

Patients suspected of having a dementing illness are best investigated in a specialist neuropsychiatric unit staffed by neurologists and psychiatrists and having easy access to pathology, neuroradiology, and nuclear-medicine facilities. Such a unit can provide a suitable milieu for patients who may be confused and behave in ways ill-understood by the staff of a general ward.

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Occupational Health

ALLERGY IN LABORATORY ANIMAL WORKERS

A. COCKCROFT J. EDWARDS
P. MCCARTHY N. ANDERSSON

MRC Pneumoconiosis Unit, Llandough Hospital,
Penarth, South Glamorgan, Wales

Summary 179 people working with small laboratory animals were studied by questionnaire, lung-function tests, skin tests with common allergen extracts and extracts of the serum and urine of five animal species, and serology. 49 people had symptoms related to animal contact, most commonly rhinitis but also asthma and skin rashes. Skin reactivity to animal extracts was related to symptoms, particularly asthma, but many people with rhinitis only had negative skin tests. Positive skin tests without symptoms were rare. 3 people had additional late skin reactions. Atopic individuals were no more likely than non-atopics to have animal-related symptoms but were more likely to have asthma. Gel diffusion revealed no precipitating antibodies, and no specific IgG was detected with the ELISA technique. Lung-function measurements were normal. Sensitisation to laboratory animals may involve heavy antigen exposure, so that relatively unreactive individuals can be affected. Exclusion of atopic individuals from work with laboratory animals will not eliminate the problem.

INTRODUCTION

In Britain about 32 000 people work with laboratory animals—12 000 Home Office licence holders¹ and an estimated 20 000 other workers. In exposed populations allergies to animals have been described by a number of authors,²⁻⁵ and the problem is apparently quite common.^{4,6-8} Indeed, animal asthma has just become a prescribed industrial disease.⁹ Apart from the laboratory-exposed population there are several million people in Britain exposed to small domestic pets.

The present study was undertaken to investigate the extent of the problem in an exposed population, the nature of the allergic symptoms, and any relationships between symptoms, atopic status, and intensity of exposure.

SUBJECTS AND METHODS

Three Medical Research Council establishments (A, B, and C) participated in the study, providing a total of 213 subjects. Of these, 179 had contact with laboratory animals in their work. The proportions of the working populations tested at the establishments are shown in table 1. "Handlers" were technicians engaged full-time in animal husbandry. "Users" were technicians or scientists who used animals experimentally, and they were classed as "heavy" users if they had contact for an average of more than 2 h daily and "light" users if they had less frequent contact. A few users with previous exposure, but none currently, were included. In establishment C, non-exposed scientists and technicians were also tested. Data from the three establishments were analysed separately and then combined by means of a Mantel-Haenszel test¹⁰ to produce a combined χ^2 value and odds ratio (OR).

Each person completed a questionnaire about past and present occupations and was asked specifically about animal contact—the species handled and the duration and extent of exposure. A modified MRC questionnaire on respiratory symptoms and any history of asthma or hayfever was administered. Subjects were asked about symptoms from animal contact—in particular, eye or nose irritation, breathing problems, or rashes.

Forced expiratory volume in one second (FEV₁) and forced vital capacity (FVC) were measured and flow-volume curves obtained with a McDermott digital spirometer.¹¹

Skin prick tests were performed on each subject with six common allergen extracts: house dust, house-dust mite, grass pollens, tree pollens, cat fur (all Bencard reagents), and *Aspergillus fumigatus*.¹² The six allergens and a saline control were introduced into one arm. Reactions were read at 15 min. Oedema 3 mm or more greater than the control reaction was considered a positive reaction. Subjects were classed as atopic if they had a positive reaction to one or more of the common allergen extracts.

Extracts were prepared from the serum and urine of male rats, mice, guineapigs, rabbits, and sheep. Urine was collected by means of metabolic cages and before use was dialysed against running tap-water, heated at 56°C for 30 min, and filtered less than 0.22 μ m. The concentration was adjusted at 5 mg/ml in saline. Serum was heated at 56°C for 30 min, filtered less than 0.22 μ m, and diluted 1-in-14 in saline to about 5 mg/ml. The animal extracts were pricked into the arm not used for the common allergens, with a saline control. Reactions were interpreted as for the common allergens. Subjects were instructed to report any late skin responses.

