Allergy to laboratory animals: a prospective study of its incidence and of the influence of atopy on its development

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ABSTRACT The pattern of incidence of allergy to laboratory animals (ALA) has been studied prospectively in 383 individuals occupationally exposed to rodents and to rabbits. The incidence of the disease after one year of exposure to animals fell from 37% in 1980 and 1981 to 20% in 1982, 10% in 1983, and 12% in 1984. A similar reduction was noted after two and three years of exposure in the 1982 and 1983 cohorts. The reduction in incidence coincided with the introduction of a site order and code of practice for working with animals and an education programme designed to focus awareness on the problem. Although rats were believed to be the major cause of the disease, objective measurements of IgE antibody against rat urine allergen were positive in only half the symptomatic individuals. Antibodies to different animal derived allergens were, however, found in several other personnel. Symptoms were generally of mild or moderate intensity and affected mainly the nose, eyes, and skin; chest symptoms were found in only 1.6% of the exposed population. A study of the influence of atopy on the development of ALA showed that after one year of exposure to animals a significantly greater proportion of atopic individuals became symptomatic (19-43% compared with 3-6%). After two and three years of exposure, however, this discrepancy was not maintained, with more non-atopic individuals developing the disease.

One of the major risks to the health of animal handlers and scientists working with laboratory animals is the development of respiratory allergy. Surveys conducted at various research establishments between 1974 and 1981 indicated that the prevalence of allergy to laboratory animals (ALA) was between 10% and 30%.¹⁻¹³ All the surveys on ALA except for that of Davies *et al*¹² have been cross sectional, and the actual incidence of the disease could have been higher than the prevalence figures suggested because "survivor" populations were studied.

The prevalence of asthma as a symptom of ALA, which is now a prescribed industrial disease, was between 3% and 11%.^{2,5-9,13} Several of the studies suggested that those with asthma were usually atopic (skin test positive to one or more environmental allergens) and usually had skin prick test reactions and

specific circulating IgE antibodies to animal allergens; those with milder symptoms appeared to be no more likely than exposed asymptomatic individuals to be atopic or to have positive skin or blood test reactions.^{6,7} In addition, it was suggested that most individuals with ALA developed their disease (usually in a mild form) during the first year of exposure to animals, whereas asthma developed in a proportion of these individuals after a longer period of exposure.^{5,8}

The study reported here represents an attempt to investigate ALA prospectively, by examining a group of exposed individuals during their first three years of exposure to animals at the research facilities of ICI at Alderley Park in order to establish the true incidence of the disease and to assess its development.

The two major objectives of this study were:

(1) To establish the pattern of incidence of ALA at Alderley Park, and

(2) To determine whether it is possible to identify at the onset of working with animals those individuals who are predisposed to develop ALA.

Material and methods

PREPARATION OF ALLERGENS

Material was prepared from the urine, epidermis, and serum of rats, mice, guinea pigs, and rabbits by the methods described by Davies *et al.*¹⁴ and assayed by the ELISA system described. After April 1982, the same material was used to prepare the skin test reagents in place of the previously used reagents described by Davies *et al.*¹²

ESTIMATION OF SERUM IGE ANTIBODIES

The modification of the method of Ceska *et al.*¹⁵ described by Davies *et al.*¹² was used. IgE antibodies were estimated in all cases only to the rat urine allergen. The remaining 11 allergens were used if either skin prick test results or the reported symptoms so suggested.

SKIN PRICK TESTS

Skin prick tests were carried out as described previously¹² using all 12 animal derived allergens. Tests for atopy were carried out using group B2 (pol-lens) grasses (2.5%) and *Dermatophagoides pteronyssinus* (1.2%) supplied by Dr Janet Dewdney.

SUBJECTS AND PROCEDURE

All individuals who entered the company's employment between 1979 and 1984 and who intended to work with animals were invited to enter the survey. All permanent and temporary staff were recruited on to the survey, but those individuals who did not complete a minimum of nine months' service were excluded from the analyses.

Immediately after starting employment each individual completed a questionnaire to determine the nature of any previous contact with animals and to establish whether there was a history of clinical allergic disease. Allergy to animals was not seen then because individuals with a history of ALA were not recruited to work with animals. Skin prick tests were

performed and a blood sample was taken for the estimation of IgE antibodies.

One year later, and then annually for a further two years (in practice, intervals of 9–15 months elapsed between visits because of the administrative difficulty of ensuring accurate compliance with regard to interview periods), a second questionnaire was completed and skin tests and serum IgE estimates were repeated. This second questionnaire detailed the development of any allergic symptoms to animals and the nature and duration of exposure to laboratory animals since the previous interview.

