL)-4 and IL-12. Th2-type cells contribute to antigen-induced airway inflammation through the generation of IL-4, IL-5, IL-9, and IL-13. Reprinted with permission from Kiekhaefer CM, Kelly EA, Jarjour NN. 2001. Antigen-induced airway disease. In: Bush RK, ed. Environmental Asthma. New York: Marcel Dekker. p 13-31.

and Th2-type cells produce IL-4, IL-5, IL-9, and IL-13 (Mosmann et al. 1986; Swain 1999) (Figure 1).

The particular type of immune response that is generated depends on a variety of factors, including the type and dose of antigen, the differential expression of B7.2 versus B7.1 costimulatory molecules, and the cytokine milieu present during the initial priming of the T-cells (Jaffar et al. 1999; Tsuyuki et al.1997). The most important factor appears to be the presence of particular cytokines. The Th2 cells are induced by the presence of IL-4, whereas Th1 cells are induced in the presence of IL-12. Elicitation of a Th2 response is the typical feature of immediate-type allergic diseases (Holt 1999).

For many allergic diseases, a genetic predisposition known as atopy is present. Individuals are defined as being atopic if they or close relatives have manifestations of allergic diseases, such as allergic rhinitis, asthma, and eczema. The genes that control the Th2-type of response have not been fully elucidated at present. However, clear-cut genetic influences do exist based on data from population studies.

A small portion of Th2 cells develop into memory T-cells that can circulate for long periods of time. Subsequent exposure to the initial sensitizing antigen elicits a vigorous and rapid response from these memory T-cells. Thus, once established, a Th2-response can continue for many years or be rekindled by subsequent reexposure to the allergen that generated the initial response (Holt 1999).

The production of cytokines by Th2-type cells leads to the production of specific IgE antibodies. IL-4, which is a necessary signal to B lymphocytes, induces the synthesis of IgE antibodies by B-cells. A similar function has also been attributed to IL-13, which has approximately 30% homology with IL-4 and shares many of its biological activities. In contrast, IFNγ suppresses the formation of IgE antibody production. IgE antibody production, therefore, represents an excess of IL-4 and IL-13 and a relative absence of IFNγ.

Although not fully elucidated, current theory holds that allergic disease results from a relative lack of production of IFNγ by individuals who have the atopic trait.

IgE antibody has unique biological characteristics. It is found in low concentrations in serum compared with immunoglobulins IgG, IgM, and IgA. IgE has the unique property of binding, through its Fc portion, to receptors found on mast cells and basophils. These cells, which contain histamine and other biochemical mediators, are found in abundance in tissues that are the site of allergic reactions. These sites include the skin, conjunctiva, respiratory system, and gastrointestinal tract.

The role of the IgE antibody in health is not completely understood. However, it is of interest that in the case of parasitic infections, specific IgE antibodies to parasite antigens arise in response to organisms that have a tissue migration phase. Interactions between parasitic antigens and IgE result in the degranulation of mast cells and recruitment of eosinophils into the site of the parasitic infection. Eosinophils have been shown to have the capacity to kill parasites, such as schistosomes, in cultures. It is especially interesting to note that many of the allergens involved in laboratory animal allergies, such as mouse and rat urinary protein, share sequence homology with schistosome antigens (Viranten et al. 1999). This molecular mimicry between the protein allergens of the mouse and rat and their close relation to schistosome allergens may, in part, account for the potency of these antigens in eliciting an IgE response in susceptible individuals (Viranten et al. 1999).

Development of Allergic Symptoms

In individuals who develop sensitivity to laboratory animal allergens, a series of events leads to the symptoms of disease. Initially, after the individual has produced IgE antibodies that have occupied the receptors on the mast cell and basophils, subsequent exposure to the allergen through inhalation or contact on the skin results in an immediate (10- to 15-min) response. Interaction of the allergen with specific IgE antibodies on the surface of the mast cell or basophil leads to the release of preformed biochemical mediators, such as histamine. In addition, activation of the arachidonic acid cascade results in the production of prostaglandins (e.g., PGD2) by mast cells and leukotrienes. Furthermore, a variety of cytokines including TNF-α, IL-1, IL-4, IL-5, IL-6, IL-8, IL-16, and the chemokines MIP-1α, MIP-1β, MCP-1, and RANTES are generated (Bissonnette and Befus 1998). The biochemical mediators (e.g., histamine and leukotrienes) result in local tissue effects, including constriction of airway smooth muscle, edema in the tissues, increased mucous secretions, and stimulation of nerves, causing itching and sneezing. The pivotal role of IgE in the early allergic response has been substantiated by studies that show administration of a monoclonal antibody to IgE can attenuate the antigen-induced early allergic response (Frew 1998).