A venous blood sample was taken from each subject. The sera were tested by double gel diffusion against antigens from the five animal species at 1 mg/ml. The enzyme linked immunosorbent assay (ELISA) technique was used on the sera, with a method described elsewhere^{13,14} except that the plates were sensitised with animal urine or serum at 100 μ g/ml in carbonate/bicarbonate buffer pH 9.5. Sheep serum and urine were not used since there was little evidence of exposure or sensitisation to this species. It was not possible to process all the sera in the study on one day, but all sera from establishments B and C were tested on single days and sera from establishment A were tested in three batches. Sera for use in the ELISA test had to be diluted to 1/1000 since at higher concentrations, such as 1/100, there is no discernible difference between sera with well-defined antibodies, detectable by gel diffusion, and precipitin-negative sera. This we attribute to a non-specific, as opposed to antibody-specific, IgG reaction.

TABLE 1—THE POPULATIONS TESTED

Establishment	Total population identified		No. tested*	% tested
A	Handlers	27	22	82
	Users	104	70	67
B	Handlers	39	23	59
	Users	86	29	30
C	Handlers	8	7	88
	Users	28	28	100
	Non-exposed	35	29	83

* There were also 4 non-exposed subjects tested in A and 1 non-exposed subject in B.

RESULTS

Population Characteristics

55 of the 179 animal-exposed subjects (31%) gave a history of asthma, hayfever, or both. The percentages in the individual establishments were 34% in A, 27% in B, and 29% in C. Of the 29 non-exposed subjects in C, 6 (21%) gave such a history. On the basis of skin tests with common allergen extracts, 70 of the 179 exposed subjects (39%) were classed as atopic: 41% in A, 42% in B, 29% in C. There were 35% skin-test atopics among the non-exposed subjects in C. The association between a history of asthma or hayfever and skin-test atopic status was significant at the 0.01% level ($\chi^2 = 46.8$, OR = 10.24).

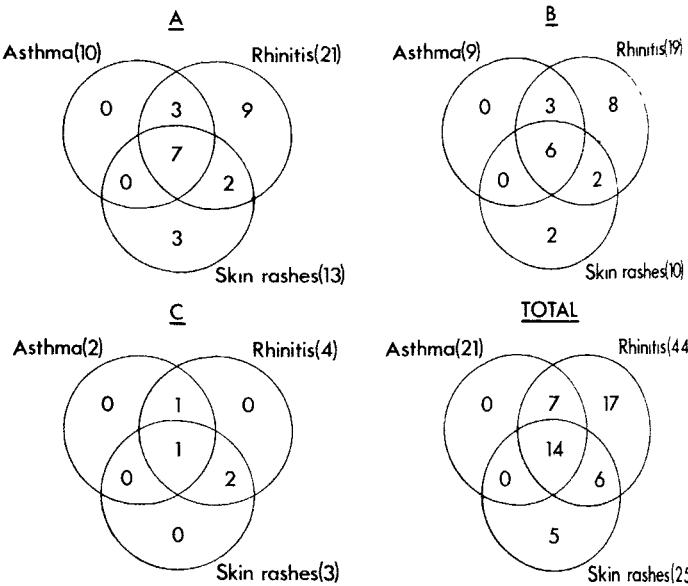
The percentages of smokers, ex-smokers, and non-smokers were: 25%, 8%, and 67% in A; 44%, 21%, and 35% in B; 29%, 20%, and 51% in C (exposed); 24%, 28%, and 48% in C (non-exposed).

Lung function was normal in the majority of subjects. 4 people had an obstructive ventilatory defect related to previously known causes—asthma in 3 and chronic bronchitis in 1. None of the subjects was tested when having symptoms.

Symptoms Related to Animal Contact

49 of the 179 exposed subjects (27%) had symptoms related to contact with the animals at work: 24/92 in A, 21/52 in B, and 4/35 in C. The various combinations of symptoms described are illustrated in the figure. The commonest symptom was rhinitis, usually associated with irritation and watering of the eyes. Immediate-type asthma from animal contact was less common and often developed after rhinitis. No subjects had asthma without other symptoms. Rashes took the form of excessive weals around scratches and local urticaria from contact with animal urine or paws.

