LABORATORY ANIMAL ALLERGY

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1995
"Asthma" and "Asthmatic" are used in different parts of this paper, as the comparatively loose terms of old Nosologies....

My examination, as far as it has extended, gives me the opinion, that most of the maladies which they call asthmatic, are cases of chronic bronchitis in some of its forms, - the chronic pulmonary catarrhs of Laennec.

Charles Turner Thackrah in "The effects of the Arts, Trades and Professions etc........." (2nd edn. 1832).

"This chapter is concerned with some of the transient or permanent pulmonary disorders which may be caused by inhalation of a variety of dusts, fumes or gases. The number of these which cause or, rightly or wrongly, are thought to cause lung damage, is very large..."

Raymond Parkes from the introduction to a chapter on "Miscellaneous Disorders" in "Occupational Lung Disorders" (1974).

"We are concerned about the number of people who have developed laboratory animal allergy. There are more cases who have not reported their problems".

From an internal memorandum to the management of a research institution (1977).
Abstract

Work with laboratory animals is associated with a range of allergic disorders including rhinitis, conjunctivitis, skin whealing, asthma and anaphylaxis. These disorders were investigated in an exposed population of 147 workers in a cross-sectional study which was part-repeated as a follow-up 6-7 years later. Workers sensitised to animal allergens but remaining in exposure were studied in a cooperative survey involving several institutions to assess the effect of respiratory protective equipment (RPE) and additional barrier precautions. The sensitivity, specificity and predictive value of atopy as a marker of proneness to laboratory animal allergy was explored together with the constancy and reliability of different concepts of atopy.

A series of experiments to optimise animal room ventilation in relation to antigen suppression were performed and the limitations of this approach were considered. The diagnosis of early and difficult cases of occupational asthma was explored in a short series of case histories.

Laboratory animal allergy was shown to be a common disorder (30%) separable on functional and immunological grounds into two predominant types rhinitis/conjunctivitis (20%) and asthma (10%). Asthma was strongly associated with positive specific skin prick tests and atopy. However atopy was not sufficiently good a predictive discriminant (35%) for it to be recommended as a screening procedure for employment exclusion. RPE provided protection which was incomplete for sensitised workers and assessment of this data using two different analytical conventions produced different results. An optimal animal room arrangement was characterised for steady-state ventilation but this was easily and seriously disrupted by operator entry and activity. Histamine challenge before and after work week exposure was more sensitive to early airways lability than FEV₁ and PEFR measurements. In challenge studies FEF₇₅₋₈₅ was similarly more sensitive than FEV₁ and PEFR. These techniques showed promise for early and difficult diagnosis. Atopy defined by subjective criteria, past personal and family history, was found to be inconstant with a 40% shift in population definition in 6-7 years.
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CHAPTER 1

INTRODUCTION
Laboratory animal allergy comprises a set of conditions of which the commonest symptoms are conjunctivitis and rhinitis. The commonly more serious manifestation is asthma and the rarest and most perturbing is anaphylaxis. The essential character of symptoms is their transience.

Laboratory animal allergy (LAA) is now a common occupational disorder; a reflection of the continued increase in the importance of in vivo studies in many fields of medicine and biological science during the 20th century. Since comprehensive records of animal workers are not kept, it is not easy to establish precisely the size of the population at risk. This is further complicated by the fact that a considerable group of transiently or casually exposed personnel (e.g., students, secretaries and maintenance staff) are known to develop LAA from time to time. Nevertheless a crude estimate of the population at risk in the UK can be put at 30-40,000 persons at any one time. Prevalence studies indicate that between 10 and 30% of these will develop some form of LAA.

In addressing these matters, the main thrust of this thesis is towards occupational medical considerations. These considerations encompass the traditional clinical concerns of diagnosis, measurement and management but continue into proactive practices of selection, prevention, information and policy. The interplay of these factors naturally offers a series of insights which are useful in the broader clinical understanding of other occupational and non-occupational conditions. Similarly in the occupational context, the lessons of principle to be learnt from the investigation of one disorder may be more widely applied to the successful pursuit of others.

The work which is described in the following pages was carried out over a period of some 12 years during the course of general occupational health practice. Nevertheless, a series of strategic objectives was defined for this research and these may be given simply and sequentially as follows:-

1. To determine whether LAA is really a problem in the workplace

2. If so; how common is it?, what are the clinical features ?, can it be measured and how is it related to work ?

3. Can it be prevented by the identification and exclusion of any especially susceptible sub-population ?
4. Can it be prevented or better controlled by the organisation of work, the provision of containment at work and the better information of the workforce?

5. Once present, can the symptoms of LAA be prevented by personal protection devices and other means deployed at work?

6. Can the causal agents be measured? Can exposure be reduced?

7. Can information garnered about the nature of the causal agents and their mechanisms of action be applied to improve preventative practices?

The various studies which were essayed in order to address these objectives are described in Chapters 2-7. The success, or otherwise, which the research described herein has achieved, the lessons learnt on the way and what is yet to be done are the subjects of Chapters 8, 9 & 10.

CONCEPTS OF THE DISORDER

Clinical perception
It may be said that LAA did not exist as a clinically defined concept much before the start of this research in 1978. More generally occupational allergic disease (O.A.D.) and especially that part of it now known as occupational asthma (O.A.), whilst acknowledged as a clinical entity, was not considered to be important or even particularly common. This perception is well characterised by the placement of O.A.D. by Parkes\(^1\) in a chapter on "Miscellaneous Disorders" in his then definitive book on occupational lung disorders. Little over a decade latter O.A.D., and O.A. in particular merited separate chapters in texts on the development and modern practice of occupational medicine\(^2,3\). Clearly a substantial change had taken place.

Historically, traditional usage demands reference to the first text exclusively devoted to occupational conditions, Ramazzini's De Morbis Artificium Diatriba, 1700. However Ramazzini's disquisition on this subject was particularly slight and vague, even taking into account the orotund usage of the time. The best early description of what might have been asthma due to LAA comes from Thackrah\(^4\) when he described what happened to hatters..." employed in the Bowing
department, that in which rabbits' fur and Spanish wool are mixed by striking a string or bow, who inhale much fine dust. The apartment, moreover, from the care which is taken to prevent currents of air disturbing the material, is particularly close. The men are rather pale, complain of tightness in the chest, particularly in damp weather, and are subject to asthma. Many are nevertheless able to pursue the employ for 20 years, though the time spent in their closed dusty rooms is generally 14 hours a day. Their exemption from urgent disease may be ascribed to the early period at which they commence the employ. Scarcely any old men, however are to be found among hatters; and I believe that the process, aided, as it often is by intemperance, decidedly shortens the duration of life."

Such a good description was not to be found again in any, standard text on occupational medicine until the 1950's and the issue of chronicity was not further pursued until the 1980's. Much of this was down to Thackrah himself who chose to adhere to Laennecian dicta and ascribed O.A.D.s within the collective frame of chronic bronchitis.

Subsequent authors, having no special interest in the subject, tended to follow along the lines set down by Thackrah. Thus Arlidge\(^5\), in describing "asthmatic breathing" in silk-gassing, a flaming-off process used in silk finishing; was inclined to the view that it was due to bronchitis "set up by the dust after long exposure". Arlidge seems to have maintained this view, even though he was aware of and quotes from the work of Hirt\(^6\). Hirt appears to have been the first to describe rhinitis and conjunctivitis in association with asthma. This was in a disease associated with the cleaning and dressing of feathers which... "Soon produces shortness of breath. This illness does not always manifest solely in the respiratory organs but very frequently in chronic inflammatory troubles of the eyes and perpetual catarrhs..." Whilst the description is clear and the connection is well made, the opportunity to differentiate the disorder from bronchitis was not taken, the effects being put down to "irritation". Of course, the differentiation of irritant from allergic effects is, even to this day, still a bugbear of research in the field.

Further opportunities to define and differentiate transient chest conditions from bronchitis continued to occur. A vivid example is quoted by Oliver in his authoritative grand ouevre "Dangerous Trades"\(^7\), 1902. The account concerns the introduction of sequoia (Western Red Cedar) into the Leeds furniture trade. The story is all the more remarkable because it was given Oliver at second hand
by a well informed layman. The description is as follows:... "The symptoms produced resemble those of a bad cold in the head or chest. There is running at the nose, with frequent fits of sneezing, irritation in the throat and chest, followed by coughing, laboured breathing and quickened pulse, and later by a sense of oppression in the pit of the stomach and a smarting sensation in the eyes. The symptoms usually last for only 24 hours." The tale goes on to state that this is most common in new workers and that tolerance develops. Similar stories were told to me in my early investigations of LAA. It was only after careful probing that a symptom free period of work was described and the admission of "tolerance" was one of having come to accept the discomfort of the condition; not that it had diminished or disappeared. Oliver was somewhat sceptical about the new condition referring to it as the "supposed effect of sawdust".

The then overall framework of perception of dust induced occupational lung disorders was succinctly summarised by Collis and Greenwood in their underrated classic of "scientific" occupational medicine, "The Health of the Industrial Worker". Their overview runs as follows:... "Generally speaking, dusts are more injurious as their chemical composition differs from that of the human body or from the elements of which the body is normally composed, whence it follows that animal dusts are less injurious than others. Dust formed from the husk of vegetable fibres tends to cause a typical asthma associated with bronchitis. Bronchitis is par excellence the chief of the pneumoconioses, and follows upon inhalation in excess of practically every form of dust which is insoluble and non-colloidal".

This theory set was very constraining when trying to understand transient asthmatic phenomena. Whilst the idea of asthma, and the idea of "colds", were popularly well-accepted as finite entities in the culture of the day; to doctors they were symptoms of a deeper, underlying set of mechanisms which rested on what we now see to be a very restrictive theoretical basis. Since the transient disorders did not fit the model at all well, and in any case seemed not as important as the commonly fatal occupational and other lung diseases of the day, it is hardly surprising that they were not deeply investigated. This situation is overtly acknowledged by Hunter\(^9\) who states that "reports as to the harmful effects of animal dusts have been very scanty and it is clear that such dusts must be accounted of minor importance in the production of respiratory diseases". Hunter also quotes Bridge who was well aware that the issues required "further investigation by clinical and radiological methods."
The work of Coca\(^{10}\) and Landsteiner\(^{11}\) made the concepts of allergy and atopy available to the thinking of those investigating occupational diseases. Thus in 1942, writing in what is essentially a contemporary digest of knowledge on occupational diseases, the American author, Johnstone\(^{12}\) refers to byssinosis as an "allergic phenomenon". As interesting as what Johnstone includes in his text, is what he leaves out and so, no mention is made of other organic agents causing allergy, nor is atopy mentioned. However the exclusion or restriction of asthmatics from work is discussed generally. Also of note is the reference made to the effects of grain dust in a Canadian publication "Guide to Diagnosis of Occupational Diseases"\(^{(13)}\), 1949. This guide states that.." large amounts of grain dust when inhaled, may produce asthma in the sensitive individual".

By the 1950's the concepts of allergy and atopy had been fully assimilated into the progression of research into occupational disorders. The publication of "Industrial Medicine and Hygiene" in 1954\(^{(14)}\) and "The Diseases of Occupations"\(^{(9)}\) in 1955 probably marked high water for the prestige of British occupational medicine and these books dominated worldwide thinking on the subject for the next 20 years. Of particular significance for the development of understanding about O.A.D.\(_s\) was the involvement of Hunter\(^{(15)}\) in an extensive investigation of allergic disease associated with exposure to platinum salts although in fact the analysis of the significance of Hunter's work was much better done by Merewether. As is often the case, the dispassionate observer, saw more and further, than the protagonist.

In his overview, Merewether identified and referred to hay-workers, hair-sorters, fur cleaners, pigeon fanciers etc. as being in "different occupations which expose the worker to the dust or emanations of animal or vegetable products" which result in "similar lung diseases".

It is clear from Merewether's reasoning that he considered that the similarity lay in their allergic aetiology. However he expressed a number of reservations which very accurately define the areas of perceptual difficulty even to this day. Thus Merewether was well-aware of the concepts of sensitisation and cross-sensitisation established by Landsteiner and others\(^{(11)}\) in contact dermatitis. He discussed the extension of this theory to allergic lung disease but found the model wanting. He cites the extensive work of Prausnitz\(^{(16)}\) which he considered had failed to establish a clear allergic aetiology for byssinosis and, in similar vein, he remarks that the failure to conjugate a sensitising antigen and test this
accurately brought into question the allergic nature of isocyanate, platinum salt and other asthmas. His most incisive analysis of the uncertainties was reserved for the asthma caused by p-phenylenediamine in fur dyers. This is worth quoting in full because it also illustrates Merewether's understanding of the ambivalence of workers attitudes to diseases in the workplace. "The characteristic asthma attacks are reported among fur dyers who weigh out the material to dissolve in boiling water"... "The asthma attacks are complained of not so much because the men have real apprehensions in regard to their health, because the attacks cease immediately exposure is discontinued, but rather because of repeated inconvenience. The intensity of the attacks varies greatly as does the period of exposure (1 - > 10yrs) before sensitisation is established. There is often a sudden onset of symptoms of expiratory dyspnoea which disappear on leaving work, but return very quickly on returning. The simple advice to discontinue his trade is not one the expert fur dyer regards as useful, so the only way is to eliminate absorption by control of the process"..... "The fur dyers asthma is a puzzle and no simple assumption that a conjugated protein complex is formed is entirely satisfying because there is an immense number of aromatic organic compounds which undergo similar oxidative changes without the slightest evidence of bronchial sensitisation in men who are constantly engaged with them".

