

Allergy to laboratory mice and rats: a review of the pathophysiology, epidemiology and clinical aspects

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Summary

Allergy to laboratory animals (mice and rats) is reviewed. Immunological aspects, the relevant allergens, epidemiology, clinical manifestations, diagnosis and prognosis are discussed. Results presented in some studies are analysed and criticized.

Keywords: Laboratory animals; Allergy; Incidence; Prevalence; Pathophysiology; Epidemiology; Clinical aspects

Allergy to laboratory animals (ALA) is a well-known occupational disease in personnel engaged in work with these animals. It has been known for more than a century that contact with certain animals could induce allergic manifestations. For a long time, however, the condition has been neglected as a specific disease. During the last 30 years the use of laboratory animals in pharmaceutical and other industries has increased almost exponentially, though declining somewhat during the last few years. Research, both medical and biological, has called for an extended use of living animals. Personnel in contact with such animals represents a large group of workers, estimated to more than 35 000 in the United States of America, and several thousand in the Nordic countries.

In this review we summarize much of the current knowledge about allergy to laboratory animals. We have included references published up to and including 1988. During the last few years research in this field has documented

many aspects of the problem in respect to prophylaxis and management. Research in immunology has provided a basis for understanding the mechanisms and pathogenesis of the disease. Formal recognition of ALA as an occupational disease in several countries has also increased interest for the problem among employers, national health services and politicians.

The review is limited to allergy to laboratory mice and rats. Other laboratory animals such as cats, poultry, rabbits, monkeys and guineapigs, may also induce allergic symptoms, but research studies of ALA to these species are less advanced. Our review is based on most of the literature published on the subject, and on the authors' personal experiences with the disease as researchers (physician and veterinarian). Among the many people affected by ALA are scientists, research technicians, laboratory technicians, physicians, veterinarians, breeders, animal caretakers, leaders in industry, universities and research institutions, people from insurance companies, and personnel engaged in health and safety at work. We hope that this review will represent a useful update, and serve as a source of knowledge.

HISTORICAL NOTES

Allergic reactions to animals are the most annoying, and in some cases potentially dangerous, occupational health problem in laboratories doing research involving animals. Prior to 1969, however, there was little interest in the problem. It was a common opinion that only hair from animals could cause ALA, that it was limited to contact with rabbits or cats, and that the incidence was very low. Only single cases

were presented in the literature and the condition was hardly mentioned in standard textbooks.

A very limited number of publications on ALA were published before 1965 (Lutsky, 1980). At that time descriptions of rodents dominated the literature (Rackeman, 1923; Rynes, 1937; Gilday, 1956; Sorrel & Gottesman, 1957; Arbesman *et al.*, 1958; Braun, 1960; Rajka, 1961). Little emphasis was given to the size of the problem, and no publications dealt with the problem among groups of employees before Rajka (1961) studied 10 workers at The Karolinska Hospital in Sweden. The diagnosis was confirmed by skin and exposure tests. He concluded that the occurrence of ALA was more frequent than previously stated. Epidemiological studies in the strict sense of the word were, however, not performed before 1972.

IMMUNOLOGY

Classification of hypersensitivity reactions

According to Gell and Coombs (1968), hypersensitivity reactions can be divided into 4 types—types I, II, III, and IV. Of these, type I is most relevant to this review.

Type I reactions are predominant in allergy to laboratory mice and rats (Gross, 1980). This reaction occurs in individuals who are predisposed to develop increased amounts of IgE class antibodies in response to antigenic stimuli. IgE antibodies bind to mast cells. Adsorption of the corresponding allergen triggers the release of histamine and other mediators from the sensitized mast cell. Common examples of this reaction are hay fever, urticaria and asthma.

Cytotoxic antibody or type II reactions are seen when antibodies react with surface antigens of cells. Examples include haemolytic anaemias.

Immune-complex (Arthus-type or type III reactions) reactions are caused by the reaction of antibody, usually of the IgG class, with a corresponding soluble allergen. Immune complexes are deposited in the walls of blood vessels. 'Farmers lung' following inhalation of bacterial or fungal allergens is a classical example of this reaction. Theoretically, this could be a frequent manifestation of ALA, since inhalation

of organic dust is unavoidable among laboratory animal workers if protection is not used. However, the literature is very scarce on such manifestations. Only one thorough case report (allergic alveolitis) has been presented (Gross, 1980).

Delayed hypersensitivity or type IV reactions occur when primed T-lymphocytes, the product of the cell-mediated immune response, encounter the corresponding allergen. The tuberculin test is a good example.

Atopy

Persons who have a hereditary predisposition to IgE reactions are said to be atopic. In daily clinical use atopy is often restricted to the development of asthma, allergic rhinitis (hay fever) or atopic eczema. Atopy can be diagnosed in individuals seeking employment which will involve exposure to allergens derived from laboratory animals. However, the relationship between atopy and the susceptibility to ALA is not yet fully established (see later discussion) and atopy is not currently regarded as a bar to employment.

The mechanism of atopy is based on the fact that atopic persons have a hereditary disposition to produce IgE. They have a much greater risk of developing specific allergic diseases, but also to react 'hypersensitively' to many different irritants, for example, cigarette smoke.

There are at least three different concepts of atopy in clinical practice. First, atopy may be defined clinically by family history. Secondly, atopy may be defined similarly by personal history. Thirdly, atopy may be defined on the basis of laboratory tests. Usually skin prick tests have been used, using a standardized range of allergens. According to a much used set of criteria (Pepys, 1975), atopy is defined as any skin-positive reaction with wheal and flare to one or more of the following: grass mixture, household dust extract or house-dust mite, or *Aspergillus fumigatus*.

Laboratory investigations of allergy

Determination of specific allergens is important. New *in vitro* techniques can give much

information on ALA. Total concentration of IgE in serum can be determined by radio-immunosorbent-test (RIST). IgE is increased in many but not all patients with allergic diseases. Determination of total IgE is only of value as part of a thorough investigation of the atopic status of an individual and is rarely helpful in the diagnosis of ALA. Measurements of IgE are, therefore, not useful in diagnosing allergy due to the other types of hypersensitivity reactions.