The severity of symptoms was variable. Often they were no more than a nuisance, but in some subjects they were so severe as to make direct or even indirect contact with animals impossible. A few subjects included in the survey had stopped animal work because of symptoms. The study population did not include people who had left the establishments.



Combinations of animal-related symptoms reported.

There was no overall tendency for the more heavily exposed subjects (the handlers) to have more allergic symptoms related to animals than the less heavily exposed subjects (the users) (table II). In establishment C the handlers had significantly more symptoms than the users ($p = 0.019$ by Fisher's exact test). The average period of animal work before symptoms developed was 3.1 years in establishment A, 2.4 years in B, and 2.5 years in C. Handlers developed symptoms more quickly than users: 2.0 years versus 3.4 years in A, 1.0 years versus 3.6 years in B, and 2.3 years versus 3.0 years in C. The difference in time to develop symptoms between the handlers and users failed to reach the 5% level of statistical significance (Wilcoxon's rank sum test).

There was no association between skin-test atopic status and symptoms from animal contact (table III, parts i and iii). However, there was an association, significant at the 2% level, between skin-test atopic status and asthma from animal contact ($\chi^2 = 5.62$, OR = 3.37) (table III, part ii). Subjects with a previous history of asthma were not significantly ($p > 0.05$) more likely to develop symptoms from animal

TABLE II—RELATION BETWEEN EXPOSURE CATEGORY AND SYMPTOMS FROM ANIMAL CONTACT

Exposure category	A		B		C		Total	
	Symptoms present	Symptoms absent	Symptoms present	Symptoms absent	Symptoms present	Symptoms absent	Symptoms present	Symptoms absent
Handlers	4	18	10	13	3	4	17	35
Heavy users	10	18	7	6	0	5	17	29
Light users	10	32	4	12	1	22	15	66

TABLE III—RELATION BETWEEN SYMPTOMS FROM ANIMAL CONTACT, SKIN-TEST REACTIVITY TO ANIMAL EXTRACTS, AND SKIN-TEST ATOPIC STATUS IN ANIMAL-EXPOSED SUBJECTS

—	A		B		C		Total	
	Atopic	Non-atopic	Atopic	Non-atopic	Atopic	Non-atopic	Atopic	Non-atopic
i. All animal-related symptoms:								
Skin test +ve	7	4	8	2	2	1	17	7
Skin test -ve	3	10	1	10	0	1	4	21
ii. Asthma from animal contact:								
Skin test +ve	5	3	6	1	2	0	13	4
Skin test -ve	1	1	0	2	0	0	1	3
iii. No symptoms related to animals:								
Skin test +ve	2	0	1	1	1	0	4	1
Skin test -ve	26	40	12	17	7	23	45	80

contact ($\chi^2=3.04$, $OR=2.99$) but were more likely to develop animal-related asthma (table IV). The association between previous asthma and animal-related asthma was significant at the 0.1% level ($\chi^2=13.1$, $OR=8.37$).

Smoking history was not related to symptoms from animal contact.

Responses to Animal-extract Skin Tests

29 of the 179 exposed subjects had a positive reaction at 15 min to at least one of the animal extracts. Skin reactivity to animal extracts was associated with a history of symptoms from animal contact at the 0.01% level of significance ($\chi^2=45.6$, $OR=21.8$) (table III, parts i and iii). Most of this overall association was due to the strong association between skin reactivity and asthma from animal contact, and many subjects with rhinitis alone did not have positive skin tests to animal extracts (table III, compare i and ii). Skin reactivity to animal extracts was associated with skin-test atopic status (table III); the association was significant at the 0.1% level ($\chi^2=13.74$, $OR=5.26$).

TABLE IV—RELATION BETWEEN PREVIOUS HISTORY OF ASTHMA AND SYMPTOMS RELATED TO ANIMAL CONTACT

Symptoms	Previous history of asthma							
	A		B		C		Total	
	Yes	No	Yes	No	Yes	No	Yes	No
Any symptoms related to animals	1	23	5	16	2	2	8	41
Asthma related to animals	1	9	4	5	2	0	7	14
No symptoms related to animals	5	63	1	30	3	28	9	121

Those subjects with symptoms from animal contact who had positive skin reactions all reacted at least to the serum or urine of the animal they thought had caused their symptoms; many also reacted to other animals to which they were exposed but which they had not noted to produce symptoms.