As Merewether had better understood Hunter's work then the man himself, so also Hunter had identified a remarkable early account which he gave the prominence of full quotation. It was published by Karosek and Karosek in an obscure U.S. State report in 1911. The comments of the authors show they were wholly attuned to the preoccupations of preventive medicine in the workplace:-
"Prevention of this syndrome can be achieved by not allowing the complex salts of platinum to reach the atmosphere of the workplace or laboratory either in the form of dust or spray. Dust is worse than spray; therefore, unless it is necessary for technical reasons, it is advisable that the double salts of platinum should not be refined. In precious - metal refineries an adequate system of exhaust ventilation must be installed. Chemists and their technicians should work with platinum salts only in fume chambers with an adequate draught.... masks give some protection, but since they introduce the human factor, they are unsatisfactory...."

In general terms, the works of Merewether and Hunter bring us up to date with the state of perception of the issues at the start of the researches described in this thesis. The quotations I have used nicely encapsulate the problems which stood as theoretical and practical challenges to the investigator.
Controversies

Once interest had developed in O.A.D. and particularly in L.A.A., it was difficult to identify an area for research which did not contain some controversy. I have already alluded to Merewether's misgivings about the possibility of explaining the aetiological mechanism of O.A.D. by using a simple allergic model. In similar vein, a cluster of controversies surrounded the epidemiological, clinical, diagnostic and management aspects of the disorder. These are summarised briefly in this section and will then be discussed in more detail later within this chapter.

By 1978, two surveys of LAA in academic and industrial institutions had been carried out in the U.K. and U.S.A.\(^{18,19}\). Because of their methodology, the surveys were range-finding in nature using a postal questionnaire sent to institution managements. The range of LAA prevalence reported was 0-18%. This wide range was the first of a series of epidemiological issues which required research. What is more, it was unclear how common and how severe LAA was and what its natural history was in worker populations. It was also suggested by the surveys, largely from anecdotal evidence, that researchers were more likely to develop LAA than animal husbandry personnel; on the face of it a surprising observation.

It was assumed that the clinical manifestations of LAA were the outward signs of a sensitisation process. It was also assumed that the antigens involved were derived from the pelts of laboratory animals in a way directly analogous to the better known pet allergies caused by dogs, cats and horses etc. This latter assumption was challenged by Newman-Taylor and his co-workers\(^{20}\) who identified the antigenic capacity of urinary proteins derived from rats in a small group of individuals with occupational asthma. Again the picture was not clear, and indeed the identification of the many antigens associated with LAA and their inter-relationships has had to be extensively pursued to clarify the situation. This work is discussed later in the chapter.

The study of the mechanisms, means and markers of sensitisation leads one naturally on to consider action on preventive strategies.

Possibly the most appealing of these are ideas for identifying special susceptibility to causal agents. These considerations, in relation to atopy, lung disease,
smoking and other factors are discussed in detail later in this chapter. Other options available in the workplace are the protection of individuals by the provision of containment, the wider separation of people from causal agents, the diminution of exposure and other measures which may be termed collectively as systematic prevention. Experiments in this field have been a constant feature of occupational medical response to the LAA problem and there has been much speculation whether any or all of the measures judged feasible in this area have been of any benefit and if so how much and whence comes the preponderant contribution. The scope and achievements of work in several centres in the U.K. and elsewhere will be described later in this chapter. The contribution made to the work by this author is described in Chapter 6 and discussed in Chapters 8, 9 & 10.

A further contribution to prevention and to protection of people at work can be derived from the use of personal protective equipment such as masks, overalls and gloves and the introduction of operating rules for personnel which have their objective in the regulation of procedures so as to enhance the objective of reduced exposure. These latter rules must be integrated with the physical arrangements described above in relation to systematic prevention. The efficacy of these protective arrangements tends to be limited by technical factors such as mask performance and perhaps more profoundly and chronically by personal compliance. A fundamental tenet of occupational health practice is the belief that preventative strategies (inherent to the system of work and provided by the employer) are superior to protective strategies (which rely on compliance by the employee and their reinforcement by management). Nevertheless, in reality, both strategies have often to be deployed and developed alongside each other and it has therefore seemed important to try and measure the efficiency of aspects of protective policy in an objective way since these were not known at the start of the study period.

Perception of the disorder and its risk.

It is apparent in retrospect that both LAA and OAD, particularly occupational asthma, had been well-described long before they became medically acknowledged as separate and well-defined clinical concepts. There are a number of reasons which can be offered for this situation. The first of these, which I have alluded to on a number of occasions already, is the restrictive view taken by physicians of asthma as a clinical entity. Perusal of medical text books upto
the early 19th century\textsuperscript{(21)} indicates the acceptability of asthma as a diagnosis and one capable of treatment. The exposition of the powers of the stethoscope by Laennec\textsuperscript{(22)} reduced asthma to the level of a symptom of bronchitis. Whilst still being treatable as a symptom, asthma lost its medical status as a disorder. However the old status of asthma as a disorder in its own right persisted in the understanding of the lay public. We have then a situation where if asthma is only a symptom then it is hardly worth investigating and, the corollary, which is that if it is not worth investigating, it cannot be much of a risk.

Even assuming that asthma were taken seriously, there was a problem of definition. Modern definitions employ a set of adjectives which imply the dynamic character of the condition (i.e "transient and reversible") and often a parametric qualifier ("causing a diminution of FEV, by X\%”). It has been the ability to measure asthma and measure it dynamically over unit time which has offered a useable perception of the disorder. It is important to note how very recently this has become possible. Thus reference to the textbooks by Schilling\textsuperscript{(23)} and Cotes\textsuperscript{(24)} offers no information on dynamic measures of lung functions for the assessment of asthma and the means proposed by Parkes\textsuperscript{(1)} are crude and ineffective. In this context the work of Burge\textsuperscript{(25)} is of great importance especially with regard to occupational asthma. Nevertheless, our current model of asthma is still conditional and in particular, does not offer absolute differentiation from the normal, physiological excursions of airway diameters.

A special subset of barriers have existed and, to some extent, still exist for the ascertainment of occupational disorders. Generations of investigators have marked the ambivalence of attitude which their activities meet from industrial workers and their managers alike. It is no accident of semantics that the use of the phrase "an occupational hazard" implies a passive acceptance of it. This was and is the case for LAA and other similar disorders and reflects a deep seated prejudice of society which has only quite recently begun to change. There is also the issue of priorities. Until very recently the pneumoconioses and occupational lung cancer preoccupied the talents and time of that small group of physicians which society cared to support in the investigation and alleviation of occupational conditions. It is hardly surprising then that such a seemingly trivial, transient and difficult to define set of conditions as the OAD's did not receive much attention. It was only the elimination of the more serious conditions and the development of relevant epidemiological and diagnostic methodologies that has now shown the extent of the burden imposed by LAA and other OADs.
Even so the conditions are still underreported and underrecorded. In this context, two dicta arise for which I shall claim the eponym:-

1. Occupational disorders do not report to the doctor, they must be actively sought in the workplace.
2. If they do report, then those reports are but a small proportion of the whole which must still be pursued.

OCCUPATIONAL HEALTH CONSIDERATIONS

Selection Criteria for Employment

The idea of setting medical criteria for employment is largely one belonging to the 20th Century. It will be recalled that the Certifying Surgeons brought into being by the Apprentices Act of 1833 were only required to certificate age of children, not fitness to work. A search of occupational health texts indicates that pre-employment medical examination did not merit discussion until the 1940's\(^{(12)}\) but has then remained a constant theme (eg Schilling 1960)\(^{(23)}\).

With regard to work with allergic substances, a folklore developed in occupational medicine and especially in the chemical industry. This I have never seen written down but it was passed on to me as a young trainee medical officer by my seniors and was considered to be one of the most important single pieces of wisdom available. The form of advice ran as follows:- "Don't employ people with a past history or family history of allergy or asthma, don't take on people with red hair, fair or thin skin. In that way you will cut down the number of allergic problems you get". That this advice was wide spread, I have confirmed in discussion with occupational physicians from France, Germany and the U.S.A. There can be little doubt that the advice was given shape by popular medical understanding of the work of Prausnitz\(^{(16)}\), Coca\(^{(10)}\) and Landsteiner\(^{(11)}\). Of these the most influential was probably Landsteiner whose work most directly linked skin and lung effects and chemical sensitisation.

Atopy is derived from \(\alpha\)TOPOS, the Greek for "strange" and has the same root as the word "atypical". It arose as an idea from the work of early immunologists who wished to provide a unifying explanation of variations in proneness to the development of allergic disorders. As a popular clinical concept, it has proved
useful and durable. Harder to understand, given the vagueness of definition and meaning, is why it should have come to be so widely used as an occupational discriminant throughout the world from the 1930's to the present day. A more objective view of atopy began to be taken by immunologists engaged in experimental and field work in the 1970's. By this time, some consensus existed for a working definition of atopy and this was enunciated by Pepys\(^{(26)}\) who defined atopy as skin prick positivity for one or more of the common environmental allergens (i.e. grass, house dust mite, aspergillus and cat). Although this was somewhat arbitrary it offered the opportunity to conduct standardised prevalence studies and it has not been particularly improved since by using reference to total IgE, specific IgE or other criteria. However the definition has been by no means applied or accepted universally and many groups use past history or family history of allergy as criteria of atopy in an entirely subjective way. This includes occupational health practitioners.

The prevalence of atopy and its relationship with respiratory disorders was explored in the field by Barbee\(^{(27)}\) and Burrows\(^{(28)}\). Their findings suggested a positive association between atopy and respiratory problems but equally significantly, an age variation in the prevalence of atopy, peaking at 34% in the age group 30-40. This latter might have suggested that atopy, like the disorders it related to, might be better seen as a dynamic status into which only some lesser part of the whole potentially atopic population might fit at any time. Given this view the assessment of the relationship between the different common concepts of atopy and LAA, which is reported in Chapter 2, should be seen as a preliminary part of the process of exploring the use of atopy as an occupational discriminant.

A more precise indication of the reliability of different concepts of atopy is given in Chapter 5 which describes a study that resampled part of the original population investigated several years earlier (in Chapter 2). This later study formally examined the specificity, sensitivity and predictive value of different concepts of atopy as a predictor of L.A.A.

A number of illnesses may be made worse by the development of L.A.A. or indeed other similar O.A.D's. The most obvious of these is pre-existing asthma but other chronic diseases come into the same frame as do cardiac disabilities. For this reason, it has become customary to advise that persons with such conditions should be carefully medically assessed on an individual basis to ensure that they are not unduly embarrassed should they develop the occupational condition. However no research has been done on this subject. Perhaps this is not surprising
since the more seriously unwell are less likely to present themselves for employment than the healthy. Additionally, many employers, recognising their legal duty of "special care", are not willing to risk employment. It may be that the effect of this is to discriminate unnecessarily against such persons.

Smoking may enhance the susceptibility of the individual to developing OAD\(^{(29)}\). This may be due to the enhancement of antigen permeability\(^{(30)}\) or the further stimulation of airways reactivity. Two questions therefore arise. These are whether smoking might be regarded as a legitimate discriminant at pre-employment or whether smoking should be discouraged or banned at workplaces where there is a risk of developing O.A.D. Smoking may also interact synergistically with atopy\(^{(31)}\). Across the board, the evidence is contradictory. Smoking is positively associated with increased risk of asthma in some studies (eg acid anhydrides, enzymes)\(^{(32)}\) but not with others (eg LAA, Azodicarbonamide)\(^{(33,34)}\). Data germane to this debate is presented in Chapters 2 and 5 and discussed in Chapters 8, 9 & 10.

In regard to preventative measures, it must be appreciated that the handling of laboratory animals encompasses a multiplicity of activities. This is in contrast to many other jobs which cause O.A.D.s where there are a relatively small number of well-defined processes. A pertinent example of this latter is crab-meat processing which, until automated and capable of producing an aerosol, did not give rise to asthma\(^{(35)}\) but which could be dealt with by quite simple and well-established ventilatory means used to draught spray processes. Once installed, these are likely to reduce exposure to low levels. This is not the case for the risks of LAA which are protean. There are two main categories of laboratory animal work. These are animal husbandry and experimental work. Animal husbandry is largely akin to intensive farming and entails feeding, cleaning, transportation and some routine handling of animals. Experimental work involves a wider range of activities which have as their main features a closer and more stressful contact with the animals. Routine experimental activities such as weighing, gavage and examination in toxicological studies fall midway between husbandry and experimental work.

Regulatory conflicts exist between optimising occupational risk prevention and Home Office regulations laid down for the well-being of animals\(^{(36)}\). Thus the regulations lay down an acceptable range for air changes in animal rooms at 12-20/hour. Such rates increase the entrainment of dust and antigens in air unnecessarily and are of no obvious benefit to the animals, yet animal facility
managers are reluctant to go against the power of Home Office inspectors. Similarly operational considerations still sway the thinking of study managers in deciding on issues such as airflow direction, particularly where experiments may be affected by transfer of pathogens from humans to animals, and especially when the experiments are long term (and hence costly) or involve SPF (pathogen free) or other special animal categories.

Whilst the wide range of activities, and the constraints upon possible solutions, have made it more difficult, attempts have been made to seek generic solutions to the prevention of exposure in the more common types of work where humans come into contact with laboratory animals. Much of this has been done in large pharmaceutical companies, mainly in the U.K. but unfortunately very little of it has been published. Most investigations have been done on room and caging systems and have been intended to benefit both animal husbandry and routine toxicology personnel.

A U.S. ventilated cage system has been on the market for many years\(^{37}\). It employs the tubed cage framework as a ventilation system with appropriately placed orifices to draw contaminated air away from the caged animals and into a scrubbed exhaust system. Its protective performance has never been validated and, being very costly, it has not proved a popular buy in Europe.