Specific IgE antibodies can be measured by radio-allergo-sorbent-test (RAST) which gives much more information than RIST. More than 50 different allergens are commercially available. Some allergy laboratories have now implemented mouse and rat RAST as a routine. In individuals who develop asthma, there is a high degree of correlation between RAST values and findings in prick tests and provoking situations (Davies *et al.*, 1983a).

In skin tests (prick test and intracutaneous provocation), diluted extracts of allergen are introduced under the skin, if the reaction is positive, an itching wheal with rubor and oedema develops.

ALLERGENS DERIVED FROM MICE AND RATS

Employees come into contact with organic material from the animals in many ways. Injections, testing, training, operations, killing, feeding or blood sampling are examples of tasks where a person will be exposed to allergens. Age, sex and strain differences in the excretion of allergenic material will be discussed in this section. We describe the nature of the allergens based on immunochemical studies. In the characterization process of the allergens, nonspecific materials containing unidentified allergens were first identified. When modern immunochemical techniques became available, specific molecular properties could be described. But even today the allergens are often mentioned as fur, hairs or dander. The presence of allergens in different excretions and materials from the animals will be summarized.

Mice

Using electrophoretic methods and Sephadex gel filtration, it has been possible to demonstrate that most of the allergenic activity is due to specific urinary proteins. Siraganian and Sandberg (1979) fractionated both serum and urine and demonstrated allergenic activity in both. They claimed that there are at least two major mouse allergens. The large allergen has a molecular weight of about 67 000 Da, and was found to be identical to mouse albumin. The small allergen has a molecular weight of about 17 000 Da, but it was not possible to characterize it in detail. Newman Taylor *et al.* (1977) found, by electrophoresis, that more than 90% of the mouse urine extract was a prealbumin (low-molecular weight, 10 000–25 000 Da) containing two antigenically similar components. A small fraction contained proteins similar to serum albumin. The low-molecular weight urine proteins were not demonstrable in the animals' sera by crossed immunoelectrophoresis. In an early study, however, prealbumin has been detected in serum in amounts 200–400 times less than in urine (Rumke *et al.*, 1970). Schumacher (1980) confirmed that a major allergen in mice is prealbumin present in urine. The molecular weight was found to be 22 000 Da. He claims that the protein complex is produced in the liver, circulates as serum protein and then is excreted in the urine. This may explain cross-reactivity between urine and serum allergens (Finlayson *et al.*, 1965; Schumacher, 1980). Longbottom (1980) identified a highly allergenic prealbumin component of mouse urine, probably identical to the prealbumin already described. No prealbumin component could be detected in serum, but again, very low concentrations may be present. Urine protein from adult mice consisted almost entirely of prealbumin (> 90%) and only small amounts of serum derived components.

In conclusion: the main allergen in mice is a urinary protein of low molecular weight, possibly prealbumin. Very small amounts may be present in serum. It is likely that serum albumin also is allergenic, but this is less clearly documented.

These allergens are present in most urine contaminated organic waste materials from the animals, and to some extent, because of circulation, in most tissues.

Rats

Wahn *et al.* (1980) studied the allergenic significance of serum albumin and found that it was an allergen for about 25% of rat-allergic persons. The data suggested the presence of at least 4 antigenic sites on the molecule. Longbottom (1980) fractionated rat urine proteins and found that, unlike mouse urine, rat urine contained significant amounts of serum derived components, especially serum albumin and globulins. Specific urinary components were prealbumin and α_2 -globulins. When tested, two urinary components were found to be equally allergenic; a prealbumin of about 17 000 Da and an α_2 -globulin component of about 15 000 Da. One study demonstrated that the bulk of rat urinary proteins was serum proteins (Newman Taylor *et al.*, 1977). In two recent studies Walls and Longbottom (1983a,b) characterized rat allergens. They confirmed earlier findings that serum albumin and specific urinary proteins were allergenic. They also found that serum had lower allergenic potency in comparison with extracts of urine, indicating that non-serum extracts are more important in allergy to rats.

There is evidence that some non-serum urinary proteins are derived from the kidney or associated genital glands (Perassi & Martin, 1973). Other proteins may be present in very low amounts in serum, but are concentrated by the kidneys (Roy *et al.*, 1966; Royce, 1968). The presence of allergens in saliva has also been highlighted (Walls & Longbottom, 1985).

In conclusion: the main allergens in rats are serum albumin, urinary α_2 -globulins and prealbumin.

Cross-reactivity between species or strains

The cross-reactivity between different material or excretions from the same animal is explained by the nature and distribution of the allergens. An interesting question is raised, however,

regarding cross-reactivity between strains or species (Longbottom, 1984).

An early case report described a technician who reacted to albino mouse dander extract and serum, as well as to sera from several other species, some of which he had not been previously exposed to (Arbesman *et al.*, 1958). This indicated cross-reactivity between mouse and other species. The extracts were, however, poorly characterized, and their potency not specifically determined. More thorough studies performed later have not been able to find cross-reactivity between mice, rats, guineapigs or cattle (Longbottom, 1980; Lutsky, 1980; Wahn *et al.*, 1980; Walls & Longbottom, 1983a). One study showed cross-reactivity between mice and rats (Wahn & Siraganian, 1980). Mouse and rat α_1 -macroglobulins seem to be identical (Newman Taylor *et al.*, 1977), but have no allergenic activity. Serum albumin molecules from horse, cat, cow and dog are almost identical, but no cross-reactive allergy is known (Møller & Würden, 1984).

Stock and strain differences have been discussed in a few papers. Total cross-reactivity between 2 unrelated stocks of rats (Ola : LH and Glx : SD) was found by Wall and Longbottom (1983a). Lutsky *et al.* (1985b) found similar cross-reactivity between 3 inbred rat strains (Lewis, Fisher and Hooded). In mice, total cross-reactivity was found between 3 strains of inbred mice (Schumacher, 1980). In another study, the possibility of strain-specific allergens was discussed (Schumacher *et al.*, 1981). The data alone do not exclude the possibility that some individuals may acquire allergic reactivity to minor non-cross-reactive allergens.

Is allergen excretion related to sex or age of the animals?