Only 5 people had positive skin reactions to animal extracts in the absence of symptoms from animal contact (table III, part iii). 4 of these were atopic; all had reactions to a single animal extract—in 1 case from an animal to which the subject was not exposed. 1 non-exposed subject, who was skin-test atopic, had a weak single-extract reaction. There were no other skin reactions to the animal extracts among the non-exposed subjects.

5 people experienced late reactions to the animal-extract skin tests. 3 of these had reactions around the site of positive 15 min reactions, with a large, oedematous, warm, red, tender area appearing, maximum at 6–8 h and disappearing over about 18 h. 1 of these also had a mild asthma attack at about 6 h. 2 others had symptoms of rhinitis, conjunctivitis, and tightness in the chest at about 4 h. All 5 had severe symptoms from animal contact and strongly positive immediate skin reactions to animal extracts. 4 of them were skin-test atopic.

Serology

No precipitins were detected in the sera by gel diffusion against the animal extracts. The ELISA results for all subjects, exposed and non-exposed, followed a gaussian distribution pattern, with no difference in IgG levels between the non-exposed and exposed subjects, between those with and without skin reactivity to animal extracts, or between those with and without animal-related symptoms. The 5 subjects who had late reactions had no greater IgG levels than non-reactors or non-exposed subjects.

DISCUSSION

We found that 27% of a population working with laboratory animals had symptoms related to contact with the animals. This figure is higher than figures reported from the U.S.A.^{4,6} but agrees with Taylor et al.,⁷ who found that 23% of an exposed population had symptoms from animal contact. The figure is likely to be an underestimate of the true frequency of symptoms produced by animal work, since the population studied were those who had “survived” in the occupation. How many left because of symptoms is not known.

Selection pressure probably affects exposure categories differently and this may be why we found no trend for the more heavily exposed handlers to have more symptoms than the users. This pattern has been noted previously.^{4,6} The handlers are younger and less highly trained than the users and cannot easily modify their work to avoid animal contact if they develop symptoms. Many users with symptoms can continue with reduced animal contact.

In view of the high turnover of animal handlers, much of which may be unrelated to symptoms, there is another possible explanation of the lack of excess symptoms among them. Many of the handlers at any time may not have been working in the laboratory long enough to develop symptoms. However, in subjects who had been working with animals for 2 years or more there was still no excess of symptoms in the handlers. Therefore the high turnover itself does not seem to be the explanation for the lack of excess symptoms in handlers and unequal selection pressure seems the more likely cause. Despite this probable distortion of the population studied there was some indirect evidence of an exposure-response relationship in that handlers tended to develop symptoms more quickly than users.

The relationship between symptoms from animal contact and skin reactivity to animal extracts was interesting. Only 5 people showed skin reactivity in the absence of symptoms, suggesting that skin tests with animal extracts to screen for people likely to develop symptoms are probably not useful. A number of people with symptoms had negative skin tests with animal extracts. The majority of these had rhinitis without asthma, and there was also a preponderance of non-atopic subjects among them. This group could represent relatively unreactive subjects who have been heavily exposed to antigen, producing a local response in the nose but not skin reactivity.¹⁵ Further work is planned to investigate this group.

Only one person with no history of laboratory-animal contact had a positive skin reaction to any of the animal extracts. This suggests that the antigens used were fairly specific and contrasts with a report that found almost as many skin reactions to animal extracts in a non-exposed group as in an exposed group.⁴

3 subjects produced late (6 h) as well as immediate skin reactions which were similar in time course and appearance to skin reactions previously described as being Arthus or type-III reactions¹⁶ seen as part of a dual skin response in allergic bronchopulmonary aspergillosis or with sensitisation to *Candida albicans*. True immune-complex-induced type-III/Arthus skin reactions undoubtedly follow a similar time course, but the lesions have a well-defined sequence of cellular events.¹⁷ We do not consider our late skin reactions to be type-III/Arthus reactions, since there was no evidence of precipitating antibody to the causative agents either by gel diffusion or by the ELISA technique. A more rational explanation for this type of late reaction has been provided by

Dolovich et al.,¹⁸ who considered that IgE antibody caused both immediate and late skin reactions in some cases. Experimentally, these workers found no deposition of immunoglobulins or β 1C in biopsy specimens of these late-response lesions, and the cellular infiltrates were predominantly eosinophilic. It seems, therefore, that there are at least two mechanisms by which a late skin reaction can develop.