Similar solutions have been sought by attempting to directionalise animal room airflow. Historically animal rooms had no special ventilation and whatever system happened to be in use in any building was adjusted to comply with Home Office rules. The commonest early arrangements for animal rooms involved air access and exhaust at ceiling level. Although no doubt capable of providing the appropriate nominal airflow, these arrangements ignored the thermodynamics of animal storage and resulted in only partial air changes with many "dead" areas where stale air accumulated\(^{38,39}\). An improved system used a bottom entry for clean air and used the natural convection currents from animals to carry contaminated air to ceiling level exit ports. This improved overall scavenging but did not have any useful impact on reducing antigen exposure. A series of studies was therefore initiated in ICI Pharmaceutical Division in the early-mid. 1980's which attempted to optimise animal room aerodynamics and at the same time reduce antigen exposure. These studies, which were in support of a major building programme for new facilities, established what is now the commonly
Fig. 1.1
Hygiene data for various work activities in animal rooms - exposure ranges

Fig. 1.2
Animal room airflow - current best practice
accepted standard patterns for animal room airflow. This is shown in Figure 1.2 and involves the delivery of air through a central valanced plenum running longitudinally along the animal room above the service walkway. Clean cool air is drawn downwards by natural convection traversing the area where husbandry and toxicology personnel normally work. The air is then drawn into and over the animal cages where convection carries it to exhaust points at ceiling level at the sides of the room.

Although offering greatly improved scouring and airflow directionality, the system still has shortcomings. In the steady state, without the presence of workpeople, there are still eddy currents which contaminate the worker breathing zone. The introduction of humans further complicates the eddy patterns and increases animal activity and hence antigen exposures. This is best illustrated in Figure 1.1 which shows the dust levels generated in animal rooms when different husbandry and experimental activities were performed. Dust levels were used as surrogates of antigen levels because of the cost and difficulty of performing direct antigen level estimations at that time. It will be seen that the steady state levels are obliterated by the ingress of humans and that exposure becomes mainly activity dependant. Thus it would seem that the opportunities offered for the reduction of exposure by room ventilation are largely illusory. However research has continued to try and improve containment and the model that was used by ourselves is described in Chapter 6.

Another large contribution to this field of study has come from Yamauchi[40,41,42,43] and his coworkers in Kagoshima, Japan. His work is important because it was thorough, organised and because an attempt was made to evaluate the clinical impact of the system improvements. The basic refinement proposed by Yamauchi was the containment of animal caging systems. This is illustrated diagrammatically in Figure 8.1. Effectively this turns them into giant fume cupboards. Air ingress to the systems is by way of holes drilled into transparent front panels which are applied to the cages in much the same way as secondary double glazing. Air is drawn across the cages and collected at the rear by an exhaust plenum applied to the rear of the containment. The transparent fronts are composed of curtains or rigid sliding panels which are easily movable for access. The ingenuity of the system lies in its simplicity and low cost. It can be applied to existing cage systems. The panels are easily removable and the
cages are simply unclipped from the exhaust system to be taken to and from cleaning. The modifications proposed by Yamauchi also claim increased efficiency in air throughput. 8 changes per hour are stated to have the same effect as 50 per hour whole room ventilation without complete scouring. There are consequently significant energy savings. However the system still suffers from the shortcoming of all such arrangements which is its disruption by the intrusion of operating personnel. It is therefore interesting that a survey of existing LAA sufferers in the facilities showed that 80% claimed an improvement in symptoms after the cage systems were modified\(^4^3\). Unfortunately only subjective symptomatic criteria were used to draw this conclusion and no objective indication of benefit is available. It may be that the very low intensity of work in the Kagoshima facilities, as compared to research and commercial facilities, is also a factor\(^4^4\).

Containment methods have been assessed in a number of industries with mixed outcome. Spray processes may be effectively contained (eg crabmeat, isocyanates) so long as they are standardised. However much work with isocyanate paints is not amenable to containment because of the size and shape of the objects being painted. In dedicated processes such as the manufacture of proteolytic enzymes it is claimed that total enclosure of the process has been completely effective in preventing the initiation of sensitisation and the manifestation of symptoms\(^4^5\). However, in the precious metal industry the reduction of exposure to platinum salt complex to nanogram levels is still associated with occupational asthma in the workforce\(^4^6\). Therefore in practical terms the presently achievable state of containment methodologies is not adequate to prevent the inception or development of O.A.D. and this is especially so for L.A.A. Other methods have to be sought.

**Risk reduction by protection**

A series of measures which increase the separation between workpeople and any noxious agent at work can be listed. Some or all of these may be necessary in any particular case. The measures include the use of personal protective respiratory equipment (masks, independently ventilated devices, gloves, overalls, limited access areas, airlocks, decreased stocking density, dedicated
transportation facilities etc.) The measures are differentiated from systematic preventative measures by requiring personal compliance. This is particularly so for personal protective equipment.

Whilst masks and ventilated helmets are now extensively used in research laboratories handling animals (at least in the UK commercial sector) there was no objective evidence that they were of any use. This issue was addressed in a collaborative study which is reported in Chapter 3\(^{(47)}\). The knowledge gained from this study has been complemented and expanded by the work of Anderson et al\(^{(48)}\) who investigated the value of protective respiratory equipment in bird fanciers. All this work is considered in the discussion in Chapter 8.

The more general measures listed immediately above were incorporated into guidance documentation which was issued by a number of pharmaceutical companies in the early 1980's, an example is shown in Appendix 1. In one company, this guidance was made mandatory and the exposed population was followed up prospectively to assess inter alia the impact of the measures on the incidence, prevalence and severity of LAA\(^{(49)}\). The results were highly encouraging with a 75% decrease on expected levels in incidence in the first two years of the prospective study. Whilst this result might have been due merely to delay in sensitisation, information from the third fourth and fifth years of the study tends to confirm that the drop in incidence was sustained\(^{(50)}\). Because no measure of compliance was made, it is not possible to say whether mandatory measures had more effect than guidance nor has it been possible to say which preventive measures had the most effect in reducing L.A.A. since the benefit of individual measures was not quantified by industrial hygiene measurements. Notwithstanding these uncertainties, there has been a tendency to move towards firmer implementation of these type of guidelines. This has been reinforced by the widespread use of the Association of the British Pharmaceutical Industry guidelines\(^{(51,52)}\) to which I contributed and the HSE Guidance Note\(^{(53)}\) which was a development from it.
Detection of disorder

I have argued above that occupational diseases are particularly liable to concealment and under reporting and that dynamic disorders are difficult to understand until they can be dynamically measured. In 1978, at the start of the period of study of LAA with which this thesis is concerned, the measurement tools required for the dynamic assessment of LAA and occupational asthmas generally were available but had not yet been assembled into a methodology which could be deployed serially in the field.

Asthma was generally defined by reference to a minimum fall in FEV$_1$, (usually 15-20%) as measured against “expected”. The first of our studies (Chapter 2) used this method and served to convince me of the inefficiency of this method for population studies of transient phenomena. The use of within-person serial measurements of FEV, was cumbersome being tied to semi-static spirometric machinery. The success of Burge$^{25}$ in demonstrating the value of using a portable peak flow meter to chart the time course and severity of occupational asthma revolutionised the investigation of such conditions. This technique was used for a study of the efficacy of ventilated helmets described in Chapter 3.

One of the desired objectives of managing LAA (see next section) is to create awareness of the condition and to encourage early reporting. Clinically this creates a new set of problems. Early symptoms have proved ephemeral and the detection of objective effect, both immunological and respiratory, difficult. To overcome these problems more sensitive methods were sought and, at the same time, the simplest and most useable in the field were preferred. To this effect, studies in individual patients with suspected early occupational asthma are reported in Chapter 7. The techniques applied have included the use of decrements in the flow volume loop (PD$_{40}$) and FEF 75-85 measurements from serial spirometric studies. Whilst these methods may not be suitable for larger population studies they show promise for the evaluation of difficult individual cases.

The immunological assessment of LAA in the field has depended largely on skin prick tests. However the assay of specific IgE by RAST or Elisa has offered an alternative and potentially more accurate diagnostic method and a number of studies have compared the benefit of this technique with skin prick testing. The
population which we studied (Chapter 2) was resurveyed by Newman-Taylor et al\cite{54}. The results were found to be comparable. Specific IgE, total IgE and specific IgG were used diagnostically in another animal exposed population\cite{55} and found to be equally accurate. However these authors indicated the possible confounding effects of total IgE and specific IgG in masking specific IgE estimations by RAST.

A small population of confirmed asthmatics cases of LAA was studied by Lutsky\cite{56} who suggested that urinary extracts gave more accurate results than epithelial extracts whatever technique was used, skin prick or RAST. Some authors have even suggested that skin prick diagnosis is superior to RAST\cite{57}. There certainly appears to be no consensus that the measurement of specific IgE or IgG is in any way superior to skin prick. However skin prick test material derived from urinary proteins is superior to that derived from epithelial proteins. The underlying immunological basis for these diagnostic tools has been extensively explored by Longbottom and coworkers\cite{58-60}. Their studies show that a large number of urinary proteins from small mammals (rat, mouse, guinea pig, rabbit) have antigenic potential and that many of these cross-react and are present in other biological fluids such as serum and saliva. These proteins are probably transferred to pelts by direct contamination and grooming.

Management

Management of an occupational condition implies the creation of policy to address the issues involved. Policy considerations will include, pre and post-employment screening, the provision of information, the identification of preventative and protective measures, the imposition of workplace rules, the provision of treatment, relocation and rehabilitation arrangements. The policies of a large number of institutions mainly in the U.S.A., were surveyed in 1987\cite{61}. Startling variations in hazard awareness, planning and execution were reported. For example only six out of over 150 institutions carried out pre-employment “hypersensitivity” screening. A similar heterogeneity of approach was identified by Yamauchi\cite{43} in his survey of Japanese institutions. In another narrower survey in U.S. establishments, Newill found that only a minority of her respondents complied with requirements to wear personal respiratory protective equipment\cite{62}.

The customary tools for improving the situation described above are regulatory, in a ranking order leading from guidance, to codes of practice and hence to
ordinance. Such specific progress for LAA has only begun in the UK although general regulations in the area of OAD are now developed\(^{(63)}\). The research which is described in the ensuing chapters has impacted on this progress considerably. Management issues will be addressed again and more extensively in discussion.
CHAPTER 2

THE PREVALENCE, NATURAL HISTORY AND ASSOCIATIONS
OF LABORATORY ANIMAL ALLERGY
INTRODUCTION

The study described in this chapter was carried out in 1978. It was designed to characterise the clinical features of L.A.A. in respect of the following parameters:

- prevalence;
- natural history
- associations - the relationship of the natural history to variables on which it might possibly be dependent (atopy, past medical history, age, sex, smoking, ethnic background, etc.), or which might better characterise it (specific skin-prick and lung function tests).

The working environment was typical of the facilities of a biologically-based research establishment of the period. Animal keeping and experimental areas were heterogeneous in type and application. Typically animals were bred or kept in husbandry areas, generally analogous to but more spacious than intensive farming units. Considerable attention was paid to animal well-being, nutrition and comfort in order to ensure a high quality, reliable stock. For toxicological studies, animals were largely kept in such facilities but might be moved temporarily elsewhere for specific procedures such as examination. For experimental purposes animals were normally transported to laboratories as required. Experiments normally terminated in sacrifice with subsequent exposure being to animal tissues. Because of the very varied work patterns and exposures, the most practical categorisation of exposure was quite non-specific, persons being grouped as follows:

- animal handlers (husbandry);
- experimental workers (graduate or equivalent);
- experimental technicians;
- auxiliaries (cleaners, helpers);
- others (e.g. fitters, secretaries), only occasionally/casually exposed.

Although non-specific there was little overlap between job categories.

METHODS

The following methods were used in the survey:-

- questionnaires - MRC respiratory questionnaire;
- in-house LAA specific questionnaire (see Appendix 2);
• structured occupational history;
• skin prick tests for common environmental allergens;
• skin prick tests with extracts from specific laboratory animal species;
• spirometric lung function tests.

The population studied comprised the entire laboratory animal exposed population of a medium-sized pharmaceutical company. Likely exposure was ascertained from inspection of job descriptions and checked with managers and individuals themselves. The entire population of 146 persons exposed to animals took part in the survey voluntarily.

All parts of the study programme were administered to each individual on one single occasion. All procedures were performed on a Friday to see whether lung function tests might act as possible indicators of a work week effect. All practical procedures were performed by one nurse.

The questionnaire in the appendix examined family and personal history of atopy and pre-employment exposure to animals. Information on symptoms attributable to allergy was then sought. The possibility of symptoms being work-related was then explored and finally correlations with exposure were sought. Details of time sequence and progression of symptoms were also recorded.

```
Questionnaire - symptoms ascertained
(Self-administered)
  ↓
symptoms linked to work
  ↓
symptoms linked with work with animals
  ↓
questionnaire reviewed by occupational physician
  ↓
case reviewed and confirmed by occupational physician
  ↓
case accepted/rejected as due to LAA
```

Fig. 2.1 Flow chart for case definition
Case definition was by symptoms attributable to a specific, subjectively identifiable cause, laboratory animals. As indicated in the previous paragraph, this identification was obtained stepwise from the questionnaire and the flow chart is illustrated in Fig 2.1. The symptoms were first identified without attribution and then linked with work and subsequently with specific agents at work. After this, the symptoms and their occupational correlations were confirmed by an experienced occupational physician. All cases of asthma identified by questionnaire as due to laboratory animals were confirmed by subsequent review. Two cases of rhinitis were excluded by review.

Standard commercial preparations (Dome) were used for skin-prick testing of atopy. Atopy was defined by Pepys criteria\(^{(26)}\) namely a wheal reaction 3mm or greater after 10 minutes; tests being carried out for grass mixture, house dust extract, house dust-mite and A.fumigatus. Similarly, standard preparations (Dome and Bencard) were used for testing reactivity to animals. Commercial test solutions were used for the following species: rat, rabbit, mouse, guinea pig, cat, dog, horse. One person refused skin-prick testing.