Several studies have documented sex differences in the levels of urinary proteins in normal rats (Roy & Neuhaus, 1967; Royce, 1968; Rumke *et al.*, 1970; Alt *et al.*, 1980). Quantitative differences in allergenic urinary proteins have also been found between the sexes. Male rats have more of the prealbumin allergen on the fur, in their urine and saliva (Walls & Longbottom, 1983a).

Rats tend to have spontaneous nephropathy with proteinuria which develops with age (Shih, 1935; Sellers *et al.*, 1950; Weaver *et al.*, 1975; Newman Taylor *et al.*, 1977; Alt *et al.*, 1980; Longbottom, 1984). No studies have, however, investigated the clinical implications of these findings. Knowledge of sex and age effects may be important in several situations, both in daily laboratory practice and in experimental research.

Table 1. Skin prick test reactions to rat or mouse skin or hair

Animal	test	Positive Number tested	Reference
Mouse	8	12	(Böhm & Braun, 1972)
	9	11	(Ohman <i>et al.</i> , 1975)
	5	6	(Neuman & Lutsky, 1976)
	4	4	(Newman Taylor <i>et al.</i> , 1977)
	3	16	(Belin, 1981)
	6	6	(Twigg <i>et al.</i> , 1982)
Rat	3	10	(Rajka, 1961)
	11	11	(Ohman <i>et al.</i> , 1975)
	9	9	(Neuman & Lutsky, 1976)
	4	5	(Newman Taylor <i>et al.</i> , 1977)
	11	19	(Belin, 1981)
	7	13	(Newman Taylor <i>et al.</i> , 1981)
	11	17	(Møller & Würden, 1984)
Pooled data: 91 139 (i.e. 65% had a positive test)			

Table 2. Skin prick test reactions to rat or mouse faeces or urine

Animal	test	Positive Number tested	Reference
Mouse	4	4	(Newman Taylor <i>et al.</i> , 1977)
	8	18	(Belin, 1981)
	15	39	(Schumacher <i>et al.</i> , 1981)
	6	6	(Twigg <i>et al.</i> , 1982)
	11	12	(Walls & Longbottom, 1983b)
Mouse and rat	24	49	(Cockcroft <i>et al.</i> , 1981)
	13	60	(Venables <i>et al.</i> , 1988a)
Rat	5	5	(Newman Taylor <i>et al.</i> , 1977)
	4	5	(Longbottom, 1980)
	11	19	(Belin, 1981)
	9	13	(Newman Taylor <i>et al.</i> , 1981)
	11	17	(Møller & Würden, 1984)
	13	14	(Agrup & Sjöstedt, 1985)

Pooled data: 134 261 (i.e. 51% had a positive test)

Skin or hair as sources of allergens

Results from human skin prick tests vary when extracts from skin or hair are used as provoking agents (Table 1). Pooled data indicate that 65% of the persons with clinical allergy (rhinoconjunctivitis, asthma or urticaria) to mice or rats react to such material.

Faeces or urine as a source of allergens

It is virtually impossible for persons in direct contact with laboratory mice and rats not to be contaminated with urine or faeces. In addition, dried material from urine and faeces will be transported with sawdust and litter. Fur, hairs and skin will also almost invariably be contaminated with these excretions. As discussed above, urine is the main source of allergenic material. This is not reflected in results from skin prick tests (Table 2). Pooled data indicate that 51% of allergic persons demonstrate positive reactions on skin prick testing. Pooled data from control persons without any allergy shows that less than 3% demonstrate positive skin prick reactions (Longbottom, 1980; Schumacher *et al.*, 1981; Walls & Longbottom, 1983b; Venables *et al.*, 1988a).

Serum as a source of allergens

Much of the activity in research involving laboratory animals concerns blood and blood products from the animals. In addition, serum proteins may be present in the urine to a considerable degree. When tested in skin prick tests, about 60% of the allergic persons will react to serum (Table 3). Only two studies are

Table 3. Skin prick test reactions to rat or mouse serum

Animal	test	Positive Number tested	Reference
Mouse	8	9	(Ohman <i>et al.</i> , 1975)
	4	4	(Newman Taylor <i>et al.</i> , 1977)
Rat	7	11	(Ohman <i>et al.</i> , 1975)
	3	5	(Newman Taylor <i>et al.</i> , 1977)
	2	5	(Longbottom, 1980)
	7	13	(Newman Taylor <i>et al.</i> , 1981)
	7	17	(Møller & Würden, 1984)

Pooled data: 38 64 (i.e. 59% had a positive test)

published using mouse serum, here more than 90% reacted (Ohman *et al.*, 1975; Newman Taylor *et al.*, 1977).

Airborne allergens

Quantification of allergens in air may be done by several techniques: morphologic identification of airborne dander samples obtained on filters, quantification of dust and extractable protein nitrogen in dust collected with an air sampler, or immunodiffusion in agar gel using antisera to known animal allergens. It is also possible to immunochemically measure airborne allergens (Twiggs *et al.*, 1982). A few papers have described the use of these techniques for measuring the allergen concentration or dust loading (ng/m^3) in different rooms in the laboratory (Longbottom, 1984). Lincoln *et al.* (1974) found $16 \text{ ng}/\text{m}^3$ in the hallway opposite the mouse room, 37 and $51 \text{ ng}/\text{m}^3$ in rooms with 475 and 800 mice, respectively. In other studies the dust loading was 2, 10 and $44 \text{ ng}/\text{m}^3$ in hallways, 59, 63 and $336 \text{ ng}/\text{m}^3$ in working areas and 300–44 000 ng/m^3 behind cages. Edwards *et al.* (1983a) also showed that reducing the air changes increased allergen levels, while increasing the humidity from 54% to 77% caused significant reductions in allergen levels.

It has been suggested that an environment containing less than 2000 particles/cubic feet was adequate to prevent the development of allergic symptoms in 10 previously sensitized subjects. This required 60 air changes per hour in the room. At 30 changes per hour, 7 of the 10 subjects showed allergic symptoms (Anonymous, 1980).