ASSIGNMENT TO COHORTS

To take account of the possibility of changes over time affecting the incidence of ALA the variable cohort was introduced into the analysis of the data. Thus all individuals who started to work with animals between 1 January and 31 December 1979 were assigned to the 1979 cohort. Similar assignments were made for the years 1980–4.

SYMPTOM EVALUATION

Symptoms reported at the annual interviews were recorded as "nasal" (stuffy or blocked nose, repeated attacks of sneezing); "eyes" (smarting, itchy); skin (rash, eczema, urticaria); or chest (tightness). Severity was graded as 1 (mild), 2 (moderate), or 3 (severe). It should be emphasised that all were subjective responses on the part of the interviewee. Clinical confirmation was obtained only in certain cases—for example, when the chest was affected or when the symptoms were a particular nuisance.

Results

ANNUAL INCIDENCE OF SYMPTOMS

A total of 383 individuals completed at least nine months employment. Table 1 shows the incidence of symptoms on an annual basis. After 1981 there was a significant and apparently progressive decrease

Table 1 Annual incidence of allergy to laboratory animals

Cohort	Symptom grade	After 1 year	After 2 years	After 3 years
1979	Grades 1–3	14/50 (28%)	13/49 (27%)	10/46 (22%)
	Grades 2–3	8/50 (16%)	4/49 (8%)	2/46 (4%)
1980	Grades 1–3	18/49 (37%)	20/46 (43%)	11/39 (28%)
	Grades 2–3	8/49 (16%)	13/46 (28%)	7/39 (18%)
1981	Grades 1–3	13/35 (37%)	5/19 (26%)	5/17 (29%)
	Grades 2–3	13/35 (37%)	2/19 (11%)	2/17 (12%)
1982	Grades 1–3	14/70 (20%)	11/53 (21%)	7/37 (19%)
	Grades 2–3	9/70 (13%)	6/53 (11%)	3/37 (8%)
1983	Grades 1–3	10/98 (10%)	8/54 (15%)	
	Grades 2–3	3/98 (3%)	6/54 (11%)	
1984	Grades 1–3	10/81 (12%)		
	Grades 2–3	3/81 (4%)		

incidence of ALA after one year of exposure to animals at Alderley Park, both in symptoms of all grades and of those graded as moderate or severe. By 1983 the incidence of total symptoms had fallen to 10% compared with the 37% in 1980 and 1981, and the improvement was maintained in 1984 with an incidence of 12%. There was also a decrease in incidence after two years of exposure as shown by the 1982 and 1983 cohorts.

In the 1979–82 cohorts two thirds of those individuals who eventually developed ALA did so during their first year of exposure to animals at Alderley Park.

SEVERITY AND CAUSE OF SYMPTOMS

Five of the 383 individuals developed symptoms that were so severe that they were excluded from working with animals.

The responses of the individuals in the 1982–4 cohorts concerning the species of animal thought to be the cause of their symptoms and the site and severity of the symptoms after one year of exposure are shown in table 2. Rats were the most commonly implicated species, 38 of the total of 51 symptoms being so attributed. Next most common were rabbits with six symptoms attributed and mice with seven. At this time no one thought that guinea pigs caused their symptoms. Nasal symptoms were the commonest, followed by skin, eyes, and then chest.

Only six of the 36 affected individuals reported chest symptoms, representing an overall incidence of 1.6% after one year of exposure.

INFLUENCE OF ATOPY ON THE DEVELOPMENT OF SYMPTOMS

In the previous communication reference was made to the relation between “the atopic state” and the development of allergy to laboratory animals.^{1,2} We are currently designating as atopic those individuals who gave a positive skin prick test response to grass pollen or to house dust mite of 4 mm or more. As the skin

tests were not carried out on all individuals before 1982 comment will be restricted to those in the 1982, 1983, and 1984 cohorts. On entry the respective incidence of atopy in these three cohorts was 45%, 30%, and 36%. The corresponding values one year later were 45%, 33%, and 36%.

Table 3 shows that after one year of exposure nearly all (93%) of the symptomatic subjects in the 1982 cohort were atopic; 42% of atopic individuals in this cohort developed ALA during the first year whereas only 3% of non-atopic individuals did so. It must be emphasised, however, that 58% of atopic subjects did not become allergic to animals. Also worthy of comment is the observation, again in the 1982 cohort, that after two and three years of exposure the proportion of symptomatic subjects who were atopic had fallen to 73% and 43% respectively, which might be taken to indicate that atopy predisposes mainly towards the early development of allergy.