Lung function tests were undertaken on a Vitalograph spirometer using standard techniques for calibration and testing. Records were made of F.E.V, F.V.C and F.E.V/F.V.C ratio. Comparisons were made between different symptomatic groups and non-symptomatic persons in exposure were used as controls.

RESULTS

Prevalence

Tables 2.1a and 2.1b address this subject. Table 2.1a illustrates the number of personnel in each work category and the percentage of persons in each group who had LAA. The proportion with LAA asthma is listed separately. For better visualisation some data in Table 2.1a are presented in histogram form in Table 2.1b. Table 2.1b shows the percentage distribution of LAA rhinitis and asthma in different categories of workpeople. It will be seen that LAA is distributed fairly evenly across the different work categories (excluding the miscellaneous "other" group) but that asthma is more closely confined to workgroups having closer contact with animals at higher exposure levels.
Natural History

The overall combination of symptoms and their linkage is shown in Table 2.2a. It may be seen that the commonest disorder in LAA is rhino-conjunctivitis. Skin urticarial reactions in the absence of other symptoms, also occur. However asthma did not occur alone and invariably followed rhinitis. The characteristics of acquisition of LAA are considered in Table 2.2b. It may be seen that there is little difference between the time course of acquisition of rhinitis in those who go on to asthma when compared with those who do not. However once rhinitis has become established the onset of asthma in those who develop it, is quite rapid with nearly 50% occurring within another year. Although marked, this rapid accumulation of further symptoms is insufficiently acute to use for setting a cut-off point for predicting who will or will not develop asthma.
<table>
<thead>
<tr>
<th>Work category</th>
<th>Number in exposure</th>
<th>% with LAA</th>
<th>% with asthma</th>
<th>% with rhinitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Experimenter</td>
<td>62</td>
<td>29</td>
<td>12</td>
<td>17</td>
</tr>
<tr>
<td>2 Technician</td>
<td>39</td>
<td>41</td>
<td>15</td>
<td>26</td>
</tr>
<tr>
<td>(experimental)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 Auxiliary</td>
<td>11</td>
<td>36</td>
<td>9</td>
<td>27</td>
</tr>
<tr>
<td>4 Husbandry</td>
<td>19</td>
<td>42</td>
<td>0</td>
<td>13</td>
</tr>
<tr>
<td>5 Other</td>
<td>15</td>
<td>13</td>
<td>0</td>
<td>13</td>
</tr>
<tr>
<td>OVERALL</td>
<td>146</td>
<td>30</td>
<td>10</td>
<td>20</td>
</tr>
</tbody>
</table>

Table 2.1a. Distribution of LAA cases according to job category

Table 2.1b
Cases with rhinitis and asthma due to LAA as percentage of cases of LAA in each work category
Table 2.2a
LAA symptom combinations in the population studied (presented as case numbers)

Table 2.2b
The natural history - its development over time
Associations

The association of atopy with LAA is explored in Table 2.3a. It will be seen that there is no statistically significant connection between LAA in general and atopy but that there is an association of high statistical significance between LAA asthma and atopy. Table 2.3b demonstrates that skin prick tests to LAA causal species was wholly specific with no asymptomatic person testing positive. However only 30% of rhinitis cases were skin prick positive as compared to 87% of asthma cases. This difference between rhinitis and asthma cases is highly significant.

Lung function findings demonstrated a small but significant decrement in group data as between assymptomatic and rhinitic cases when compared with asthmatics. It is not possible to say whether or not this is a work-week effect or more acute or more chronic.

The results were analysed for the effect of a number of other factors which might have been associated with LAA. Age, sex, ethnic grouping, smoking and pet-owning were considered. None were found to significantly modify the study.

<table>
<thead>
<tr>
<th></th>
<th>Assymptomatic</th>
<th>LAA</th>
<th>Rhinitis</th>
<th>Asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atopes</td>
<td>15</td>
<td>20</td>
<td>8</td>
<td>12</td>
</tr>
<tr>
<td>Non-atopes</td>
<td>83</td>
<td>28</td>
<td>25</td>
<td>3</td>
</tr>
<tr>
<td>$X^2 = 2.00$ NS at $p = 0.05$</td>
<td>$X^2 = 14.7$ sig. at $p = 0.001$</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2.3a
Association of LAA symptoms with atopy, presented as case numbers

<table>
<thead>
<tr>
<th>Specific Skin Prick</th>
<th>Assymptomatic</th>
<th>LAA</th>
<th>Rhinitis</th>
<th>Asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td>+ ve</td>
<td>0</td>
<td>22</td>
<td>9</td>
<td>13</td>
</tr>
<tr>
<td>- ve</td>
<td>98</td>
<td>26</td>
<td>24</td>
<td>2</td>
</tr>
<tr>
<td>$X^2 = 14.7$ sig. at $p = 0.001$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2.3b
Association with specific skin prick tests to LAA causal species; presented as case numbers
### Table 2.3c.
**FEV1/FVC ratio in Asthma Cases, Rhinitis Cases and Assymptomatic Persons**

<table>
<thead>
<tr>
<th></th>
<th>FEV1/FVC mean + S.E</th>
<th>t-value</th>
<th>2-tail significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma v Rhinitis Cases</td>
<td>77.1 ± 2.39</td>
<td>-2.19</td>
<td>P = &lt;0.05</td>
</tr>
<tr>
<td>Asthma v Assymptomatics</td>
<td>77.1 ± 2.39</td>
<td>-2.800</td>
<td>P = 0.01</td>
</tr>
</tbody>
</table>

**Summary**

This study showed that LAA was a common disease in laboratory animal workers. The most common symptom set was rhino-conjunctivitis from which a proportion of individuals progressed to asthma. The distribution of asthma was not uniform for different occupational sub-groups. Rhinitis was not strongly associated with animal-specific skin prick positivity but asthma was.
CHAPTER 3

THE EFFICACY OF RESPIRATORY PROTECTION
INTRODUCTION

In the hierarchy of protective measures deployed to prevent occupational conditions, the use of personal protection comes low. This is because of the intrinsic weaknesses of any system that has to rely on individual compliance. Also, it is subject to the vagaries of fit variance. Nevertheless the use of personal protection for the purpose of attempting to reduce exposure to occupational allergens is commonplace.

This paradoxical situation acknowledges that there is a set of uncertainties concerning the control of aeroallergens. They are not easy to measure routinely. There is little knowledge of the exposure-sensitisation or the exposure-response relationship. Nevertheless, protective equipment, and particularly respiratory protective equipment (RPE), offers to the individual a comprehensible and useable form of practical, preventive measure.

The problem though is that the protection afforded is unquantified and thus may give spurious reassurance. It may be that acute symptoms are being prevented but yet there is sufficient exposure to cause chronic disease. Additionally, the use of RPE may encourage the wearer to ignore monitory signs and symptoms or not fully appreciate their significance.

An extensive literature exists concerning the quantification of protection and the quality of effect to be derived from various R.P.E\(^6\). This is based, for obvious reasons, on standard simulations of tasks and exposures. Contemporaneously these is a dearth of information on how R.P.E performs in real-life practice in terms of the subjective and objective experience of the persons ostensibly in protection. This study describes the first attempt to quantify protection, detriment or deficiency to be derived from using R.P.E for the prevention of LAA, its symptoms or indeed any other O.A.D.

Objectives

1. To assess the protection from LAA afforded by R.P.E in common use.

2. To see whether more rigorous routine protective procedures combined with R.P.E make a further contribution to prevention of LAA.
3. To study the correlation between perceived symptoms of LAA and objective lung function decrements.

**Methods**

Eleven persons with LAA were studied over a seven week period. The format was a within-person study in three modalities and these are illustrated below.

<table>
<thead>
<tr>
<th>Week</th>
<th>Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 1</td>
<td>no exposure</td>
</tr>
<tr>
<td>Weeks 2-5</td>
<td>routine exposure + routine precautions</td>
</tr>
<tr>
<td>Weeks 6-7</td>
<td>routine exposure + special precautions</td>
</tr>
</tbody>
</table>

In the first week of the study, subjects were excluded from all work and other exposure in the workplace to animal species of interest.

In Weeks 2-5, normal work routines were pursued and all subjects wore a helmet respirator when in exposure. In Weeks 6-7, a stricter, standardised regime of protective clothing use and changing was imposed in addition to the use of R.P.E.

Certain very practical factors make this type of study difficult to organise. Firstly, people who develop the more serious symptoms of LAA such as asthma, are usually advised to manage the condition by relocating themselves to avoid exposure. Many accept the advice proffered and indeed this is the most desirable course of action. Thus only a small proportion of individuals, usually career-dedicated, will stay in exposure and become available for study. The recruitment of sufficient cases to study can therefore be difficult. The eleven cases identified as having LAA and still working in exposure to causal species were the pooled cases available from three large UK pharmaceutical companies R&D staffs. Considerable care had to be and was exercised to ensure uniformity of routines, recording procedures etc., across a number of widely separate operating sites.

The first week of the study was spent out of exposure in order to provide a baseline and also to permit discernment of recovery from any chronically depressed lung function state. This first week of the study thus acted as a within-person control period. The main body of time (Weeks 2-5) was spent in "normal work", no attempt having been made to direct, standardise or
otherwise influence routine work patterns. A stricter protective regime (overclothing, gloves, clothes-changing schedules) was imposed for Weeks 6-7; the measures imposed were considered the most intrusive that would be tolerated by the participants for the period of the study.

Other interventions were considered for the trial. The most obvious and significant of these was a practical challenge involving a period in exposure without R.P.E. This would have had the benefit of confirming the diagnosis, chronicling the current state of the disease and allowing comparison with any amelioration offered by R.P.E. This was rejected on ethical grounds because disease status had been established by questionnaires and skin test response to animal urine extracts. All persons used the then standard AH-1 helmet respirator with AS 60023 filter. Peak expiratory flow measurements (PEFR) were obtained throughout the study using Wright mini-peak-flow meters. The results were self-recorded by the subjects 2-hourly alongside contemporaneous notes of LAA symptoms and recording of presence at work (or not) and in exposure (or not).

Subjects were asked to continue PEFR recordings in and out of exposure during waking hours.

Skin prick tests were performed in order to assess reactivity to specific LAA antigens and atopic status. Commercial and experimental test solutions were used as described in Chapter 2. For the purposes of this study, a skin prick test was considered positive if a wheal of 2mm or more was raised after 10 minutes, but alternative positivity criteria were considered in analysis. It was noted that one subject had completed a grass pollen desensitising course just before the study began. No other subjects were on any medical treatment. In order to avoid any possible confusion by hay fever or other similar seasonal complaints, the study was performed outside the hay-fever season.

At the time this study was carried out (published 1985), the diagnostic criteria for occupational and other asthma were based on percentage variability in daily PEFR readings. Conventionally, a diagnostic hurdle was set at 15 or 20% deficit related to specific exposure. These criteria were applied in this study in its original form. Raw data were coded and analysed blindly by independent assessors. Retrospectively, it was found interesting to use additional criteria to sub-divide the PEFR results further to produce "muted" variability (defined as 7-15% deficit,
Fig. 3.1: PEFR Records - Efficacy of Ventilated Helmets in Asthma due to LAA

1. Flat Record. 2. Muted Record. 3. Asthma.

↑ - daily maximum reading  0 - daily minimum reading  — = daily mean
90% of working days) and "flat" records (<7% deficit, 90% of working days) (see Fig. 3.1).

In this chapter, the data have been reworked by calculating 95% confidence intervals for summed PEFR data from Week 1 to use as a comparator for weeks 2-7. However this does not allow for diurnal variation so that low PEFR readings in Weeks 2-7 are defined as those below 95% CI plus diurnal variation (in Week 1) combined. Further conservatism is added by discarding the first 2.5% of "low" readings in Weeks 2-5 and 6-7 on the basis that they may have arisen by chance alone.

**Results**

**Disease status**

The questionnaire confirmed that all eleven subjects had had LAA symptoms in the twelve months prior to the start of the study. Additionally, two asthmatics and the two rhinitics considered that their symptoms had worsened in severity, frequency or duration or in a combination of these qualities. The skin prick data are presented in Table 3.1 and show that all subjects were atopic and all had positive skin prick reactivity to one or more specific antigens of LAA. Alternative criteria of positivity, using 3 or 4 mm wheal or 2mm larger than negative control, did not affect this outcome.

<table>
<thead>
<tr>
<th>TEST</th>
<th>ASTHMATICS (9)</th>
<th>RHINITICS (2)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ATOPY</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grass Mix</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>House Dust Mite</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>Aspergillus</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>TOTAL (+ve to one or more)</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td><strong>SPECIFIC ANTIGENS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mouse Dander</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Rabbit Dander</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Rat Dander</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Mouse Urine</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Rabbit Urine</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Rabbit Urine</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Guinea Pig Urine</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>TOTAL (+ve to one or more)</td>
<td>9</td>
<td>2</td>
</tr>
</tbody>
</table>

**Table 3.1**

Skin prick test results for asthmatics and rhinitics.
(Numbers responding positively in asthmatics column out of 9, numbers responding in rhinitics are out of 2).
Inspection of PEFR records

Independent, blind assessment of PEFR plots adjudged that two out of nine asthmatics had had overt asthma during the study period. One of these cases was considered not to be occupational because of the pattern of asthma. One of the two rhinitic cases was diagnosed as having developed frank occupational asthma during the study. Sample records obtained during the study are shown in Fig. 3.1.

Using statistical rather than impressional criteria, eight of eleven cases, including one former rhinitic, experienced low PEFR readings when comparing Week 1 (out of exposure) with Weeks 2-7 (in exposure) (Table 3.2). In six cases over 10% of readings in the study period were low. Low readings were noted both in and out of exposure but no clear pattern emerged. This may be contrasted with the observations immediately below where Weeks 2-5 are compared with Weeks 6-7.