Air concentration measurements of allergenic material show that the loading is correlated to the number of animals in the room, distance from the animals, air circulation and humidity (Davies *et al.*, 1983b; Platt-Mills *et al.*, 1986).

Conclusions

Allergens from mice and rats have traditionally been generally mentioned as fur, hairs or dander. Using modern immunological techniques it has been possible to characterize the allergens. In

mice, the main allergen is a urine molecule of low molecular weight, possibly prealbumin. Serum albumin is also an important allergen candidate. In rats, serum albumin, α_2 -globulin and prealbumin are the predominant allergens. There is no significant cross-reaction between species, but cross-reactivity between strains seems likely because of an almost identical structure of proteins.

The allergens are present in hair, skin, faeces, urine and other material from the animals when measured by skin prick tests. This probably reflects the fact that allergenic serum proteins are present in organic material from the animals and that urine proteins will be found due to contamination. Air in laboratory rooms will also show a significant loading of allergens.

In conclusion: the allergens are widespread wherever the animals are kept, and it is not possible to be in contact with the animals without having contact with allergenic material.

EPIDEMIOLOGY

Epidemiology is concerned with the patterns of disease occurrence in human populations. The information from an epidemiological study may elucidate the aetiology of a specific disease, evaluate the consistency of current hypotheses and provide the basis for developing preventive procedures.

Definitions and methodology

To express morbidity or frequency, two general types of rates are available: incidence and prevalence.

The incidence rate is the number of new cases of a disease occurring in the population during a specified period of time, expressed as per cent of the number of persons exposed to risk of developing the disease during that period of time.

The prevalence rate is the current number of cases of disease present in the population at a specified time, expressed as per cent of the number of persons in the population at that specified time. Thus the incidence rate is a direct estimate of the probability, or overall risk, of developing a disease during a specified period of time.

Several epidemiological studies of ALA have been published. Most of them are prevalence studies, only a few concern the incidence. In addition, incidence studies should be prospective in order to be valid. The epidemiological studies of ALA suffer from several drawbacks. They are not consistent in describing the criteria for clinical diagnosis. Furthermore, they are not consistent in the way the diagnosis was confirmed, whether this is done by history alone, by the patient himself or a doctor, or by specific tests and provocation techniques.

Many studies have scarce descriptions of the population at risk. The employees may have had different degrees of contact with animals, they may have been appointed for different periods of time and it may not always have been appropriate for them to tell others about their health problems.

An inherent problem in epidemiological studies is that it is often difficult to define the population at risk. The epidemiological study may uncover the fact that those who were severely affected by the disease quitted due to medical reasons, while those only slightly affected also quitted for reasons of heightened awareness of their condition. Thus a true high prevalence may be masked.

Prevalence

In 1975, Lutsky and Neuman (1975) surveyed laboratory animal dander allergy at 39 American research facilities, including 23 medical and veterinary schools, 9 research institutes and hospitals, 5 pharmaceutical manufacturers, and 2 commercial laboratory animal producers. The data collected established that 191 workers out of a population of 1293 in daily contact with laboratory animals had clinical symptoms of hypersensitivity, i.e. a prevalence of 14.7%.

Table 4 lists prevalence studies of ALA. Some of the studies do not distinguish between different species, and some record allergy to 'small laboratory animals'. The studies are heterogeneous according to how the population is defined, but we think they represent the best studies available. Pooled data from the studies of 4988 persons at risk indicate a prevalence of

Table 4. Prevalence of ALA, mainly to mice and rats, but some studies include some other species

<i>No. exposed</i>	<i>Percentage with ALA</i>	<i>Reference</i>
60	32	(Böhm & Braun, 1972)
238	11	(Lincoln <i>et al.</i> , 1974)
1293	15	(Lutsky & Neuman, 1975)
474	23	(Taylor <i>et al.</i> , 1976)
399	15	(Gross, 1980)
79	36	(Belin, 1981)
179	27	(Cockcroft <i>et al.</i> , 1981)
585	20	(Davies & McArdle, 1981)
145	19	(Newman-Taylor <i>et al.</i> , 1981)
121	32	(Schumacher <i>et al.</i> , 1981)
146	30	(Slovak & Hill, 1981)
56	27	(Lee <i>et al.</i> , 1982)
69	22	(Beeson <i>et al.</i> , 1983)
67	22	(Møller & Würden, 1984)
138	18	(Agrup <i>et al.</i> , 1986)
549	24	(Bland <i>et al.</i> , 1986)
124	33	(Venables <i>et al.</i> , 1988a)
156	46	(Venables <i>et al.</i> , 1988b)
110	21	(Weissenbach <i>et al.</i> , 1988)
Pooled data:		
4988	20.9	

ALA of about 20%. Two relatively large studies found 11 and 15%, respectively, while 6 studies describe a prevalence of more than 30%.

The different studies reviewed here have not provided consistent results, but nevertheless a coherent picture of the problem emerges. Under-reporting in some studies may be due to different working conditions or to variations in method. Some studies relied on questionnaires where the respondents themselves decided if they were allergic or not, others gave specific criteria and some demanded diagnostic tests. In addition, the amount or type of animal exposure is imprecisely quantified. Some populations may thus show dilution by including persons administratively ascribed to a laboratory, but not actually having contact with animals. Assuming that these suppositions are true, the figures from these prevalence studies are likely to be underestimates rather than overestimates.

It is not possible from the present data to interpret any differences between species, so it is not possible to answer the question of 'allergenic potency' of rats compared to mice. Some of the results presented in Table 4 are

obviously a mixture of specific allergies to mice, rats or other small laboratory animals, but mice and rats dominate. One study found rather small differences in the proportions of ALA measured as a percentage of those who actually worked with the different species (Bland *et al.*, 1986). Almost half of the employees seem to be allergic to more than one type of animal if exposed (Lutsky & Neuman, 1975; Hook *et al.*, 1984; Bland *et al.*, 1986).

In conclusion: the prevalence is about 20%. The studies almost certainly give an under-estimation of the problem. Some persons that develop ALA will leave their jobs, and thus the statistics are based on 'survivor' populations.