In approximately half of allergic subjects, the early phase response is followed by a late phase reaction, which occurs 3 to 4 hr after the initial exposure to antigen. These reactions typically peak at 4 to 8 hr and resolve after 12 to 14 hr. The late response differs in character from the early phase response in that it involves the influx of inflammatory cells, consisting largely of eosinophils and basophils, into the target tissues. Factors that influence the occurrence of the late phase reaction include the amount of allergen delivered, time of day, and type of allergen (Mohiuddin and Martin 1990).

The T-lymphocytes are key players in orchestrating the late phase response. Increased numbers of activated T-lymphocytes (those showing increased expression of the IL-2 receptor [CD25] and MHC class II molecules [HLA-DR]) are detected in peripheral blood and tissues (Azzawi et al. 1990; Corrigan et al. 1993; Robinson et al. 1993). In addition, an increased number of cells expressing TH2 cytokines, including IL-4, IL-5, and IL-13, have been noted (Humbert et al. 1997; Robinson et al. 1992). Furthermore, cytokines IL-4 and IL-9 contribute to mucous secretions.

IL-5 is a potent stimulus for eosinophilic inflammation because it can initiate eosinophilopoiesis and is a terminal differentiating factor for eosinophil progenitor cells. In addition, IL-5 increases the expression of VCAM-1, an adhesion molecule on endothelial cells with selectivity for binding the eosinophil. IL-5 also prolongs the survival of eosinophils in tissues and primes the eosinophils to respond to activating factors (Elsner and Kapp 1999).

IL-5 alone is not sufficient to account for the recruitment of eosinophils into tissues. Many chemokines are chemotactic for eosinophils, including RANTES, MCP-1, MCP-4, and eotaxin (Nickel et al. 1999). Eotaxin may be of particular importance because it is selective for eosinophils; it has been shown to act in concert with IL-5 for eosinophil recruitment (Mould et al. 1997).

The presence of eosinophils in tissues is a hallmark of allergic inflammation, and the eosinophil is probably the key effector cell in the airway inflammation that occurs in allergic asthma. Eosinophils release a variety of mediators that contribute to further tissue inflammation, including granular proteins (e.g., major basic protein) and the generation of leukotrienes, cytokines, and matrix metalloproteinases. Eosinophils that have been recruited into the airways of patients with allergic asthma, including those with LAA, have increased expression of EG2 and eosinophilic cationic protein, enhanced survival, and a marked increase in release of eosinophil granules into the airway (Sedgwick et al. 1991).

Clearly, the eosinophil alone is not the only cell involved in the inflammatory response in allergic reactions. Macrophages, lymphocytes, and neutrophils also play a significant role. It has also been shown in nasal tissues that the basophil may be a contributor to further release of chemical mediators (e.g., histamine) into the tissues.

In the lower airway, epithelial cells are more than a simple barrier. They are the first tissues or cells to encounter airborne allergens. Polito and Proud (1998) have shown that epithelial cells can generate various cytokines, including RANTES and eotaxin. Eotaxin can play an important role in

recruitment and activation of eosinophils and other inflammatory cells in the airway. In addition to the immune system, the airway epithelial cells may also act as effector cells in the initiation of airway inflammation in asthmatic reactions to laboratory animal allergens. Their exact role is yet to be fully defined.

In summary, the mechanism underlying LAA involves a complex series of events. Genetic factors may play a role in governing the ability of the individual to generate an allergic response. Through airborne or skin contact, the allergens produced by laboratory animals lead to their uptake by antigen processing and presenting cells. These cells in turn interact with T-lymphocytes and in the appropriate cytokine milieu lead to the generation of Th2 CD4+ T-helper cells. The Th2-cells then elaborate cytokines, such as IL-4 and IL-13, that are involved in the production of IgE. The production of IL-5 results in maturation and enhances the recruitment of eosinophils into sites of allergic reactions in the tissues.