<table>
<thead>
<tr>
<th>Case No</th>
<th>low PEFR %</th>
<th>symptoms %</th>
<th>sensitivity %</th>
<th>specificity %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>15</td>
<td>10</td>
<td>8</td>
<td>89</td>
</tr>
<tr>
<td>2</td>
<td>23</td>
<td>&lt;1</td>
<td>2</td>
<td>100</td>
</tr>
<tr>
<td>3</td>
<td>38</td>
<td>4</td>
<td>5</td>
<td>97</td>
</tr>
<tr>
<td>4</td>
<td>36</td>
<td>5</td>
<td>3</td>
<td>94</td>
</tr>
<tr>
<td>5</td>
<td>27</td>
<td>0</td>
<td>-</td>
<td>100</td>
</tr>
<tr>
<td>6</td>
<td>29</td>
<td>1</td>
<td>3</td>
<td>100</td>
</tr>
<tr>
<td>7</td>
<td>8</td>
<td>8</td>
<td>50</td>
<td>96</td>
</tr>
<tr>
<td>8</td>
<td>7</td>
<td>1</td>
<td>15</td>
<td>100</td>
</tr>
<tr>
<td>9</td>
<td>0</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>0</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>11</td>
<td>0</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 3.2  Low PEFR records, diaried asthmatic symptoms - frequency and association during the active study period (Weeks 2-7)

Notes: 1. low PEFR = readings below diurnal variation in Week 1 + 95% C.I. of readings in Week 1.
2. % PEFR data is minus first 2.5% for each case, discounted as they might occur by chance.
3. sensitivity and specificity refer to diaried symptoms as an indicator of a contemporaneous low PEFR reading.
<table>
<thead>
<tr>
<th>Case No.</th>
<th>Low PEFR %</th>
<th>Improvement Weeks 6 - 7 on Weeks 2 - 5</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Weeks 2-5</td>
<td>Weeks 6-7</td>
</tr>
<tr>
<td>1</td>
<td>14</td>
<td>17</td>
</tr>
<tr>
<td>2</td>
<td>21</td>
<td>26</td>
</tr>
<tr>
<td>3</td>
<td>33</td>
<td>52</td>
</tr>
<tr>
<td>4</td>
<td>22</td>
<td>55</td>
</tr>
<tr>
<td>5</td>
<td>37</td>
<td>8</td>
</tr>
<tr>
<td>6</td>
<td>23</td>
<td>43</td>
</tr>
<tr>
<td>7</td>
<td>2</td>
<td>21</td>
</tr>
<tr>
<td>8</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>11</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**Table 3.3** Low PEFR records comparing effect of normal working precautions (Weeks 2-5) and enhanced working precautions (Weeks 6-7).

**Notes:**
1. low PEFR defined as Table 3.2
2. Y = yes, N = no.

In Table 3.3, which shows comparisons of PEFR records in Weeks 2-5 and Weeks 6-7, it may be noted that 6 out of 8 cases, who had had low readings in Weeks 2-5, got worse in Weeks 6-7, often markedly so. When comparing improvement or lack of improvement in Weeks 6-7, it was observed that low PEFR’s diminished when in exposure in 4 of 6 cases but in all cases got worse out of exposure; this latter being the dominant effect. Given the increased level of care and personal protection used in the last two weeks this in an unexpected finding.

**Subjective symptom records**

Both asthmatics identified by blind assessment of PEFR records experienced subjective work-related symptoms of asthma at least once during the study; as did other asthmatics. In all, 7 of 11 cases experienced asthmatic symptoms during the active study period (Table 3.2). Five asthmatics also had episodes of rhinitis, usually but not always associated with chest symptoms.
The relationship between diaried symptoms and contemporaneous PEFR recordings is examined in Table 3.2. There were far fewer diaried episodes of asthmatic symptoms than there were low PEFR recordings. The reported presence of symptoms is tested as an indicator of low PEFR recordings and is demonstrated to have very low sensitivity.

Comment

Different criteria for effect of exposure, objective and subjective, identify different parts and proportions of the population. This is a theme to be revisited in Chapter 5. The association between low PEFR and actual symptom reporting was poor. A stricter protective work regime appeared ineffective in reducing objective functional detriment. Because these issues should affect the management and disposal of "cases" they are important and are extensively discussed in Chapters 8 and 9.
CHAPTER 4

LONG TERM FOLLOW-UP OF LAA CASES
INTRODUCTION

Whilst cross-sectional studies of the type described in Chapter 2 remain the most common design of observational epidemiology carried out in clinical occupational health practice, they hold within their nature an inherent shortcoming. This is that they describe survivor populations. Leaver populations are seldom pursued but, of course, are unlikely to be similar to the survivor population for any variable of interest which adversely affects employment. Thus an underestimate of the burden of disease attributable to an exposure is probable. The skew attributable to the leaver population is likely to be unquantifiable. Nevertheless the transformation of a cross-sectional population into a prospective cohort for follow-up purposes is proper for the benefit of that population. Additionally, the data derived from studying longer-term effects in that population can still yield useful information even if this must be interpreted with caution. Accordingly a sample from the population surveyed in Chapter 2 was resurveyed in 1985/6, an interval of 7-8 years after the original study.

Objectives

The basic objective of the follow-up was to determine whether any medium term or long term changes attributable to LAA might be discovered in the sample. Objectives were further sub-divided as follows:

1. In those with LAA, did the disorder get better or worsen with time and how was this affected by remaining in exposure, or withdrawing, to other work out of exposure?

2. In those without LAA in the first survey, had any case developed?

3. In those without LAA, and who had not subsequently developed it, were there any covert subclinical or otherwise unreported effects?

4. Was there any difference in decrement of lung function tests in LAA when compared with unaffected controls?
METHODS

All LAA cases (rhinitis/conjunctivitis and asthma) in the original 1978/9 study were matched with persons who had not reported having LAA in that study, nor had shown any skin prick or serological positivity for specific animal antigens. Cases and controls were matched for age, sex and length and similarity of occupational experience with potential causal species. This sampling approach was taken in preference to complete re-survey because of resource constraints. Overall, there was a 15% loss to survey, with cases and controls evenly matched (8:8). Loss to survey was exclusively among leavers and represented 60% of leavers but 40% were successfully traced and included in the survey.

The questionnaire described in Chapter 2 was readministered to the study population. This was followed by an additional brief questionnaire addressing changes observed in the time between the two studies (see Appendix 3). Skin prick and lung function tests were performed according to the protocols described in Chapter 2 and blood was taken for specific IgE estimations. IgE estimations were performed by Longbottom and co-workers at the Brompton Hospital according to conventional methods. Persons in control groups who had developed LAA related symptoms and positive skin prick tests were excluded from appropriate comparative analyses.

RESULTS

Cases - symptomatic and immunological findings.

Out of 15 asthma cases attributed to LAA in the original survey, 3 were lost on follow-up. All but 3 of those traced had relocated to work not involving animals. Of these persons 2 out of 9 reported themselves wholly free of symptoms even when occasionally exposed to causal species. 7 of 9 reported symptoms when occasionally exposed but were subjectively better in terms of exposure tolerance and severity. Those who had chosen to remain in exposure under strict personal protection regimes had not done so well. One reported subjective improvement, one no change and one worsening of symptoms.

Despite relocation and subjective improvement of symptoms, specific skin prick tests remaining persistently positive: indeed there was an increase in frequency from 1.4 positives per case in 1978/9 to 2.0 per case in 1985/6. Similar
persistence in elevated binding levels was noted for specific IgE but with no consistent trend discernible in relation to relocation/non-relocation or symptom severity. These data are illustrated in Table 4.1.

Of 22 rhinitis/conjunctivitis cases targeted for resurvey, 5 were not traced. Amongst the remainder, two cases had developed overt asthma attributable to LAA although in one case there was a possibility that asthma had been present during the earlier survey and might have been concealed. Both these cases were atopic and had positive skin prick tests to LAA causing species but only the "older" case had raised specific IgE levels. Both asthma cases had been reallocated to non-animal areas of work.

Rhinitics not progressing to asthma showed remarkable stability of status in parameters of interest. Only one had relocated away from animal work and this for career reasons. Nevertheless symptoms experienced remained the same for all cases and had not worsened or become more frequent in the intervening years. Skin prick and specific IgE data remained essentially unaltered. The data for these cases and rhinitis cases which progressed to asthma are shown in Tables 4.2a and 4.2b.

Controls

Controls for the comparative part of this study were derived from persons asymptomatic in the 1978/9 survey. Since control status was ascribed blindly from this derivation it was inevitable that some of these controls would develop LAA and it is illuminating to review these cases briefly. In total there were 31 traceable controls. Of these two had developed rhinitis subsequently progressing to asthma attributable to laboratory animal exposure. One of these cases, who had not been atopic in 1978/9 had developed atopy (defined by skin prick tests) by 1985/6 but did not have any positive animal specific skin prick test results. This case had no specific IgE binding at >1% in 1978/9 or 1985/6. The other case had been atopic in 1978/9 and remained so at resurvey. Skin prick test result for rat had changed from negative to positive and specific IgE binding for rat had risen from 3-4.8%. In this same case specific IgE for guinea pig had declined from 3.8->1.0%. Two other cases had developed rhinitis attributed to their animal work. They showed no positive skin prick test results or raised binding levels.
<table>
<thead>
<tr>
<th>STATUTORY</th>
<th>CASE/DATE</th>
<th>POSITIVE SKIN PRICK TESTS (LAA ANIMALS)</th>
<th>SPECIFIC IgE &gt;1% BINDING</th>
<th>COMMENTARY: SUBJECTIVE SYMPTOMS ETC.</th>
</tr>
</thead>
<tbody>
<tr>
<td>REGULARLY</td>
<td>Case A 1978/9</td>
<td>R</td>
<td>R12.2 RA1.9 M2.1 GP1.5</td>
<td>better, using helmet, but see Case 5 (Ch. 3)</td>
</tr>
<tr>
<td></td>
<td>1985/6</td>
<td>R RA M GP</td>
<td>R.49 RA2.5 M1.6 GP1.6</td>
<td></td>
</tr>
<tr>
<td>IN</td>
<td>Case B 1978/9</td>
<td>R RA refused test</td>
<td>R3.4 RA2.0 M1.9</td>
<td>no change</td>
</tr>
<tr>
<td></td>
<td>1985/6</td>
<td></td>
<td>R2.2 RA1.1 M1.2</td>
<td></td>
</tr>
<tr>
<td>EXPOSURE</td>
<td>Case C 1978/9</td>
<td>R RA M GP</td>
<td>R13.2 RA4.2 M4.7 GP2.2</td>
<td>worse. ? why no +Ve skin pricks in 1978/9</td>
</tr>
<tr>
<td></td>
<td>1985/6</td>
<td></td>
<td>R6.6 RA14.2 M4.0 GP6.3</td>
<td></td>
</tr>
<tr>
<td>NOT</td>
<td>Case D 1978/9</td>
<td>-</td>
<td>R10.1 RA4.7 M7.6 GP2.7</td>
<td>? why no +Ve skin pricks in 1978/9</td>
</tr>
<tr>
<td></td>
<td>1985/6</td>
<td>R RA M</td>
<td>R9.6 RA6.8 M5.9 GP3.8</td>
<td></td>
</tr>
<tr>
<td>IN</td>
<td>Case E 1978/9</td>
<td>-</td>
<td>nil</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>1985/6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EXPOSURE</td>
<td>Case F 1978/9</td>
<td>-</td>
<td>nil</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>1985/6</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1985/6</td>
<td>Case G 1978/9</td>
<td>R</td>
<td>R2.5 M1.8 GP1.2</td>
<td>Retiree</td>
</tr>
<tr>
<td></td>
<td>1985/6</td>
<td></td>
<td>R1.2 M1.2</td>
<td></td>
</tr>
<tr>
<td>Case H 1978/9</td>
<td>R G refused test</td>
<td>R15.3 RA9.7 M6.5 GP11.1</td>
<td>still rapid onset of symptoms in transient exposure</td>
<td></td>
</tr>
<tr>
<td>1985/6</td>
<td></td>
<td>R8.1 RA5.1 M3.1 GP7.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case I 1978/9</td>
<td>R M GP</td>
<td>R5.5 M1.2</td>
<td>greatly reduced reactivity in transient exposure</td>
<td></td>
</tr>
<tr>
<td>1985/6</td>
<td></td>
<td>R2.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case J 1978/9</td>
<td>R RA</td>
<td>R1.8 RA1.6 M1.5 GP18.9</td>
<td>still rapid onset of symptoms in transient exposure</td>
<td></td>
</tr>
<tr>
<td>1985/6</td>
<td>R M GP</td>
<td>R5.3 RA5.3 M5.4 GP16.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case K 1978/9</td>
<td>R M GP</td>
<td>R9.7 RA4.4 M5.4 GP1.6</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>1985/6</td>
<td>R M</td>
<td>R7.1 RA1.9 M2.9 GP1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case L 1978/9</td>
<td>-</td>
<td>nil</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>1985/6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+ THREE CASES LOST TO SURVEY</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 4.1**

The fate of LAA asthma cases diagnosed in 1978/9 and resurveyed in 1985/6 on skin prick, specific IgE and symptom findings.