Incidence

We have found only two prospective studies of the incidence of ALA, both from Imperial Chemical Industries in England (Davies *et al.*, 1983a; Botham *et al.*, 1987). In the first report (Davies *et al.*, 1983a), a one-year incidence of ALA was determined in all individuals who entered the company's employment to work with laboratory animals during a 2-year period. One hundred and forty-eight people entered the study. Five (3.4%) reported the development of allergic symptoms within one year of employment and another 17 reported symptoms at an anniversary interview, giving a total incidence of 14.9%. The overall incidence of asthma was 2% or one of 7 of those with symptoms. As we shall discuss later the symptoms that developed during the first year were slight or moderate and the incidence of asthma probably increased later. In the second study from ICI (Botham *et al.*, 1987), 383 individuals occupationally exposed to rodents and rabbits were examined during their first 3 years of exposure at the research facilities. These people were assigned to one-year cohorts (35-98 in each). Symptoms were recorded at annual interviews and severity was graded as mild, moderate or severe. In 1979, the incidence of total symptoms was 28%, 12% had mild while 16% had moderate or severe symptoms. A maximum was reached in 1980 and 1981 when 37% got ALA during the first year of employment.

Table 5. Median time for development of ALA

No. exposed	Median time (years)	Variation	Reference
19	1	1 month-3 years	(Böhm & Braun, 1972)
50	2	Weeks-22 years	(Lutsky & Neuman, 1975)
10	2	1 week-9 years	(Neuman & Lutsky, 1976)
59	0.5	Weeks-4 years	(Gross, 1980)
48	3	Not stated	(Slovak & Hill, 1981)
50	2	Weeks-15 years	(Hook <i>et al.</i> , 1984)

In 1983 and 1984 the total incidence had fallen to about 10% and only 3% had moderate or severe symptoms. Two-thirds of those individuals who eventually developed ALA did so during their first year of exposure. The reduction in incidence during the last years may be due to lower loading of allergens following the introduction of a new code of practice for working with animals. Another interesting finding from the study was about 8% of those not having clinical ALA were found to have developed IgE antibodies to rat urinary proteins after one year of exposure.

In Table 5 the median time for development of ALA is listed. The data from 6 studies suggest that 50% of those who will subsequently develop ALA, do so within less than 2 years. There is great variation in exposure time in those investigated and also great variation in the length of the period before allergy is clinically present. Some experience almost immediate reactions, whilst others may have contact with the animals for 15-20 years before they react.

The studies indicate that about 2% of those at risk may develop asthma during the first year of employment and that this rate will hold true also for the subsequent years. It should be noted that asthma apparently follows the rhinitis or conjunctivitis after some time with a time lag of months to many years. This emphasizes the chronicity and severity of ALA if the exposure continues (Davies *et al.*, 1983a).

In conclusion: an incidence of 10–20% of ALA during the first year of employment should be expected if no special precautions are taken. Only a few develop asthma during the first year.

Exposure as a factor. Is 'much' better than 'less'?

There is a common assumption that intensity and duration of exposure are equivalent in causing disease. However, this should be investigated both for occupational disease in general, as well as for the specific disease. In an editorial commenting on the prevention of occupational asthma in general (Venables, 1987), it is suggested that short periods of high exposure are possibly more important than the equivalent 'dose' accumulated by lower exposure over longer time.

In 1980 a study was reported where sensitization was more common among those who had only intermittent exposure to animals (Anonymous, 1980). Staff who worked more than 10 h per week with an animal species appeared less frequently affected. Beeson *et al.* (1983) found that the persons with ALA worked 8.3 h per week in the presence of animals as compared to 13.3 h for the controls. The difference, however, was not statistically significant. Likewise, no difference in the prevalence of ALA was found between the groups working more or less than 10 h per week with animals. Consideration was also given to different animal-handling procedures, but no differences were found in this and in another study (Bland *et al.*, 1986). One study related the symptoms to mouse exposure, graded according to the number of days of exposure. This subdivision did not influence the incidence (Schumacher *et al.*, 1981). When comparing heavy users with light users, no overall tendency was found (Cockcroft *et al.*, 1981).

Many studies referred to here are not well designed, they lack specified inclusion or subdivision criteria, and conditions from one study can hardly be compared to those from another. It seems reasonable to conclude that no evidence so far proves that degree of exposure significantly influences the prevalence of ALA.

Table 6. Relation between work category and symptoms of ALA

Work category	No. exposed	No. with symptoms	%
Caretakers	169	58	34
Technicians	228	66	29
Scientific staff	120	29	24
Technicians and scientific staff	428	127	30
Others/indirectly	132	28	21

The results are based on pooled data from 5 references (Cockcroft *et al.*, 1981; Schumacher *et al.*, 1981; Slovak & Hill, 1981; Agrup *et al.*, 1986; Venables *et al.*, 1988a).

Type of job as a factor

Lutsky (1980) reports that several facility directors had noted an apparently greater prevalence of ALA among scientific personnel than among the animal handlers. The statement was, however, not documented. Lincoln *et al.* (1974) found an increased frequency of a positive history and skin test in individuals with a college or university degree. In Table 6, pooled data from 5 studies indicates that no major differences exist between different exposure categories, except for those only indirectly exposed or for very light users. Cockcroft *et al.* (1981) discussed pressure and suggested that heavily exposed caretakers have a high turnover, have less training than users, and thus cannot modify their work to avoid animal contact. Many users can continue work with reduced animal contact. Many caretakers may not have worked long enough to have developed symptoms. However, no excess of symptoms was found in subjects who had been working more than 2 years.

The role of smoking

Smoking may be a risk factor for allergy, possibly by increasing mucosal transport of allergens. Investigations convincingly demonstrate that cigarette smoking is a strong determinant for airflow obstructive conditions (Anonymous, 1984). Animal experiments have demonstrated that inhalation of tobacco smoke potentiates sensitization by inhaled allergens (Zetterström *et al.*, 1981). However, several studies failed to demonstrate a relationship between ALA and

smoking (Cockcroft *et al.*, 1981; Slovak & Hill, 1981; Lutsky *et al.*, 1985a; Agrup *et al.*, 1986). A slight excess of current smokers in those with symptoms suggestive of occupational asthma was found in a recent study (Venables *et al.*, 1988a). This led the investigators to further examine the question. In their final report they demonstrate an association between smoking and several indices of ALA (Venables *et al.*, 1988b).