Circulating IgE, which is antigen specific, binds to the surfaces of mast cells and basophils. Interaction between the specific allergen, such as rat or mouse urinary protein, triggers the release of preformed mediators, such as histamine, and the generation of other vasoactive biochemical mediators, such as leukotrienes and prostaglandins. Furthermore, the release of chemokines, such as RANTES and eotaxin, results in the recruitment of inflammatory cells (particularly eosinophils) into the tissues. There, further release of leukotrienes and other mediators results in the typical inflammation seen in allergic reactions during the late phase response. The biochemical mediators and inflammatory cells contribute to the allergic symptoms. Over time these events may lead to chronic disease states, such as asthma.

Symptoms of Laboratory Animal Allergy

Symptoms of LAA are the result of the release of biochemical mediators and the generation of inflammation in the tissues induced by IgE response. The nature and intensity of the symptoms are dependent on the level of exposure to the laboratory animal allergen by the individual. These symptoms can range from mild skin reactions to severe asthma. The most common symptoms are related to allergic reactions involving the nose and eyes (Aoyama et al. 1992; Cullinan et al. 1994) and are known as allergic rhinitis and allergic conjunctivitis, respectively. Nasal symptoms include congestion, runny nose, sneezing, and itching; ocular symptoms include redness and itchy, watery eyes. Up to 80% of workers with LAA report nasal symptoms (Bush et al. 1998).

Skin reactions include hives at the site of contact with animal urine or dander as the result of scratches from rough tails and claws. Other rashes include maculopapular (measles-like) rashes, which are typically quite itchy and occur in about 40% of symptomatic individuals (Bush et al. 1998).

Asthma may affect 20 to 30% of symptomatic workers exposed to laboratory animals. Symptoms of asthma consist of cough, wheezing, and shortness of breath. It is important

to recognize that symptoms related to laboratory animal exposure may continue for several hours after exposure to the animals ceases. In addition, individuals may experience symptoms of asthma when exercising and when exposed to cold air, dust particles, or strong odors. This phenomenon, known as nonspecific airway hyperresponsiveness, occurs in other situations of allergen-induced asthma.

Systemic allergic reactions, known as anaphylaxis, can occur (albeit rarely) as a result of an animal bite (Teasdale et al. 1993) or from puncture wounds (e.g., needles contaminated with animal proteins) (Watt and McSharry 1996). These reactions can manifest by generalized itching, hives (urticaria), swelling (angioedema) of the lips, eyes, and/or extremities, respiratory distress due to edema of the larynx, hypotension (shock), or acute asthma attacks. These reactions are potentially fatal. Occasionally, a milder form of systemic reaction can manifest in which the allergic individual develops a maculopapular rash or hives under protective clothing as a result of a respiratory exposure to laboratory animal allergens.

Time from the onset of exposure to development of symptoms is variable but generally occurs within 3 yr of beginning employment. Approximately one third of individuals will develop symptoms in the first year and 70% within 3 yr. Again, this estimate is quite variable depending on the individual study reported (Seward 1999).

In a study from the United Kingdom, the mean duration of employment before the onset of nasal symptoms was 214 days, 335 days for skin symptoms, and 365 for the development of chest symptoms (asthma) (Cullinan et al. 1994).

Diagnostic approaches to LAA and its treatment are discussed elsewhere in this volume (Bush 2001).

Epidemiology of Laboratory Animal Allergy

Estimates of the number of individuals exposed to laboratory animals in their occupation vary considerably. Bland et al. (1987) estimated that 90,000 individuals were exposed to laboratory animals in the United States, and 32,000 workers in the United Kingdom were similarly exposed. In contrast, Seward (1999) estimated that 40,000 to 125,000 individuals are exposed to laboratory animals in the United States.

The definition of LAA (reported symptoms vs. confirmatory evidence of IgE-mediated sensitivity) leads to significant variability in the reported prevalence and incidence (percentage of new cases occurring in the population over a given period of time) of this occupational problem. Furthermore, the sample size included in the study influences the results. In the United Kingdom, exposure to laboratory animals has consistently ranked in the top three causes of occupational asthma and comprises 5% of all cases reported to that country's surveillance of work-related and occupational respiratory diseases program since 1989 (S. Gordon, Imperial College School of Medicine, London, UK, personal communication, 1999). These statistics are striking because laboratory animal workers comprise only a small portion of

the total UK work force. In the United States, the National Institute of Occupational Safety and Health has formally recognized LAA as an occupational hazard since 1989.