(R = rat; RA = rabbit; M = mouse; GP = guinea pig).
Table 4.2a
LAA rhinitis cases diagnosed in 1978/9 progressing to asthma by 1985/6 - skin prick, specific IgE and symptom findings.
(R = rat, RA = rabbit, M = mouse, GP = guinea pig)

<table>
<thead>
<tr>
<th>CASE/DATE</th>
<th>POSITIVE SKIN PRICK TESTS (LAA ANIMALS)</th>
<th>SPECIFIC IgE &gt;1% BINDING</th>
<th>COMMENTARY: SUBJECTIVE SYMPTOMS ETC.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case M 1978/9 1985/6</td>
<td>RA GP R RA GP</td>
<td>R1.5 RA5.5 GP16.5</td>
<td>early concealed case in 1978/9 now severe</td>
</tr>
<tr>
<td>Case N 1978/9 1985/6</td>
<td>- -</td>
<td>not done</td>
<td>recent onset LAA asthma</td>
</tr>
</tbody>
</table>

Table 4.2b
LAA rhinitis cases diagnosed in 1978/9 and not progressing to asthma at 1985/6 - skin prick and specific IgE findings
(R = rat; RA = rabbit; M = mouse; GP = guinea pig)

Lung Function Tests
FEV₁/FVC ratios and FEV₁ decrements are presented in Tables 4.3a and 4.3b. For FEV₁/FVC ratios, the data show no significant trends with disease category or time. However, a non-significant trend may be discerned for asthmatics when
<table>
<thead>
<tr>
<th>STATUS</th>
<th>CASE/DATE</th>
<th>POSITIVE SKIN PRICK TESTS (LAA ANIMALS)</th>
<th>SPECIFIC IgE &gt;1% BINDING</th>
<th>COMMENTARY: SUBJECTIVE SYMPTOMS ETC.</th>
</tr>
</thead>
<tbody>
<tr>
<td>REGULARLY</td>
<td>Case A 1978/9</td>
<td>R RA M GP</td>
<td>R12.2 RA1.9 M2.1 GP1.5</td>
<td>better, using helmet, but see Case 5 (Ch. 3)</td>
</tr>
<tr>
<td></td>
<td>1985/6</td>
<td></td>
<td>R4.9 RA2.5 M1.6 GP1.6</td>
<td></td>
</tr>
<tr>
<td>IN EXPOSURE</td>
<td>Case B 1978/9</td>
<td>R RA refused test</td>
<td>R3.4 RA2.0 M1.9</td>
<td>no change</td>
</tr>
<tr>
<td></td>
<td>1985/6</td>
<td></td>
<td>R2.2 RA1.1 M1.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Case C 1978/9</td>
<td>R RA M GP</td>
<td>R13.2 RA4.2 M4.7 GP2.2</td>
<td>worse. ? why no +Ve skin pricks in 1978/9</td>
</tr>
<tr>
<td></td>
<td>1985/6</td>
<td></td>
<td>R6.6 RA14.2 M4.0 GP6.3</td>
<td></td>
</tr>
<tr>
<td>NOT IN EXPOSURE</td>
<td>Case D 1978/9</td>
<td>-</td>
<td>R10.1 RA4.7 M7.6 GP2.7</td>
<td>? why no +Ve skin pricks in 1978/9</td>
</tr>
<tr>
<td></td>
<td>1985/6</td>
<td></td>
<td>R9.6 RA6.8 M5.9 GP3.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Case E 1978/9</td>
<td>nil</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1985/6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Case F 1978/9</td>
<td>nil</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1985/6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Case G 1978/9</td>
<td>R</td>
<td>R2.5 M1.8 GP1.2</td>
<td>Retiree</td>
</tr>
<tr>
<td></td>
<td>1985/6</td>
<td></td>
<td>R1.2 M1.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Case H 1978/9</td>
<td>R G refused test</td>
<td>R15.3 RA9.7 M6.5 GP11.1</td>
<td>still rapid onset of symptoms in transient exposure</td>
</tr>
<tr>
<td></td>
<td>1985/6</td>
<td></td>
<td>R8.1 RA5.1 M3.1 GP7.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Case I 1978/9</td>
<td>R M GP</td>
<td>R5.5 M1.2</td>
<td>greatly reduced reactivity in transient exposure</td>
</tr>
<tr>
<td></td>
<td>1985/6</td>
<td></td>
<td>R2.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Case J 1978/9</td>
<td>R RA</td>
<td>R1.8 RA1.6 M1.5 GP18.9</td>
<td>still rapid onset of symptoms in transient exposure</td>
</tr>
<tr>
<td></td>
<td>1985/6</td>
<td></td>
<td>R5.3 RA5.3 M5.4 GP16.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Case K 1978/9</td>
<td>R M GP</td>
<td>R9.7 RA4.4 M5.4 GP1.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1985/6</td>
<td></td>
<td>R7.1 RA1.9 M2.9 GP1.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Case L 1978/9</td>
<td>nil</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1985/6</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

+ THREE CASES LOST TO SURVEY

**Table 4.1**
The fate of LAA asthma cases diagnosed in 1978/9 and resurveyed in 1985/6 on skin prick, specific IgE and symptom findings.

(R = rat; RA = rabbit; M = mouse; GP = guinea pig).
CASE/DATE | POSITIVE SKIN PRICK TESTS (LAA ANIMALS) | SPECIFIC iGe >1% BINDING | COMMENTARY: SUBJECTIVE SYMPTOMS ETC.
--- | --- | --- | ---
Case M 1978/9 1985/6 | RA GP R RA GP | R1.5 RA5.5 GP16.5 | early concealed case in 1978/9 now severe
Case N 1978/9 1985/6 | - | not done | recent onset LAA asthma

Table 4.2a
LAA rhinitis cases diagnosed in 1978/9 progressing to asthma by 1985/6 - skin prick, specific IgE and symptom findings.
(R = rat, RA = rabbit, M = mouse, GP = guinea pig)

| CASE/DATE | POSITIVE SKIN PRICK TESTS (LAA ANIMALS) | SPECIFIC IgE >1% BINDING |
--- | --- | ---
Case O 1978/9 1985/6 | - R M | - |
Case P 1978/9 1985/6 | R - | - |
Case Q 1978/9 1985/6 | R M GP R GP | R5.4 RA5.1 M3.4 GP2.0 R4.8 RA3.4 M2.9 GP1.4 |
Case R 1978/9 1985/6 | - | GP2.3 GP1.5 |
Case S 1978/9 1985/6 | - | R1.1 |
+ 10 cases without any skin prick or specific IgE >1% binding

Table 4.2b
LAA rhinitis cases diagnosed in 1978/9 and not progressing to asthma at 1985/6 - skin prick and specific IgE findings
(R - rat; RA = rabbit; M = mouse; GP - guinea pig)

Lung Function Tests
FEV₁/FVC ratios and FEV₁ decrements are presented in Tables 4.3a and 4.3b. For FEV₁/FVC ratios, the data show no significant trends with disease category or time. However, a non-significant trend may be discerned for asthmatics when
compared with rhinitis cases discussed and controls. Wide confidence intervals are also seen in the FEV\(_1\) decrements ascribed to cases and controls and no significant trend can be inferred.

<table>
<thead>
<tr>
<th>LAA disease category</th>
<th>Study date</th>
<th>Cases (95% CI)</th>
<th>Controls (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RHINITIS</td>
<td>1978/9</td>
<td>0.84 (0.72 - 0.96)</td>
<td>0.85 (0.69 - 1.01)</td>
</tr>
<tr>
<td></td>
<td>1985/6</td>
<td>0.79 (0.76 - 0.83)</td>
<td>0.80 (0.64 - 0.96)</td>
</tr>
<tr>
<td>ASTHMA</td>
<td>1978/9</td>
<td>0.78 (0.58 - 0.78)</td>
<td>0.84 (0.78 - 0.90)</td>
</tr>
<tr>
<td></td>
<td>1985/6</td>
<td>0.76 (0.68 - 0.84)</td>
<td>0.82 (0.75 - 0.89)</td>
</tr>
</tbody>
</table>

**Table 4.3a**
FEV\(_1\)/FVC ratios in LAA asthma and LAA rhinitis cases compared with controls and comparing results in 1978/9 and 1985/6

<table>
<thead>
<tr>
<th>LAA disease category</th>
<th>Cases (95% CI)</th>
<th>Controls (95% CI) ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>RHINITIS</td>
<td>370 (+50 - 790)</td>
<td>510 (+70 - 1570)</td>
</tr>
<tr>
<td>ASTHMA</td>
<td>450 (+190 - 1090)</td>
<td>270 (+130 - 1070)</td>
</tr>
</tbody>
</table>

**Table 4.3b**
Decrement in FEV\(_1\) between LAA asthma and LAA rhinitis cases and controls in 1978/9 through 1985/6

**Summary**

The results of longer term follow-up of LAA asthma and rhinitis cases suggest that it is right to persist with the idea of differentiating between the two disease categories. LAA rhinitis cases, except for those few progressing to asthma, remained stable despite remaining in habitual occupational exposure. Contrariwise, asthma cases did best when removed from exposure for many years. This was demonstrated subjectively by symptom experience and objectively by persistence of skin prick positivity and raised specific IgE. FEV\(_1\)/FVC ratio and FEV\(_1\) decrement analysis did not provide tight confidence intervals and failed to offer any meaningful insight into disease group differences in the relatively small groups studied.
CHAPTER 5

THE RELIABILITY AND PREDICTIVE VALUE OF DIFFERENT CONCEPTS OF ATOPY
INTRODUCTION

It is of prime interest to occupational physicians to be aware of any means of identifying groups of people at special risk of developing an occupational disease. Most directly, this is because an opportunity for primary prevention of disease becomes or may become available. Additionally, in legal terms, special risk implies special care so that there is a duty to explore the likely use of discriminants predictively to avoid disorders. In scientific and therapeutic terms, additional benefit may accrue from investigation by the insights which may be offered on the nature of the disease in its relation to possible predictive factors.

Perhaps it is for these sorts of reasons that atopy has assumed a central position as a discriminant for occupational allergic disease. What is remarkable is that this position has been reached in the absence of any science or scientific literature base to support it. In contrast, the relationship between atopy and oncogenesis has been well explored\[^{64}\].

Generally, studies of occupational allergic disease have confined themselves only to considering the associational connection of atopy with the condition under study\[^{33,34,35,40,49,65-71}\]. These studies have usually used atopy as defined by skin prick tests as the discriminant of choice. However, in clinical practice, it is still much more common to use family or personal history as indicators of atopy. This harks back to the original meaning of the term introduced by Coca and Cooke in 1923\[^{10}\] where atopy was described as "a syndrome of common allergic disease including eczema, urticaria, hay fever and asthma and which had a genetic basis".

The preceding text indicates that there exist at least three different concepts of atopy defined by personal history, family history and skin prick tests. It seemed useful and important to discover whether these different concepts were synonymous and, if not, how great were the differences between the populations thus identified. This study appears to be the first to consider such an analysis. Also, to assess the true worth of atopy as a discriminant for occupational disease, in this case LAA, it is necessary to consider formally the sensitivity, specificity and predictive value of the concept. The work described below addresses these matters.
OBJECTIVES

1. To explore the concordance between different concepts of atopy namely, personal history, family history and skin prick tests.

2. To consider the sensitivity, specificity and predictive value of atopy as a discriminant in LAA.

METHODS

Analyses in this chapter derived from material collected during the course of the studies described in Chapter 2 and Chapter 4. The questionnaire used obtained evidence of family history (parents, grandparents, siblings) and personal history of allergy. Family or personal history of allergy were taken as positive if such had been diagnosed at any time by a clinician. Such definition naturally lacks precision but both family and personal history are essentially subjective criteria and the definitions were intended to reflect the commonality of everyday clinical practice. Tighter definitions would have offered somewhat spurious precision and would have underestimated true rates.

Standard skin prick tests to grass mixture, house dust and Aspergillus (all Bencard) were used, atopy being defined as the presence of a 3mm wheal (or greater) to any one of the three tests after 10 minutes. Skin tests for cat, dog and horse hair were also performed but not included as criteria for atopy because of the possibility of cross-reactivity with LAA antigens.

Subjects were divided into three according to their symptoms. The first group consisted of those who had LAA asthma, the second comprised people with LAA rhinitis (without asthma) and the third group comprised the rest of the study population, having no evidence of laboratory animal allergy.

RESULTS

Table 5.1 shows the numerical data which were used to derive the sensitivities, specificities and predictive values shown in Table 5.2. Atopy defined by skin prick tests with common allergens was a sensitive (80%) and quite specific (82%) test for LAA asthma. Atopy defined by personal or family history was less well discriminating. For LAA rhinitis, all three definitions of atopy were insensitive
(24-39%) and rather non-specific (65-77%). Predictive value of atopy for disease was low even for skin prick criteria (LAA asthma 34%, LAA rhinitis 23%).

<table>
<thead>
<tr>
<th>Atopy defined by personal history</th>
<th>LAA asthma</th>
<th>LAA rhinitis</th>
<th>No LAA</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atopy +</td>
<td>8</td>
<td>9</td>
<td>18</td>
<td>79</td>
</tr>
<tr>
<td>Atopy -</td>
<td>8</td>
<td>24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atopy defined by family history</td>
<td>7</td>
<td>13</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>Atopy +</td>
<td>9</td>
<td>20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atopy defined by skin prick tests with common allergens</td>
<td>12*</td>
<td>8</td>
<td>15</td>
<td>+1**</td>
</tr>
<tr>
<td>Atopy +</td>
<td>3</td>
<td>25</td>
<td>82</td>
<td></td>
</tr>
<tr>
<td>Atopy -</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Results reaching statistical significance at \( p \leq 0.05 \)
** One subject refused skin prick tests.

**TABLE 5.1**

*Concepts of atopy, basic numerical data*

The concordance between different criteria of atopy are shown in Table 5.3. Of those people classified as atopic by personal history, 65% would have been so classified by family history. Similarly for atopy classified by personal history as against skin prick test and atopy classified by family history versus skin prick test, the percentages were 72% and 64%.