In conclusion: we now have some studies that could not find any relationship between ALA and smoking, and one well-designed study that did. We agree with Venables *et al.* (1988b) who stated that prospective studies should be performed, noting atopy and smoking at first exposure to animals and estimating their effect on the incidence of ALA and on its latent interval. If the association proves true, smoking cessation could reduce the development of ALA. Employers could offer education and courses on stopping smoking not only because of health in general, but for specific occupational reasons.

The role of atopy

The question then arises as to whether atopic individuals are more likely to get ALA than others. *A priori* reasoning would indicate that this would be so. Several studies have scrutinized this question. We have found two reports that did not support a relationship between atopy and ALA, the first found no difference in family history of allergy between ALA and non-ALA subjects (Taylor *et al.*, 1976), the second used personal history in order to define atopy (Davies & McArdle, 1981).

Family history of allergic disease is easy to collect from the worker, and if it could be proved to be a good measure of susceptibility to ALA, applicants could be advised not to start working with animals. However, only one study has shown a relationship between family history and ALA (Neuman & Lutsky, 1976), and the study suffers from inappropriate control groups. A well-designed study (Slovak & Hill, 1987) found no significant difference in the incidence of ALA (asthma, rhinitis or both) between individuals with or without a family history of allergy.

Table 7. Atopy and the prevalence of ALA. Data from Slovak & Hill (1987)

	Asthma	Rhinitis	Non-ALA	Total
(a) Personal history				
Atopy +	8	9	18	35
Atopy -	8	24	79	101
(b) Skin prick tests				
Atopy +	12	8	15	35
Atopy -	3	25	82	110

The numbers indicate the number of patients.

Personal history seems to be a better ALA risk indicator. Several studies have demonstrated a statistically significant relationship between pre-employment symptoms of allergy and later ALA development (Lincoln *et al.*, 1974; Neuman & Lutsky, 1976; Gross, 1980; Schumacher *et al.*, 1981; Agrup *et al.*, 1986; Bland *et al.*, 1986; Slovak & Hill, 1987). Data from the study of Slovak and Hill (1987) are presented in Table 7. Eight of the 16 people with asthma had atopy as defined by history (50%), 9 of the 33 with rhinitis had atopy (27%), but only 18% of the non-ALA group were atopic ($P < 0.05$). The total prevalence of atopy was 35%, and is in accordance with the literature of allergy in general. From the data we can calculate that of the 35 atopic individuals, 8 developed asthma (23%) while only 8 of 101 non-atopics developed asthma (8%). There was no significant difference in the occurrence of rhinitis.

Prick tests with a standardized range of allergens are most frequently used in order to examine the relationship between ALA and atopy, and a great number of studies have indeed shown that those with atopy have a significantly increased risk of getting ALA (Neuman & Lutsky, 1976; Cockcroft *et al.*, 1981; Slovak & Hill, 1981; Beeson *et al.*, 1983; Lutsky *et al.*, 1985a; Agrup *et al.*, 1986; Botham *et al.*, 1987; Slovak & Hill, 1987; Venables *et al.*, 1988a; 1988b). Data from two studies will be discussed in some detail. Agrup *et al.* (1986) investigated the prevalence of ALA among all technicians working with animals in the research laboratories of a university. Of the 19 with ALA symptoms, 13 (68%) had a history of atopic dermatitis,

rhinitis, or asthma before they started work at the laboratory, or reacted to one or more allergens in the standard battery, or both. Of the 30 with no animal related symptoms, 6 (20%) had a history of atopic disease, or a positive reaction to a standard test, or both. Thus, atopy was more common among those with positive tests and the difference was statistically significant at the 0.1% level.

Data from Slovak and Hill's study (1987) can also be used when atopy is defined by skin prick tests. From Table 7 it can be concluded that 12 of 35 skin prick positive persons developed asthma while only 3 of 110 non-atopics did. This difference is, of course, highly statistically significant and also of great clinical interest.

On the basis of clinical and immunological findings, an earlier study by Slovak and Hill (1981) concluded that there are 2 syndromes, termed 'regional' and 'progressive', associated with ALA. The regional type is more localized with rhinitis or urticaria, has a weak association with atopy, is usually prick test negative and is seldom RAST positive. The progressive type has asthma and combined symptoms as clinical features, has a strong association with atopy, has positive prick tests to specific allergens and is RAST positive. This distinction may be interpreted from several studies (Cockcroft *et al.*, 1981; Newman Taylor *et al.*, 1981; Slovak & Hill, 1981; De Groot & Messerschmidt, 1984).

One study had access to data on pre-employment skin prick reactivity. The reactivity did not alter between pre-employment examination and the period of the survey (mean 2.6 years, range 1–6). The theoretical consideration that the development of ALA in itself alters atopic status is, therefore, unlikely (Slovak & Hill, 1987). There is also some evidence that symptoms may appear earlier and are more likely to progress to asthma in atopic individuals (Lutsky & Neuman, 1975; Phillips *et al.*, 1977; Cockcroft *et al.*, 1981; Newman Taylor *et al.*, 1981; Slovak & Hill, 1981).

In conclusion: there is no doubt that atopy defined from personal history or by skin prick tests increases susceptibility to ALA. These results

have important implications for pre-employment screening. Some authors suggest that atopic persons should be excluded from working with animals (Patterson, 1964; Lincoln *et al.*, 1974; Schumacher *et al.*, 1981), while many others claim that too many atopics never develop ALA (Newill *et al.*, 1986). The exclusion of about one-third of the population from employment would, therefore, not be justified. However, some subgroups may be defined and the answers need not be the same for all positions, persons or type of atopy.

What is the real risk of getting allergy?