The first reported cases of allergic symptoms due to laboratory animals occurred in the 1950s (Sorrel and Gottesman 1957). The high prevalence of this condition did not become apparent until cross-sectional epidemiological studies were conducted in the 1970s and -80s (Cockcroft et al. 1981; Gross 1980; Lutsky and Neuman 1975) (Table 1).

Gross (1980) observed that symptoms of affected individuals usually began within 6 mo of exposure and rarely occurred after 2 to 3 yr of employment. In that study, species associated with the workers' symptoms and the percentages of workers affected were as follows: rats (65%); rabbits (72%); mice (66%); and guinea pigs (33%). Nasal symptoms preceded chest symptoms in 45% of the individuals, whereas 55% experienced nasal and chest symptoms simultaneously. Chest symptoms never occurred in the absence of nasal symptoms. One third of the individuals had no prior history of any allergic disease.

In Cockcroft's (1981) evaluation, 49 of 179 individuals were symptomatic with mainly nasal symptoms. Skin testing was conducted and showed a good correlation between the presence of rhinitis and positive skin tests to relevant laboratory animal allergens. Five individuals had positive skin test to laboratory animal allergens but were asymptomatic.

In Schumacher and colleagues' (1981) study, of the 39 individuals who experienced respiratory sysmptoms or skin rashes, one third reported severe symptoms. Virtually all of these individuals had demonstrable sensitivity by positive skin tests to laboratory animal allergens.

Slovak and Hill (1981) examined 148 workers of whom 48 (30%) had a history of symptoms related to their laboratory animal exposure. Of the 48, 22 had positive skin tests and demonstrated rhinitis symptoms that progressed to asthma.

In a similar study of workers in the pharmaceutical industry in the United Kingdom, Beeson et al. (1983) reported that of the 15 workers with LAA, slightly more than half (eight) had positive skin tests to animal allergens. Sixty-seven percent of the individuals were sensitive to allergens other than laboratory animals.

In Agrup and colleagues' (1986) evaluation, there was a high level of frequency of self-reported symptoms, but the numbers of individuals with symptoms were reduced when they were interviewed by clinicians. Nineteen of the 30 laboratory technicians with reported symptoms had positive skin tests or in vitro tests indicating sensitivity to laboratory animal allergens. Only two of the animal keepers had positive skin tests.

Laboratory animal exposure results in significant lost time from work. More than one third of individuals working at the US National Institutes of Health reported lost time from work due to their symptoms from laboratory animal allergy sensitivity (Bland et al. 1986). According to completed questionnaires, 131 of 549 individuals (23.9%) reported symptoms due to their occupational exposure to laboratory animals.

In perhaps the highest prevalence rate reported, Venables et al. (1988) found that 46% of 156 pharmaceutical workers in the United Kingdom had laboratory animal sensitivity. In a review of pooled data from reported studies, Hunskaar and Fosse (1990) found an overall prevalence of LAA of 20.9% in 4988 individuals. Subsequently, in a large series conducted in Japan (Aoyama et al. 1992), 1304 of 5641 (23.1%) workers had symptoms related to their laboratory exposure. This survey was conducted among 137 research facilities, 76 medical schools, 57 research institutes, and four breeding facilities. Rhinitis was the most common symptom. Seventy percent of individuals developed symptoms within 3 yr of exposure. The survey revealed sensitivity to a variety of

Table 1 Reported cases of allergic symptoms of individuals working with laboratory animals

| Study (year)[a] | Country | Facilities | | Workers | |
		No.	Type	No. evaluated	No. with allergic symptoms (%)
Lutsky and Neuman (1975)	United States	39	[b]	1293	181 (14%)
Gross (1980)	United States	393	Research	393	59 (15%)
Cockcroft (1981)	United Kingdom	179	Research	179	49 (27%)
Schumacher et al. (1981)	Australia	121	Research	121	39 (32%)
Slovak and Hill (1981)	United Kingdom	148	Pharmaceutical research	148	22 (14.8%)
Beason et al. (1983)	United Kingdom	62	Pharmaceutical research	62	15 (22%)
Agrup et al. (1986)	Sweden	124	Pharmaceutical research	124	21 (16.8%)
Bland (1986)	United States	549	Research	549	131 (23.9%)
Venebles et al. (1988)	United Kingdom	156	Pharmaceutical	156	72 (46%)