Comparison of those responding positively to the different atopy criteria in 1978/9 and 1985/6 is of interest and the data are shown in Table 5.4. The correlation between skin prick results during the two different study periods is good (95%). Correlations between a positive personal and or a positive family history of atopy in 1978/9 and 1985/6 are less sure (both 60%). These figures were calculated after allowing for and excluding those cases where the personal history of allergic disease was that attributed to LAA and which had or might have developed during the period between the two studies.
<table>
<thead>
<tr>
<th>Criteria of atopy</th>
<th>LAA Asthma</th>
<th></th>
<th>LAA Rhinitis</th>
<th></th>
<th>No LAA</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sensitivity</td>
<td>Specificity</td>
<td>Positive</td>
<td>Sensitivity</td>
<td>Specificity</td>
<td>Positive</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>predictive value</td>
<td></td>
<td></td>
<td>predictive value</td>
</tr>
<tr>
<td>Personal history</td>
<td>50</td>
<td>79</td>
<td>23</td>
<td>27</td>
<td>77</td>
<td>26</td>
</tr>
<tr>
<td>Family history</td>
<td>44</td>
<td>65</td>
<td>13</td>
<td>39</td>
<td>65</td>
<td>25</td>
</tr>
<tr>
<td>Skin prick tests</td>
<td>80</td>
<td>82</td>
<td>34</td>
<td>24</td>
<td>76</td>
<td>23</td>
</tr>
<tr>
<td>with common allergens</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 5.2
Concepts of atopy sensitivity and positive predictive value (expressed as percentages) of atopy for LAA asthma and LAA rhinitis, without asthma. Negative predictive value is for absence of atopy as indicator for absence of LAA.
### Table 5.3
Concordance between difference criteria of atopy (original study)

<table>
<thead>
<tr>
<th>Population</th>
<th>Concordance (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Personal history vs family history</td>
<td>65</td>
</tr>
<tr>
<td>Personal history vs skin prick test</td>
<td>72</td>
</tr>
<tr>
<td>Skin prick test vs family history</td>
<td>64</td>
</tr>
</tbody>
</table>

### Table 5.4
Percentage change in different criteria of atopy between 1978/9 and 1985/6 in same study population

<table>
<thead>
<tr>
<th>Population</th>
<th>Changes (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin prick</td>
<td>5</td>
</tr>
<tr>
<td>Family history</td>
<td>40</td>
</tr>
<tr>
<td>Personal history</td>
<td>40</td>
</tr>
</tbody>
</table>

Among other considerations of note was the possibility that atopic status might have altered between the start of employment and the start of the first study period in 1978/9. This was tested by tracing pre-employment skin prick reactivity in medical records. In 32% of individuals such a record was found and these data suggested that the atopic status of individuals had not been changed as a consequence of their work in exposure to allergenic species (mean pre-employment - study date period 2.6 years, range 1-6 years). There was no reason to believe that the 32% were a group in any way unrepresentative of the full survey population.

The data core, as stated in the methods section, was derived from cross-sectional studies and thus represented a survivor population. It was thus necessary to consider the possible preferential loss of vulnerable sub-groups from the study, especially atopics with LAA. However, examination of the data suggests this to be unlikely since the percentage of atopics in the study was similar overall to that in the general population and there was an excess of atopics among those with asthma.
Six people were skin test positive to cat fur, three to dog and one to horse hair. Of these, only one, who responded to cat, dog or horse was not also responsive to grass or house dust mite. The exclusion of cat fur in the skin prick definition of atopy therefore had an insignificant effect on the number defined by the criterion.

Curves of different sensitivity and specificity may be derived from the data and drawn out in relation to prevalence of a condition thus demonstrating predictive value graphically. This is done in Fig. 5.1. The middle curve is that for the best sensitivity and specificity achieved in the study (80 and 82%) and the lower curve is for the worst (39 and 65%). For illustrative purposes the 95% sensitivity and specificity curve is also displayed. Intercepts at the prevalence rates in the cross-sectional study (Chapter 2) are shown.

Fig 5.1 -
Predictive value of atopy at worst and best levels of sensitivity and specificity found in this study
bottom = sensitivity 39%; specificity 65%;
middle = sensitivity 80%; specificity 82%;
top = sensitivity 95%; specificity 95%;
last drawn for illustrative purposes only;
intercepts at study prevalence rates of LAA (33%) and asthma (10%)
Summary

The three dominant concepts of atopy, those defined by personal history, family history and skin prick tests, are imprecise discriminants for the prediction of LAA disease. Of the three, skin-prick testing was the most sensitive and specific. A marked lack of concordance was shown between populations identified using different atopy criteria. For two out of three of these criteria, there was also notable time variance in positivity which further undermined predictive value in the practical and colloquial senses.
CHAPTER 6

INDICATIVE STUDIES OF CONTAINMENT
INTRODUCTION

Mention was made in Chapter 3 of a "hierarchy of protective measures" which may be deployed in the prevention of occupational disorders. It is timely, in this chapter, to enunciate that hierarchy fully in order to place the work to be described in context.

The preferred measures are those which are brought to bear before the occurrence of any exposure to a causal agent and include substitution, (which is not practicable in this case), and prophylactic screening. These may be termed primary measures. Secondary measures seek to interpose effective barriers between causal agents and susceptible individuals. They comprise measures which are inherent to the system of work, such as containment and local exhaust ventilation (LEV), which do not require any special effort or action on the part of individual workpeople. Tertiary measures consist of the use of various personal protective devices such as RPE which require personal compliance and are subject to the vagaries of personal fit.

In this chapter a series of experiments to address the secondary prevention of LAA in a strategic or systematic way is described. This work is one of a series of studies which were carried out in UK pharmaceutical companies in the 1980's. Most of the work has remained unpublished, despite its undoubted value and importance.

Fortunately much of the useful information to come out of these studies was presented at meetings and widely discussed at the time by interested parties so that it has not been wholly lost. The early findings of interest, mainly obtained as the result of a programme of occupational hygiene work at ICI (Rackham, personal communications), are now given in summary below because they inform the work presented in this chapter and are the subject of further consideration in discussion in Chapters 8 and 9:-

1. In general terms, levels of antigens (of LAA) are dependant on stocking density and animal activity. The second is more important.

2. Animal activity is affected by the entry of people into animal rooms and especially by the type of work they do there.
3. A ranking order of types of work shows that high exposure is associated with experimental activities (shaving, surgery, other high stress procedures), intermediate exposures are associated with routine procedures (gavage, routine examination) and low exposures are associated with animal husbandry.

The work here described exploits the hygiene investigations, which were undertaken during pharmaceutical company building developments, in order to prescribe experimental studies to aid optimal animal containment and efficient room design.

**OBJECTIVES**

1. To optimise animal room design in order to ensure antigen containment as far as reasonably practicable.

2. To assess the performance of conventional caging systems in relation to 1.

3. To assess the potential of alternative caging systems in enhancing optimal animal room protection.

**METHODS**

The work described in this chapter was specified by me and Fisons animal husbandry managers and, in consultation with engineering personnel, was contracted to Messrs. IDC Consulting Engineers, and was carried out by them in 1986/7. A full-size animal room mock-up was constructed at Messrs IDC's premises at Stratford-on-Avon and equipped with standard rabbit cages for testing purposes. Details are given at the end of the section.

Conventional best design prior to this study is represented in Fig. 6.1. This design was the consequence of earlier unpublished experimental work carried out at ICI in 1978-80 and the design features had been adopted widely elsewhere. Main feature is the central valance feeding clear air into the room. In theory, this clean, cooler air is drawn downwards and spreads into the caging areas where it becomes warmed and contaminated by animals and is then drawn into a filtered exhaust system thus protecting people working in the room who will spend most of their time working in the zone swept by clean air.
Whilst superior to preceding designs, the system described above had not been associated with any diminution of LAA where installed and was known to be prone to entrainment of contaminated eddy currents in the breathing zones of animal room workers (see Fig. 6.1). Therefore, this "state of the art" design was taken as the basis of a series of experiments involving configurational variations in animal room design which variations were considered, in engineering terms, to have potential to offer improved containment. These configurations are presented diagrammatically in cross-section in Fig. 6.2.

The experiments used 12 different configurations and 2 nominal air change rates (20 and 40 cph). Effects were assessed using a combination of 1-minute and 4-minute smoke pellets and hand-held smoke generators. These did not of course give quantitative data but did allow a qualitative pattern of performance to be construed quickly so that a large number of test configurations might be tested in rapid order.

Existing caging was used in these experimental systems. However these conventional cages presented a series of ventilation problems in their own right since they were designed to be free standing and not to be integrated into a larger system of directionalised ventilation. Therefore it became appropriate to consider how the design of cages themselves might be altered to optimise the integration sought. The mock-up design which was developed for this purpose is shown diagrammatically in Fig. 6.3.

The main objective of the above studies was to optimise the steady-state conditions of the animal room. At the end of these studies some simple experiments were performed to assess the results of disturbing the steady state by:

1. introducing individuals to stand in front of cage racks to simulate observation of animals;

2. removing perspex screening at the front of the caging system to simulate an animal accessing manoeuvre.
Fig 6.1
"State of the Art" animal room configuration in cross-section showing a) inlet, exhaust and theoretical airflow between and b) actual airflows.
NB: Bulb-in-box represents rabbit.
Fig. 6.2
12 experimental configurations tested in the study - cross-sections as Fig. 1. Some detail omitted for clarity.

(NB: Configurations 1-8 arrows indicate special features, configurations 9-12 - arrows indicate available routes of airflow)
Fig. 6.3

Conventional and experimental cage configurations
The test room was constructed of studding and ply and glazed strategically to permit outside observation. Air entry and exhaust were as in Fig. 6.1. Room dimensions were 5 x 3 x 3M. Cages used were NICP-A1 with A6 rack (rabbit) which have open fronts, rear ventilation slots and are arranged in racks on a wheeled frame. The cages have front fitting food and water containers. For experimental purposes, rabbits were simulated by a metal container of rabbit-like proportions into which a 10W output light bulb was inserted to represent the thermal effects attributable to the animal.

Smoke from pellets was introduced via air inlets to mimic general airflow and by hand-held generator to illustrate airflow at specific points in the room. It was necessary to take considerable care to be able to interpret outcomes accurately. Only the first few seconds of general airflow studies were of benefit since the room rapidly filled with smoke. Similarly, large releases of smoke from generators were also unhelpful and very small release aliquots were used.

**RESULTS**

**The effect of airflow**

The base test rate of 20 cph was used in the test configuration because it is the minimum demanded by the Regulations governing animal husbandry. There was no qualitative difference in the tests carried out at 20 and 40 cph in any of the 12 configurations. Tests run at up to 100 cph in some configurations increased turbulence at cage and valence edges thus enhancing spillages of contaminated air into potential worker breathing zones.

**Smoke tests**

Figures 6.4-6.10 show the airflow patterns, eddies and working notes for the different configurations. In "open" configurations (Fig. 6.2, 1-6) air flowed preferentially around the sides, tops and bottoms of cage racks following the line of least resistance and not effectively clearing contaminated air from caged areas. Positioning of the cage racks flush or recessed to exhaust headers had no effect on airflow patterns. Valances had no effect on airflow patterns or eddies except that inclined valances increased eddy formation. "Closed" configurations (Fig. 6.2, 7-12) forced air to flow through caging and created better scouring and unidirectional flow. Eddies, bringing contaminated air back
into the worker breathing zone were present in all configurations except those where cage fronts were screened by perspex sheets. Thus, the greater the element of "closure", the better the result.

**Caging Design**

Fig. 6.11 shows the airflow patterns associated with conventional caging and the effect of better matching inlet and exhaust apertures in an experimental design. This was also mimicked by the use of perspex sheeting as part of the configurations 10-12 above. Containment was much improved by the experimental design.

**Disturbance of the system**

Both simulations of work activities (observation and cage-opening) were assessed on the optimal steady-state model (configuration 11). In both cases a profound and maintained disruption of the established smoke patterns and eddies was obtained which was worsened by movement.