The correspondence of symptoms and atopy was less pronounced (60%) after one year in the 1983 cohort but had risen again to 80% by 1984. As with the 1982 cohort, the 1983 results for two years of exposure showed a pronounced decrease in the proportion of symptomatic subjects who were atopic.

RELATION BETWEEN SYMPTOMS AND IMMUNOLOGY

All the individuals in the 1982 cohorts were skin tested with the complete range of allergens but IgE estimates are complete only for rat urine allergen, tests for antibodies to the other allergens being carried out only on selected individuals. The relation between symptoms and antibodies to rat urine (as shown by skin test or the presence of circulating IgE antibody) is shown in table 4. In general the agreement between symptoms and antibody to urine after one year of exposure was unconvincing, being evident in 64%, 60%, and 40%, respectively, for the three cohorts. Both estimates (skin and serum) of antibody

Table 2 Severity and cause of symptoms of allergy to laboratory animals after one year of exposure in the 1982–4 cohorts. (Total number of volunteers with symptoms = 36.)

Symptom site and grade	No of symptoms											
	Eyes			Nasal			Skin			Chest		
	1	2	3	1	2	3	1	2	3	1	2	3
Implicated species:												
Rabbits (6)	1			1	2			1				1
Mice (7)	1		2		1	1			1			1
Guinea pigs (0)											1	3
Rats (38)	4	2	1	10	5	2	5	4	1			
Totals	6	2	3	11	6	5	5	5	2	0	1	5
		(11)			(22)			(12)			(6)	

Table 3 *Relation between atopy and the development of allergy to laboratory animals*

Cohort	Symptoms of ALA (of any grade)	No	Atopic	Non-atopic	Atopic with symptoms (of any grade)*	Non-atopic with symptoms (of any grade)†
1982	After 1 year:					
	Positive	14	13 (93%)	1 (7%)	13/32 (41%)*	1/38 (3%)†
	Negative	56	19 (34%)	37 (66%)		
	After 2 years:					
	Positive	11	8 (73%)	3 (27%)	8/27 (30%)	3/26 (12%)
	Negative	42	19 (45%)	23 (55%)		
1983	After 3 years:					
	Positive	7	3 (43%)	4 (57%)	3/17 (18%)	4/20 (20%)
	Negative	30	14 (47%)	16 (53%)		
1984	After 1 year:					
	Positive	10	6 (60%)	4 (40%)	6/32 (19%)*	4/66 (6%)†
	Negative	88	26 (30%)	62 (70%)		
	After 2 years:					
	Positive	8	2 (25%)	6 (75%)	2/20 (10%)	6/34 (18%)
	Negative	46	18 (39%)	28 (61%)		
1984	After 3 years:					
	Positive	10	8 (80%)	2 (20%)	8/29 (28%)*	2/52 (4%)†
	Negative	71	21 (30%)	50 (70%)		

*9/32, 1/32, and 3/29, respectively, had symptoms of grade 2 or 3.

†1/38, 2/66, and 0/52, respectively, had symptoms of grade 2 or 3.

gave similar results. There are several possible explanations for this apparent discrepancy: unsuitable or inappropriate allergens were used for the test; the tests themselves were too insensitive; the symptoms were not due to animals; antibody was not responsible for the symptoms; and the symptoms were due to species other than rats (but see table 2). With regard to the last possibility, antibodies to allergens other than rat urine were detected in a further seven individuals giving concordance between symptoms and antibody of 86%, 70%, and 70%, respectively, for the three cohorts. This relation was little changed after two or three years of exposure in the 1982 and 1983 cohorts.

Discussion

There are some limitations inherent in this study. Not least is the subjective nature of the assessment of symptoms, which was simply as stated by the individual at the time of interview. Possibly not all the reported symptoms were due to ALA and, for various reasons, some symptoms were not reported. Further difficulties of interpretation were introduced by the actions taken to reduce the incidence of allergy—for instance, some individuals become symptom free when respiratory protection was used, or, as was to be expected, when their contact with animals was reduced or removed.