[a]See text for complete references.
[b]Facilities that received questionnaires included 23 medical and veterinary schools, 9 research institutes, 5 pharmaceutical firms, and 2 commercial laboratory animal-producing facilities.

animals for which the percentages of affected workers are as follows: sensitivity to guinea pigs—31% of workers; to mice—26.1%; to rats—24.9%; to cats—30.1%; to dogs—24.9%; and to nonhuman primates—23.6%. It is important to note that virtually any laboratory animal can cause occupational allergy although the mammals listed above are the most commonly involved.

In another survey from Australia, Bryant et al. (1995) reported that 73 of 138 exposed individuals had symptoms of LAA. Of these individuals, 92% had positive skin tests to laboratory animal allergens; 23% of asymptomatic individuals also had positive skin tests to laboratory animal allergens. Bronchial hyperresponsiveness, a marker of asthma, was present in 21% of exposed individuals compared with 8% in a nonexposed control population.

From the United Kingdom, where good occupational disease reporting is available for workers in the laboratory animal field, 44% of 32,000 individuals indicated they had symptoms related to their work exposure in 1988. By 1994, this number had decreased to 31%. However, when skin testing was performed in those symptomatic individuals in 1988, only 13% had positive skin tests. In 1994, 10% had positive skin tests (S. Gordon, personal communication, 1999). In a recently reported preliminary study from the University of Wisconsin, 29 of 147 (19.7%) workers exposed to laboratory animal allergens in a research facility related allergic symptoms to their work exposure (Patel 2000). However, of the 147 workers, only 12% had positive skin tests that correlated with histories suggestive of LAA.

As can be seen, prevalence and incidence rates may vary considerably based on whether a questionnaire is used to establish the presence of LAA or whether confirmatory testing is required. The low prevalence of skin tests or in vitro tests showing IgE sensitivity may be related in part to the poor quality of skin testing and testing reagents available. Nonetheless, LAA does represent a significant health risk for the population of exposed individuals. Furthermore, few data are available on the number of individuals who end their employment due to LAA. Failure to capture this population in epidemiological studies could result in a significantly lower estimate of true prevalence or incidence (Monso et al. 2000).

The overall incidence of LAA is estimated at approximately 15% (Seward 1999). The incidence of asthma due to LAA is estimated to be approximately 2% (Seward 1999). However, in a study at a pharmaceutical company involving workers exposed to laboratory animals, the incidence of laboratory animal asthma was as high as 10.3% (Fisher 1998). After the institution of environmental control measures to reduce allergen exposure, the incidence decreased to 0.

Risk Factors for Development

Epidemiological studies have been useful in determining factors that may lead to the development of LAA. The most important risk factor for an individual is the level of exposure

to laboratory animal allergens. Methods have been developed that allow quantitative estimates of the exposure to laboratory animal allergens, as discussed elsewhere in this volume (Harrison 2001).

Controversy exists as to whether individuals with co-existing allergies to substances outside the laboratory have an increased risk of developing LAA, although the majority of reported studies suggests it is an important risk factor. In the study by Gross (1980), one third of workers had no prior allergic disease before developing LAA. Schumacher et al. (1981) correlated the development of LAA with the presence of atopy. Atopy was defined as positive skin test to one or more inhalant allergens. Slovak and Hill (1981) documented the belief that atopy predisposes individuals to the development of asthma related to their animal exposure. Several other studies (e.g., Aoyama et al. 1992; Bland et al. 1986; Botham et al. 1995; Bryant et al. 1995; Cullinan et al. 1999; Fuortes et al. 1996) indicate that atopy is a risk factor for the development of LAA. However, in contrast, Hederick et al. (1999) found atopy to be a risk factor only for individuals exposed at low levels; and Renstrom et al. (1994) believe that atopy is not a significant risk factor but that total IgE level is. These latter investigators are from the same research group and share the same subject pool. In a recent review (Bush et al. 1998), it was concluded that in individuals with a history of work-related symptoms and objective evidence of allergy as demonstrated by a positive skin test or in vitro test, the odds ratio for developing LAA was 3.35 in atopic compared with nonatopic workers. In many of these studies, the relation between atopy and the development of LAA suggests that a genetic predisposition to form IgE antibodies is a significant risk factor. The exact genetic defect has not yet been identified.