There is currently considerable interest in the possibility of identifying "susceptible" individuals and excluding them from occupations where they are at increased risk of developing symptoms. Some authors^{4,19} have suggested that atopic people should not be allowed to work with animals because they are at increased risk of developing allergic symptoms. In the present study we found no tendency for atopic individuals to have more animal-related symptoms than non-atopic individuals, and the sensitivity of the study was such that if there had been a three-fold increased risk we would have been 95% confident of detecting it. This result agrees with the finding by other authors that pre-employment atopic symptoms did not increase the likelihood of developing animal allergy.⁸ Atopic subjects were more likely than non-atopic subjects to develop asthma from animal contact. Even so, in establishment A (the largest in the study) nearly half the subjects with animal-related asthma were non-atopic. Similarly, although a previous history of asthma increased a subject's chances of having symptoms, particularly asthma, related to animal contact, two-thirds of the subjects with animal-related asthma had no previous history of asthma.

Future efforts to prevent or reduce allergy among animal workers will have to be concerned mainly with finding ways of reducing exposure; since excluding atopic individuals will not solve the problem, and screening new entrants is unlikely to be successful in view of the long average exposure period before symptoms develop and the fact that skin reactivity to animal extracts is rarely present without symptoms.

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Requests for reprints should be addressed to A. C.

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References continued at foot of next column.

Prescribing

BRITISH NATIONAL FORMULARY 1981

THE Joint Formulary Committee has produced a new edition of the *B.N.F.*^{1,2} which even its best friends will hardly recognise. It has been completely redesigned and appears in a glamorous light-blue cover. But it is not simply a pretty face. Much larger than before (though still just able to fit into the pocket of a white coat) it contains a great deal of useful information for prescribers. Arrangement of the information seems at first bewildering. A considerable effort is needed to find one's way around the book. It is worth persevering through the introductory pages and then browsing for some time in the main chapters, since, having grasped the layout, it is comparatively easy thereafter to find what is wanted.

Fifteen chapters are concerned with drugs used in the treatment of diseases of the various systems and of malignant disease, with drugs acting on the eye, the ear, nose, and throat, and the skin, with anaesthetics, and with vaccines. Each chapter is subdivided into sections, with brief, clear, and helpful notes for prescribers. There is advice on prescription writing, prescribing for the elderly, for children, and for patients with liver disease or renal impairment, and an account of the emergency treatment of poisoning. Older users will recognise with nostalgia the very small part which remains of the original formulary listing linctuses, lotions, mixtures, and suppositories.

Whereas in the past only a selection of preparations were included which "had the confidence of the Committee" the new edition mentions most of the products available to prescribers in the United Kingdom. The committee now feel able to give more advice about how to use drugs. In the text we find, in heavy print, instructions indicating drugs that are *obsolete*, or *not recommended*, and sometimes *deprecated*. Occasionally we are told sternly that in certain circumstances products should *not be prescribed* and even *never be used*. Strong stuff! And much better than before. Tentative steps have been taken to reinforce this guidance by indicating which preparations the committee considers to be "less suitable for prescribing". These appear in print which is smaller than the main text—but not much smaller—and sometimes it was difficult to be sure that a drug really was in this category. It is a pity that they did not go further by using almost unreadable print. The late Prof. A. G. MacGregor's long-departed *Proplis* did something similar, but unequivocally, by using black-shrouded pages for the useless drugs.

Another new feature is the indication (necessarily crude) of prices, which must rightly be an important consideration when prescribers are faced with a choice of otherwise similar preparations. The index is comprehensive and lists both proprietary (in italics) and non-proprietary names. It is now hard to see what purpose will be served by the previously all-pervasive *MIMS*, which now becomes redundant. The old *Formulary* appeared so infrequently that it quickly became out of date. The new *B.N.F.* is to be revised twice each year and should be greeted with enthusiasm by doctors, pharmacists, nurses, and students.

Guy's Hospital,
London SE1 9RT

R. K. KNIGHT

1. *British National Formulary 1981*, number 1. London: British Medical Association and the Pharmaceutical Society of Great Britain 1981. Pp 387. £3.80.
2. Note. The revised *B.N.F.* *Lancet* 1981; **i**: 399.

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