Table 4 *Relation between the development of allergy to laboratory animals and the presence of antibodies to animal allergens*

Cohort	Symptoms of ALA	No	Antibody to rat urine*	Antibody to any animal allergen*
1982	After 1 year:			
	Positive	14	9 (64%)	12 (86%)
	Negative	56	4 (7%)	†
	After 2 years:			
	Positive	11	7 (64%)	9 (82%)
	Negative	42	5 (12%)	†
1983	After 3 years:			
	Positive	7	5 (71%)	5 (71%)
	Negative	30	4 (13%)	†
1984	After 1 year:			
	Positive	10	6 (60%)	7 (70%)
	Negative	88	5 (6%)	†
	After 2 years:			
	Positive	8	6 (75%)	7 (88%)
	Negative	46	5 (11%)	†
1984	After 3 years:			
	Positive	10	4 (40%)	7 (70%)
	Negative	71	3 (4%)	†

*As shown by skin test or the presence of IgE antibody.

†Data incomplete.

Nevertheless, a progressive and significant annual decrease in the proportion of individuals reporting symptoms is apparent after 1981. This coincided with the introduction at Alderley Park of a site order and code of practice for working with animals (the overall aim of which was to decrease the exposure of scientists and others working with animals to airborne allergens) and also with a series of lectures designed to focus awareness on the problem. It is not, however, possible to conclude that the reduction in incidence of ALA is due simply to the lowered exposure to the allergen as no environmental monitoring was carried out. Attempts to rectify this omission are now being made. It is unlikely that the appearance of allergic symptoms has merely been delayed by the precautionary measures because, as table 1 suggests, the improvement was maintained for up to three years of exposure.

The vexed relation between ALA and atopy has become a little clearer from the results of this study. It appears that at least during the first year, most of those with symptoms due to animals are also atopic as shown by skin tests to either grass pollen or house dust mite. It must be emphasised, however, that the reverse does not hold good. Most atopic subjects do not develop ALA during their first year of contact. This latter finding is particularly relevant to those institutions whose recruitment policy forbids the employment of atopic individuals to work with animals. Furthermore, the positive correlation apparent during the first year is not maintained during the second and third years. The importance of atopy in determining the nature and severity of the symptoms was not carried out; in any case most of the symptomatic individuals were atopic during the first year and the numbers becoming symptomatic in the two succeeding years of the 1982 cohorts were small. This matter will be dealt with in more detail in a subsequent communication.

The tests of IgE antibody (either by skin test or by estimation of specific circulating antibody—and in general, these two estimates gave the same result) disclosed a complex situation. After one year of exposure, between 40% and 64% of symptomatic subjects in the 1982–4 cohorts had IgE antibody to rat urine allergen. If antibody to other animal allergens was included the correlation rose to 70–86% but many of these other antibodies were to species other than those reported as being responsible for the symptoms. Further evidence of complexity was seen when the detailed results from selected individuals of the 1982 cohort were analysed (again, this will be detailed in a subsequent communication). Many different patterns of response were seen. High levels of circulating (specific) IgE antibody do not necessarily indicate severe, or indeed occasionally, any,

allergy developing during the first three years. Possibly the appropriate source of allergen was not used, either because it was not present in the preparation or was from a source (saliva, for example) not represented. At present tests for antibody appear to be of value as an aid to diagnosis but they do not replace careful clinical evaluation.

That rats are a common cause of allergy is confirmed by the results shown in table 2. Although rats are the most commonly used species in this establishment this does not, in our judgement, fully account for their allergenicity since large numbers of the other species are also used. The absence of reports of allergy to guinea pigs during the first year was surprising; they do, however, figure in the reports of subsequent years and this matter of responsible species will again be taken up in a later communication. The sites affected were more or less as expected, nasal symptoms being the commonest followed by skin, eyes, and chest. The severity of the symptoms was usually mild or moderate. Although some severe reactions were reported, they resulted in only four of the 383 individuals in this survey transferring to jobs where there was no exposure to animals.

The results and conclusions presented in this paper are concerned with a prospective study of ALA only during the first years of contact with animals and cannot be compared with studies derived from a cross section of individuals at a given time. One of our major objectives was to identify early those likely to become allergic to animals. Not surprisingly, this was not fully achieved. Although most of those who developed allergy during the first year were atopic, many of them never developed ALA, and during the second and third years an increasing proportion of non-atopic subjects became allergic to animals. Tests for IgE antibody are of great theoretical interest but, at present, they do not do more than aid diagnosis. Attempts to include the nature and frequency of contact with animals as additional indicators of those individuals likely to develop ALA were frustrated by the numerous types of procedures used and the impossibility of obtaining an accurate record of exposure. We expect that our current studies on monitoring exposure to allergen will provide more useful information.

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