Tobacco smoking has also been associated as a risk factor for the development of LAA. However, as with atopy, controversial data have arisen. Venables et al. (1988) reported a positive association between cigarette smoking and the development of LAA, as did Fuortes et al. (1996) and Cullinan (1999). In contrast, Agrup et al. (1986) and Heederik et al. (1999) found no effect. Of note is the study by Fuortes et al. (1997), which showed individuals with a smoking history had more significant declines in pulmonary function compared with nonsmokers. This finding would be an expected effect of tobacco smoke exposure in addition to the exposure to the laboratory animals.

Conclusion

The level of exposure to laboratory animal allergens by the individual certainly is an important factor in determining whether the worker develops LAA. It is still controversial as to whether individuals who have coexisting allergies to other inhalant allergens are more at risk. Of note is the study by Hollander et al. (1996), who found that sensitivity to mites or pollens was not associated with risk for developing LAA; however, sensitivity to cats and dogs was associated. Analysis

of the available data suggests that pre-existing atopy is an important factor contributing to the development of LAA. Tobacco smoke has been shown to elevate serum IgE levels. This increase may also predispose an individual to an increased risk for LAA, although this possibility remains controversial.

References

Agrup G, Belin L. Sjöstedt L, Skerfving S. 1986. Allergy to laboratory animals in laboratory technicians and animal handlers. Br J Ind Med 43:192-198.

Aoyama K, Ueda A, Manda F, Matsushita T, Ueda T, Yamauchi C. 1992. Allergy to laboratory animals: An epidemiological study. Br J Ind Med 49:41-47.

Azzawi M, Bradley B, Jeffery PJ, Frew AJ, Wardlaw AJ, Knowles G, Assoufi B, Collins JV, Durham S, Kay AB. 1990. Identification of activated T lymphocytes and eosinophils in bronchial biopsies in stable atopic asthma. Am Rev Respir Dis 142:1407-1413.

Beeson MF, Dewdney JM, Edwards RH, Lee D, Orr RG. 1983. Prevalence and diagnosis of laboratory animal allergy. Clin Allergy 13:433-442.

Bissonnette EY, Befus AD. 1998. Mast cells in asthma. Can Resp J 5:23-24.

Bland SM, Evans R III, Rivera JC. 1987. Allergy to laboratory animals in health care personnel. Occup Med 2:525-546.

Bland SM, Levine Ms, Wilson PD, Fox NL, Rivera JC. 1986. Occupational allergy to laboratory animals: An epidemiologic survey. J Occup Med 28:1151-1157.

Botham PA, Lamb CT, Teasdale EL, Bonner SM, Tomenson JA. 1995. Allergy to laboratory animals: A follow-up study of its incidence and of the influence of atopy and pre-existing sensitization on its development. Occup Environ Med 52:129-133.

Bryant D, Boscato LM, Mboloi PN, Stuart MC. 1995. Allergy to laboratory animals among animal handlers. Med J Aust 163:415-418.

Bush RK. 2001. Assessment and treatment of laboratory animal allergy. ILAR J 42:55-64.

Bush RK, Wood RA, Eggleston PA. 1998. Laboratory animal allergy. J Allergy Clin Immunol 102:99-112.

Cockcroft A, Edwards J, McCarthy P, Andersson N. 1981. Allergy in laboratory animal workers. Lancet 1:827-830.

Corrigan CJ, Haczku A, Gemou-Engesaeth V, Doi S, Kikuchi Y, Takatsu K, Durham SR, Kay AB. 1993. CD4 T-lymphocyte activation in asthma is accompanied by increased serum concentrations of interleukin-5. Effect of glucocorticoid therapy. Am Rev Respir Dis 147:540-547.

Cullinan P, Cook A, Gordon S, Nieuwenhuijsen MJ, Tee RD, Venables KM, McDonald JC, Newman-Taylor AJ. 1999. Allergen exposure, atopy and smoking as determinants of allergy to rats in a cohort of laboratory employees. Eur Respir J 13:1139-1143.