An applicant to a position, where contact with laboratory animals is part of the work, expects to be given a clear answer to the headline question. The answer is neither quantitative (% risk) nor qualitative (great/little). We must first know something about the working conditions. From the incidence and prevalence studies we can say that there is a general risk of about 10–15% of getting ALA within the first year of employment. Two per cent will get asthma each year. The prevalence is about 20%. The median time (the time span until half of those who will get ALA have actually got it) is less than 2 years. However, these numbers were collected some years ago when modern ventilation and equipment were not frequently used. In new buildings with good animal rooms and a clean working environment, the risk is possibly less. Secondly, we must know something about the job. Although exposure *per se* does not influence the risk, persons with different jobs seem to be at different risks (Table 6). Thirdly, we must know something about the person. Is there a family history of allergy? Does the person have a personal history of allergic disease? Does he or she smoke? Does he or she react hypersensitively to irritants or smoke? Is there enough information to diagnose the applicant as atopic, and by which definition?

Based on collected information an answer to the question of the personal risk may vary from slight to large. Whether or not the person has been tested or screened prior to employment,

each applicant has the right to know his/her estimated risk of getting ALA.

CLINICAL MANIFESTATIONS

Symptoms

For practical reasons we shall consider 3 groups of symptoms: eye and nose symptoms, chest, or skin manifestations. Eye and nose symptoms are characterized by rhinoconjunctivitis with its red and itching conjunctiva, sneezing, nasal stenosis or watery discharge, and a strong feeling of irritation. The main chest symptom is bronchial obstruction or asthma with periodic wheezing sounds, cough, mucoid sputum and dyspnoea. Skin rashes are either general or contact urticaria (Agrup & Sjöstedt, 1985). In the general form itching wheals occur all over the body. In contact urticaria the wheals occur only at the contact area, usually on the face, hands and underarms (Rudzki *et al.*, 1981). Occasionally, angio-neurotic oedema occurs. The symptoms develop very shortly after exposure. In a series of 102 cases inhalation of allergen produced symptoms immediately or within 5 min in 71% and within 10 min in 95% of the workers. Anaphylactic reactions with severe systemic effects like hypotension and shock seem to be an extremely rare manifestation of ALA (Teasdale *et al.*, 1983).

Symptom distribution

Eye and nose symptoms are the most frequent, some studies report that every person with ALA experiences rhinoconjunctivitis (Lutsky & Neuman, 1975; Gross, 1980). Immediate type asthma and skin reactions are less common; about 40% of patients develop such symptoms. Table 8 lists the symptom distribution based on 13 prevalence studies. Rhinoconjunctivitis is found in 53–100%, asthma in 13–71% and skin reactions in 13–70%. The pooled data, however, give a rather consistent picture of symptom distribution. Of 10 persons with ALA, 8 will have rhinoconjunctivitis, 4 will have asthma and 4 will have urticaria.

Symptom of sequence

A progressive pattern of symptom severity and development of ALA is seen in many patients.

Table 8. Symptom distribution (in per cent) of ALA based on prevalence studies

No. of patients	Chest	Eye/nose	Skin	Reference
26	48	81	56	(Lincoln <i>et al.</i> , 1974)
60	50	100	—	(Carrol <i>et al.</i> , 1975)
195	71	100	58	(Lutsky & Neuman, 1975)
108	39	74	47	(Taylor <i>et al.</i> , 1976)
36	—	53	14	(Belin, 1981)
48	43	89	51	(Cockcroft <i>et al.</i> , 1981)
117	16	56	29	(Davies & McArdle, 1981)
27	41	85	15	(Newman Taylor <i>et al.</i> , 1981)
39	13	74	41	(Schumacher <i>et al.</i> , 1981)
44	32	67	—	(Slovak & Hill, 1981)
15	20	67	13	(Beeson <i>et al.</i> , 1983)
60	25	85	42	(Venables <i>et al.</i> , 1988a)
23	61	91	70	(Weissenbach <i>et al.</i> , 1988)
Pooled data:	43	80	43	

Not many authors have emphasized these questions, but it seems common that initial contact with animals induces acute or chronic rhinitis, often with an associated conjunctivitis (Lutsky, 1980; Davies *et al.*, 1983a; Agrup *et al.*, 1986). Days or weeks after the appearance of such symptoms many notice itching or whealing of the skin at sites of animal contact which may or may not progress to general urticaria. Bronchial obstruction or asthma develops after several months to many years after first exposure (Gross, 1980; Agrup *et al.*, 1986). Asthma may, however, develop directly in sensitized patients without the prior phase of rhinitis (Slovak & Hill, 1981). Only a portion of those who develop rhinitis progress to asthma.

Symptom overlap

As previously commented in this review, allergy is a mixture of symptoms and syndromes which may overlap considerably. When prevalence studies are performed in a 'steady state' population of persons exposed to laboratory animals, some patterns of overlap are found. These patterns are results of the sequence of development, the risk of getting each allergic

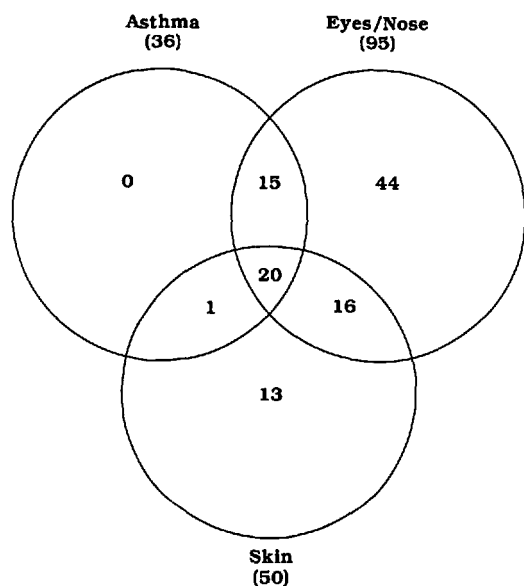


Fig. 1. Symptom overlap and frequency among 109 persons with ALA, having 181 symptoms. The figure is based on data from 2 references (Cockcroft *et al.*, 1981; Venables *et al.*, 1988a). All numbers refer to the number of persons with the actual symptom.

manifestation and the selection of workers that endure working conditions despite their illness.

Figure 1 describes the symptom overlap as pooled from two well-performed studies. One hundred and nine persons had a total of 181 symptoms (mean 1.7 per person). Almost 90% experienced eye and nose symptoms, and among these more than half also had other symptoms, equally distributed between asthma, skin or both. Only a few experienced skin problems alone and none had asthma without any other allergic manifestation. Twenty (18%) had both eye and nose symptoms, skin manifestations and asthma.