Cullinan P, Lowson D, Nieuwenhuijsen MJ, Gordon S, Tee RD, Venables KM, McDonald JC, Newman-Taylor AJ. 1994. Work-related symptoms, sensitization and estimated exposure in workers not previously exposed to laboratory rates. Occup Environ Med 51:589-592.

Elsner J, Kapp A. 1999. Regulation and modulation of eosinophil effector functions. Allergy 54:15-26.

Fisher R, Saunders WB, Murray SJ, Stave GM. 1998. Prevention of laboratory animal allergy. JOEM 40:609-613.

Frew AJ. 1998. Effect of anti-IgE in asthmatic subjects. Thorax 53(Suppl 2):S52-S57.

Fuortes LJ, Weih L, Jones ML, Burmeister LF, Thorne PS, Pollen S, Merchant JA. 1996. Epidemiologic assessment of laboratory animal allergy among university employees. Am J Ind Med 29:67-74.

Fuortes LJ, Weih L, Pomrehn P, Thorne PS, Jones M, Burmeister L, Merchant JA. 1997. Prospective epidemiologic evaluation of laboratory animal allergy among university employees. Am J Ind Med 32:665-669.

Gross NJ. 1980. Allergy to laboratory animals: Epidemiologic, chronological and physiologic aspects, and a trial of cromolyn in its management. J Allergy Clin Immunol 66:158-165.

Harrison DJ. 2001. Controlling exposure to laboratory animal allergens. ILAR J 42:17-36.

Heederik D, Venables KM, Malmberg P, Hollander A, Karlsson A-S, Renström A, Doekes G, Nieuwenhuijsen M, Gordon S. 1999. Exposure-response relationship for work-related sensitization in workers exposed to rat urinary allergens: Results from a pooled study. J Allergy Clin Immunol 103:678-684.

Hollander A, Doekes G, Heederik D. 1996. Cat and dog allergy and total IgE as risk factors of laboratory animal allergy. J Allergy Clin Immunol 98:545-554.

Hollander A, Heederik D, Doekes G. 1997. Respiratory allergy to rats: Exposure-response relationships in laboratory animal workers. Am J Respir Crit Care Med 155:562-567.

Holt PG. 1999. Development of T-cell memory against inhalant allergens: Risks for future. Clin Exp Allergy 29(Suppl 2):8-13.

Humbert M, Durham SR, Kimmitt P, Powell N, Assoufi B, Pfister R, Menz G, Kay AB, Corrigan CJ. 1997. Elevated expression of messenger ribonucleic acid encoding IL-13 in the bronchial mucosa of atopic and nonatopic subjects with asthma. J Allergy Clin Immunol 99:657:665.

Hunskaar S, Fosse RT. 1990. Allergy to laboratory mice and rats: A review of the pathophysiology, epidemiology and clinical aspects. Lab Anim 34:358-374.

Jaffar Z, Roberts K, Pandit A, Linsley P, Djukanovic R, Holgate S. 1999. B7 costimulation is required for IL-5 and IL-13 secretion by bronchial biopsy tissue of atopic asthmatic subjects in response to allergen stimulation. Am J Respir Cell Mol Biol 20:153-162.

Kiekhaefer CM, Kelly EA, Jarjour NN. 2001. Antigen-induced airway disease. In: Bush RK, ed. Environmental Asthma. New York: Marcel Dekker. p 13-31.

Lutsky IK, Neuman I. 1975. Laboratory animal dander allergy. I. An occupational disease. Ann Allergy 35:201-205.

Mohiuddin AA, Martin RJ. 1990. Circadian basis of the late phase asthmatic response. Am Rev Respir Dis 142:1153-1157.

Monsó E, Malo J-L, Infante-Rivard C, Ghezzo H, Magnan M, L'Archevèque J, Trudeau C, Gautrin D. 2000. Individual characteristics and quitting in apprentices exposed to high-molecular-weight agents. Am J Respir Crit Care Med 161:1508-1512.

Mosmann TR, Cherwinski H, Bond MW, Giedlin MA, Coffman RH. 1986. Two types of murine helper T-cell clones. Definition according to profiles of lymphokine activities and secreted proteins. J Immunol 136:2348-2357.

Mould AW, Matthaei KI, Young IG, Foster PS. 1997. Relationship between interleukin-5 and eotaxin in regulating blood and tissue eosinophilia in mice. J Clin Invest 99:1064-1071.

Neuman I, Lutsky IK. 1976. Laboratory animal dander allergy. II. Clinical studies and the potential protective effect of disodium cromoglycate. Ann Allergy 36:23-29.

Nickel R, Beck LA, Stellato C, Schleimer RP. 1999. Chemokines and allergic disease. J Allergy Clin Immunol 104:723-742.

Patel NJ, Olson P, Lumby D, Fine JP, Bush RK. 2000. Laboratory animal allergy. (Abstract). J Allergy Clin Immunol 105:S372.

Platts-Mills TAE, Longbottom J, Edwards J, Cockcroft A, Wilkins S. 1987. Occupational asthma and rhinitis related to laboratory rats: Serum IgG and IgE antibodies to the rat urinary allergen. J Allergy Clin Immunol 79:505-515.

Polito JA, Proud D. 1998. Epithelial cells as regulators of airway inflammation. J Allergy Clin Immunol 102:714-718.

Renström A, Malmberg P, Larsson K, Sundblad B-M, Larsson PH. 1994. Prospective study of laboratory-animal allergy: Factors predisposing to sensitization and development of allergic symptoms. Allergy 49:548-552.

Robinson D, Hamid Q, Bentley A, Ying S, Kay AB, Durham SR. 1993. Activation of CD4 T cells, increased TH2-type cytokine mRNA expres-

sion, and eosinophil recruitment in bronchoalveolar lavage after allergen challenge in patients with atopic asthma. J Allergy Clin Immunol 92:313:324.

Robinson DS, Hamid Q, Ying S, Tsicopoulos A, Barkans J, Bentley AM, Corrigan C, Durham SR, Kay AB. 1992. Predominant TH2-like bronchoalveolar T-lymphocyte population in atopic asthma. N Engl J Med 326:298-304.

Schumacher MU, Tait BD, Holmes MC. 1981. Allergy to murine allergens in a biological research institute. J Allergy Clin Immunol 68:310-318.

Sedgwick JB, Calhoun WJ, Gleich GJ, Kita H, Abrams JS, Schwartz LB, Volovitz B, Ben-Yaakov M, Busse WW. 1991. Immediate and late airway response of allergic rhinitis patients to segmental antigen challenge. Characterization of eosinophil and mast cell mediators. Am Rev Respir Dis 144:1274-1281.

Seward JP. 1999. Occupational allergy to animals. Occup Med 14:285-302.

Shearer WT, Fleisher TA. 1998. The immune system. In: Middleton E Jr, Reed CE, Ellis EF, Adkinson NF Jr, Yunginger JW, Busse WW, eds. Allergy Principles and Practice. St. Louis: Mosby-Yearbook, Inc. p 1-13.

Slovak AJM, Hill RN. 1981. Laboratory animal allergy: A clinical survey of an exposed population. Br J Indust Med 38:38-41.

Sorrell AH, Gottesman J. 1957. Mouse allergy—A case report. Ann Allergy 15:662-663.

Swain SL. 1999. Helper T cell differentiation. Curr Opin Immunol 11:180-185.

Teasdale EL, Davies EG, Slovak R. 1993. Anaphylaxis after bites by rodents. Br Med J 286:1480.

Tsuyuki S, Tsuyuki J, Einsle K, Kopf M, Coyle AJ. 1997. Costimulation through B7-2 (CD86) is required for the induction of a lung mucosal T helper cell 2 (TH2) immune response and altered airway responsiveness. J Exp Med 185:1671-1679.

Venables KM, Upton JL, Hawkins ER, Tee RD, Longbottom JL, Newman-Taylor AJ. 1988. Smoking, atopy, and laboratory animal allergy. Br J Ind Med 45:667-671.

Virtanen T, Zeiler T, Mäntyjärvi R. 1999. Important animal allergens are lipocalin proteins: Why are they allergenic? Int Arch Allergy Immunol 120:247-258.

Watt AD, McSharry CP. 1996. Laboratory animal allergy: Anaphylaxis from a needle injury. Occup Environ Med 53:573-574.

Whitton JL. 1998. An overview of antigen presentation and its central role in the immune response. Curr Top Microbiol Immunol 232:1-14.