The distribution supports the view that asthma is an end-stage of ALA. A prospective study that recorded symptoms and symptom development would be welcome.

Symptom severity

The symptoms of ALA may be experienced very differently by different people. Slight discomfort can be the result of rhinorrhoea or nasal congestion. Bronchial obstruction and asthma

can be experienced as an unbearable condition accompanied by fear and frustration. Severity in the medical sense of the word may be measured as prognosis, number of sickness certificates, the need for medical therapy or employment resignation.

The actual severity is variable and dependent on exposure, tolerance among the workers or the possibility of resting or refraining from contact. These questions have been investigated to a minor degree in ALA. Davies & McArdle (1981) report that 9% of the animal worker population or 48% of those who reported symptoms had to stop work, permanently or temporarily, because of their symptoms. In another survey almost one-third changed jobs or refrained from contact and more than half of this group resigned from their jobs (Lutsky & Neuman, 1975). Among 131 patients with ALA one-third had to be out of work at least temporarily, 45% needed medication (Bland *et al.*, 1986). The need for medical therapy is in itself a measure of severity. ALA is caused by an external agent associated with a place of work. In principle, it is unacceptable that it should be necessary to use medication in order to go to work. Further discussion of these topics is beyond the scope of this article.

DIAGNOSIS

The diagnosis of ALA is mainly clinical. A proper history will identify an allergic disease. The physician must look for the connection between allergic symptoms and contact with the specific allergens. The type of allergic reaction and the symptom group(s) the patient belongs to should be identified by history in typical cases. For therapeutic purposes only this may be enough, but as medico-legal aspects often will be involved, examinations and laboratory tests should also be performed (Lutsky & Toshner, 1978; Longbottom, 1984).

In rhinoconjunctivitis, a profuse watery nasal discharge and nasal obstruction, together with conjunctival injection, may be observed. In bronchial asthma, a hyperresonant percussion note and pathological breath sounds may be noticed, together with prolonged expiration. Urticaria is easily recognized.

Pulmonary function tests are indicated when bronchial obstruction is suspected. Forced expiratory volume (FEV₁), peak expiratory volume and forced vital capacity provide a fairly reliable indication of the degree of airway obstruction. The tests can also be used to determine whether, and to what extent, it can be relieved by drugs. The tests thus have an important place in the diagnosis.

Skin prick tests with allergenic material may be performed, mainly by dermatologists and allergologists. More than 50%, however, will react positively to skin tests (Edwards *et al.*, 1983b). An increasing number of laboratories determine specific antibodies against mouse or rat allergens. Physicians can, therefore, send serum or plasma for RAST determination. More than 60% will be positive by immunoassay. Almost all asthmatic individuals react positively to both skin prick tests and RAST, with a good correlation between the tests (Davies *et al.*, 1983a).

PROGNOSIS

The clinical course of ALA, if exposure is continued, has been described earlier. Here we want to comment on the prognosis in terms of consequences of the disease when exposure is sustained. Both medical and social consequences are relevant.

Medical consequences of rhinoconjunctivitis or urticaria in itself are few or absent. No long-term complications or lasting injury are expected, but side effects from treatment may occur. Subclinical but significant bronchospasm remains for days to weeks after an acute attack of asthma. However, the long-term consequences of asthma are few, but may be serious. There is no evidence that it leads to permanent pulmonary parenchymal damage in the form of chronic bronchitis or emphysema. While the overall mortality for all forms of asthma is 0.1% per year, the rate increases markedly (2–4%) for patients with episodes of status asthmaticus. These remarks presuppose that identification of the allergen has been done, that any known allergens or irritants have been avoided, when possible, and that the condition has been properly treated.

The social consequences of ALA are many and affect quality of life. Some persons are forced to resign (see previous section on Symptom severity) and perhaps leave an occupation they like and for which they are qualified. For those who endure working, daily symptoms, effects of drugs or the use of personal protection may, in some cases, reduce well-being only slightly but for many people this can reach unacceptable levels. The endurance threshold varies considerably between individuals and is as such subjective and cannot be predicted.

CONCLUDING REMARKS

This topic has been reviewed previously (Lutsky, 1980; Newman Taylor, 1982; Longbottom, 1984; Olfert, 1986).

Several criteria for critical readers or investigators have been suggested in order to evaluate the validity and applicability of reported results. Many studies reviewed by us suffer from imperfection, and many others cannot contribute to knowledge because of insufficient data, analysis or interpretation. Much of the literature concerning ALA consists of case reports. In these papers one or a few cases are described and a short discussion follows. Such papers may be important to remind veterinarians, physicians and researchers about the condition, but very seldom give new and valid information. The prevalence studies are often biased due to lack of randomization. There is great heterogeneity in the type of symptoms, patients are seen at different times, and it is difficult to record the natural history of the disease retrospectively. It is essential for validity that studies are randomized with control groups where appropriate. Exclusion or loss of persons in a study may bias the results, especially since those who do especially well or especially poorly may be more likely to be unavailable for follow up. Some persons with ALA may quit their jobs very soon, while those without symptoms may be selected to undertake specially exposed jobs. Those without symptoms may not wish to undergo experimental procedures or diagnostic tests. In long-term follow-up studies, different treatments may alter the

outcome. Investigators cannot let people with asthma remain untreated in order to elucidate the natural history of the disease.

In studies that report no differences between groups, it is essential to know whether the sample size used was adequate to detect clinically important differences. And vice versa, highly statistically significant differences may be without clinical significance.

Conditions in laboratories may differ considerably in respect to ventilation, contact patterns and use of protection. So even with good descriptions comparisons may be difficult. Over

the years the working conditions may have improved due to information about ALA. Such factors may confound the interpretation. Based on the data in many of the articles, it is often difficult to draw strong conclusions, if at all.

Papers from the latest years are in general of much higher quality. To our satisfaction we now notice several research groups that concentrate their research on ALA. Thus the problem will be investigated in greater profundity by more experienced and qualified researchers in the future.

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