**Summary**

The experiments described in this chapter succeeded in identifying an optimal "steady-state" configuration for animal rooms. It is of interest to note that no benefit was derived from increased airflow. These optimal arrangements may be characterised as requiring the placement of the caging system within a largely closed ventilation and exhaust system, essentially a cabinet with LEV or colloquially a "box within a box". These findings have a series of echoes in the studies of Yamauchi and co-workers\(^\text{[40-43]}\) and question the validity of some of their conclusions. These are discussed in Chapters 8 and 9. It is perhaps all too apparent, in the meanwhile, that, from the foregoing, it is precisely those activities which are most associated with high exposure that least well lend themselves to systematic control.
NOTES:
1. SMOKE EXITS FROM TOP FRONT OF ALL CAGES
2. MUCH EDDYING, PATTERNS NOT DISTINCT
3. SMOKE FLOWING BETWEEN CAGES

FIG. 6.4

CONFIGURATION NO. 1

Basic arrangement with cages flush of exhaust header
NOTES:
1. SMOKE EXITS FROM TOP PART OF ALL CAGES
2. LESS EDDYING - PATTERNS MORE DISTINCT
3. SMOKE FLOWING BETWEEN CAGES

FIG. 6.5

CONFIGURATION NO. 2
Basic arrangement with cages 50mm from rear wall
NOTES:
1. SMOKE EXITS FROM CAGES AT TOP FRONT
2. MUCH EDDYING
3. MORE SMOKE DRAWN BETWEEN RACKS
4. CONFIGURATION 4 PROJECTS SMOKE INTO AISLE

Fig. 6.6

CONFIGURATION NO. 3 & 4

Valance added to restrict air movement over cages.
Cages flush with face of exhaust header
- 3

As above with inclined baffle added
- 4
NOTE:
1. SMOKE EXITS FROM TOP FRONT OF ALL CAGES
2. LESS EDDYING
3. SMOKE DRAWN BETWEEN RACKS
4. CONFIGURATION 4 PROJECTS INTO AISLE

EXHAUST  SUPPLY  EXHAUST

Fig. 6.7

CONFIGURATION NO. 5 & 6

Valance - cages moved back 150mm
- 6
Inclined valance - cages moved back 150mm
- 5
NOTES:
1. SMOKE EXITS FROM Front OF ALL CAGES
2. MORE DISTINCT AIR PATTERNS - CONFIGURATION 7BEST
3. INCREASED FLOW BETWEEN RACKS

Fig. 6.8

CONFIGURATION NO. 7 & 8

Space at top and bottom of cages blocked
- with valances at front

As above - minus valance
NOTES:
1. SMOKE EXITS FROM TOP FRONT OF ALL CAGES
2. DISTINCT AIR PATTERN
3. VERY LITTLE DRAWN BETWEEN OR AROUND RACKS. EXCEPTIONALLY HIGH AC RATE

Fig. 6.9

CONFIGURATION NO. 9

Exhaust via apertures matching holes in back of cages
NOTES:  
1. UNIDIRECTIONAL AIRFLOW THROUGH CAGES.  
2. MORE TURBULENCE WITH CONFIGURATION 12.  
3. UNIDIRECTIONAL AIRFLOW EASILY DISTURBED,  
   BY MOVEMENT (WALKING) IN ROOM  

Fig. 6.10

CONFIGURATION NOs. 10, 11 & 12

Exhaust via apertures matching holes in back of rack  
Perspex front on cages  
As 10 with valance  
As 11 with valance at 30°
CHAPTER 7

EARLY AND DIFFICULT DIAGNOSIS OF OCCUPATIONAL ASTHMA WITH SOME ILLUSTRATIVE CASE HISTORIES
INTRODUCTION

A natural and direct consequence of the studies described in earlier chapters of this thesis is the desire to explore methods for the earlier and more reliable diagnosis of occupational asthma generally and LAA in particular. A spur to this line of investigation was given by another piece of work carried out by the author when examining the disorders associated with exposure to the blowing agent, azodicarbonamide\(^{34}\). This was one of the earliest studies of occupational asthma to challenge the then universal impression of transience and total reversibility of the condition. It was shown that persons who persisted in remaining in exposure for more than 3 months from the inception of symptoms were more likely than not to have symptoms of increased airways reactivity persisting for years after they had ceased to have contact with the specific causal agent. Such a finding stimulated the search for methods of better and earlier diagnosis of asthma so that if it was not possible to anticipate the onset of LAA, it could at least be detected as early as possible. A useful secondary goal was to try and chart something of the natural history of its early development. The screening techniques considered were applications of those described in earlier chapters namely questionnaires, immunological and lung function tests.

Questionnaires are organised history-taking; there is no such thing as a perfect questionnaire. Among the important factors which influence questionnaire design are the following:-

- target population - its intelligence and motivation;
- target disorders - the need to distinguish features of relevance and interest;
- purpose of questionnaire - screening, survey, research;
- epidemiological considerations - requirements of compliance, useability, sensitivity and specificity (often conflicting).

The relative importance of these various factors was gauged by trial and error. Early questionnaires were similar to those used in the cross-sectional study reported in Chapter 2. When used for screening on exposed but largely asymptomatic population, it was found that the format was overlong, and being irrelevant to the majority, the quality of response was poor. Similarly the level of compliance, as measured by returns from postal distribution was low.
A series of attempts were made between 1980 and 1990 to improve various facets of questionnaire performance. One line of development was to structure questionnaires so that questions were placed into two categories, key and supplementary. Respondents could move through a shorter list of key questions, skipping supplementaries relevant to their history. This ploy improved response quality but not compliance. Eventually it was recognised that supplementary questions were repeated and explored further at nurse or doctor interview if the key responses were suggestive of disorder. So, the supplementary questions were discarded and a very short "critical questions" list is now applied for screening purposes (Appendix 4). This may reduce specificity, although it has not been formally tested, but undoubtedly improves useability and compliance. This is in line with the general objective of screening which is to enhance sensitivity; specificity being subsequently sharpened by interview.

Our experience of postal survey in a well-informed and well-motivated workforce at risk of LAA showed that compliance was in the order of 60%. Not surprisingly, the compliance rate was skewed positively by persons with symptoms to report as shown by interview of non-responders. A single postal reminder to individuals, accompanied by a further questionnaire, evoked a supplementary response to bring overall compliance to ~80%. The majority of respondents at this stage used the form sent out with the reminder and not the original, suggesting that loss or discard are important factors in non-response to postal canvassing. Further written reminders produced little additional response but telephone contact raised returns to the ~90% level. Full compliance appeared not to be achievable by these combination techniques, even with heavy investment in retrieval time. Accordingly a new technique was deployed where all individuals were given an appointment to attend at a surgery or other convenient location to complete a "key questions" questionnaire on-line on a portable P.C. This method of data gathering resulted in 100% compliance and had the added advantage of permitting medical staff to view and analyse the returns without further recording effort.

Another problem with screening is the vexed question of optimal frequency. Knowledge of the natural history, and crucially the progression, of a disorder are the key factors here. From the natural history of LAA, it is possible to infer that the maximal screening effort should be deployed for the early years of individual exposure with screening frequency being rapidly tailed off after the first 3-5 years. After the study described in Chapter 2, an elaborate system of
differentially timed screening schedules was attempted to cater for different at-risk sub-populations in the work group. This rapidly fell into disuse because of its administrative complexity and the incomprehension of the workforce. An annual format came to be universally applied. Given the power and ease of use now available from computer driven screening processes, and having regard to manpower optimisation, it is perhaps timely to reconsider the scheduling of screening.

Data presented in studies described in Chapter's 2 and 5 have suggested that there is little difference between the quality of information derived from skin prick tests and estimations of specific IgE in LAA. It is therefore sad to record the continuing commercial unavailability of skin-prick material prepared from urinary protein extracts. Admittedly, the commercial hair-extracts have been shown to be nearly as good but knowledge that their antigenicity is probably largely secondary to urinary contamination is scientifically dissatisfying. Nevertheless skin prick tests, with the relative immediacy of their outcome, continue to be enormously useful in workplace diagnosis.

The working criteria used for determining the selection of persons for skinprick tests derived from two considerations. The first of these was posterior probability, the likelihood of getting a result which would add significantly to the making of a diagnosis. The second was the regard which had to be taken of the scarcity and uncertainty of supply of skin-prick testing solutions derived from urinary proteins. Thus the persons in the at risk population who were screened in this way comprised those who gave a history of markedly worsening LAA rhinitis and those who gave a history of recent onset of LAA asthma.

The numbers who were examined in this way over the years were small, usually nil, one or at most two per annum in the population of some 150 which was available for this author to study. The reasons for these small numbers are several and include relatively low recruitment and turnover rates and perhaps improved working conditions. It must therefore be left to others to present prospective cohort data and to record here only the salient trends discernible from the small group of 8 persons who satisfied the criteria listed above. Four of these four individuals had asthmatic symptoms, all of them were atopic and had positive skin prick tests to specific causal species (one of these is the subject of Case history 3 in this chapter). These individuals had rhinitis symptoms alone at first follow-up interview, all were atopic and had positive skin
After counselling, 2 of 3 of these relocated to work away from animals and did not develop asthma. One individual remained in animal work for career reasons and developed asthma within six months of initial screening. He then relocated to other work. In the last case, the individual had no rhinitis or asthma symptoms but had an anaphylactic attack after a mouse bite; his case will be discussed along with that of Case history 3.

The cases described above were all subjected to serial peak flow studies. In no case was a clear-cut, positive record of occupational asthma obtained within 6 months of initial screening (criteria of two episodes of work related decrements of >15% with recovery out of exposure). In only one case was such a record finally obtained and this was in the person who persisted in exposure and progressed from rhinitis to asthma.

It seemed therefore, that early screening for LAA identified immunologically competent potential "cases" but, perhaps understandably, PEFR screening yielded negative results. The reluctance of some individuals to accept relocation on the basis only of some unquantifiable likelihood of developing an overt chest disorder led to a search for more subtle markers of early airways effect. In the laboratory, the measurement of small airways related decrements evoked by histamine challenge in the flow volume loop (PD\textsubscript{40}) was investigated\textsuperscript{[2]} and is described in use in Case history 3. At a more practical level, the likely benefits of using a more accessible test which could be applied in the works surgery was tested. The Vitalograph\textsuperscript{®} spirometric computer analysis package offers FEF\textsubscript{75-85} as a parameter stated to be selectively specific for small airways obstruction\textsuperscript{[23]}. The results obtained from using this technique are discussed in Case histories 1 and 2.

**CASE HISTORIES**

**Case history 1**

Both this case and that following were investigated for occupational asthma not attributed to LAA. Nonetheless they illustrate features of interest in the early diagnosis of asthma which are educative and may find application in LAA diagnosis.
Case 1 was a twenty three year old man of previous good health who worked as a pharmaceutical process operator. He developed occupationally related wheezing and chest tightness with a marked late onset element. Symptoms were worst in the evening and early night and usually resolved by the next morning. Two processes were suspected as potentially causal. One involved handling a powdered milk protein preparation (Process S) and the other a powdered pancreas extract (Process B). Serial peak flow studies involving occupational exposure to these processes were carried out sequentially and the results are shown in Fig. 7.1.

![PEFR Record Case 1](image)

**Fig. 7.1**
Serial PEFR Record Case 1. Exposure to two suspect processes, process S and process B. (S = work with product S, B = work with product B).

These studies suggested that the effect was due to the milk protein compound and this was tested using tipping challenge and spirometry in the works surgery. The workplace exposure was assessed to ensure that the tipping exposure was always markedly less than that which had been experienced in the actual job. Fig. 7.2 shows the data derived from the latter study. It will be seen that a 20% decrement in FEF 75-85 could be repeatedly obtained on exposure to the suspect compound whilst PEF and FEV were only slightly diminished at the level of exposure used.
Fig. 7.2
Tipping studies on suspect process compound S in Case 1. 
FEV<sub>1</sub>, PEFR, FEF<sub>75-85</sub> records.  ○ = FEV<sub>1</sub>, ● = PEFR, * = FEF<sub>75-85</sub>

This case, where the diagnosis was obtained from "classical" serial PEFR measurements, was used to test the sensitivity of FEF<sub>75-85</sub> against PEF and FEV<sub>1</sub>. The results were sufficiently promising to try the technique in the next case.

Case history 2

The popular reaction against artificial colourings and other additives in the late 1980's resulted in many manufacturers substituting "natural" ingredients into the excipients used in pharmaceutical manufacture. Among these was the natural colorant carmine which had already been noted to be capable of causing occupational asthma<sup>(24)</sup>. In a pharmaceutical unit for which the author had clinical responsibility, three suspect cases of carmine asthma were reported within a few months of the product being introduced into manufacture.

Serial PEFR measurements in two out of three cases were ambivalent or negative. In the other case the diagnosis was confirmed by PEFR. The two questionable cases went on to tipping challenge, again with the quantal precautions in regard to exposure levels as with Case history 1. The data derived from one case is shown in Fig. 7.3 and illustrates a pattern similar to that
seen in Case history 1. It seems reasonable to suggest that exposure and effect are associated. The other case was wholly negative on testing and subsequent questioning suggested that the complaint was made on a "me-too" basis.

Fig. 7.3
Tipping studies with carmine in Case 2.
FEV₁, PEFR, FEF₇₅-₈₅ records. ◊ = FEV₁, ○ = PEFR, * = FEF₇₅-₈₅

Case history 3
At the start of her history, the individual was twenty six years old and worked in animal experimentation. She was atopic and had complained of occasional LAA rhinitis for 1-2 years. Because of this history and her atopy, she was regularly asked to undergo serial PEFR measurements. None of these had a positive result. 2 years later, she began to experience occasional chest tightness but still remained reluctant to leave her work because of her interest and dedication. Also, since PEFR studies contained to remain negative, neither physician nor patient were sure of the significance of the symptomatic complaints. At the onset of chest symptoms, airways responsiveness was tested randomly using histamine challenge and was found to be abnormal (PD₄₀ = 3.2mg/ml histamine, normal >16mg/ml) but still no work related effect had been demonstrated. Accordingly, an attempt was made to maximise the likelihood
of finding an effect by testing histamine reactivity after a 2 week holiday break and then assessing the effect of subsequent animal exposure. Tests were carried out on the morning of return to work before any exposure had occurred and at the end of the ensuing work week in exposure. The results of the histamine challenge tests are shown in Fig. 7.4. Start-week and end-week results showed a three-fold increase in airways reactivity over the week in exposure which is highly suggestive of a work related effect. The patient was thus finally led to relocate away from whole-animal work.

Fig. 7.4
FEV₁, PEFR and PD₄₀ (histamine challenge)

Subsequently, when collecting biological material for in vitro studies, this person was bitten by a mouse and developed an anaphylactic reaction. This appears
to be a rare phenomenon and has only been reported three times, in the world literature\(^{75,76,77}\) (once jointly by this author). Nevertheless it is of interest that this case, like those published, had no history, or an ambivalent or atypical history of LAA despite all having specific skin prick positivity and raised specific IgE for causal animals on immunological testing immediately after their anaphylactic episodes.

**Summary**

Existing techniques of diagnosis for LAA and occupational asthma more generally appear to have significant limitations when applied to the desirable and seemingly laudable objective of early diagnosis of LAA. The contribution of innovations in method, particularly questionnaire usage and alternative lung function tests has been considered in this chapter. Of necessity the evidence presented, derived from small case numbers, must been seen only as suggestive of useful lines for further investigation.
CHAPTER 8

DISCUSSION
INTRODUCTION

In the first chapter of this thesis, a number of strategic objectives were set out for the better understanding of LAA. These objectives were in the areas of epidemiology, selection, prevention, protection, detection (diagnosis) and management. Chapters 2 and 4 addressed the prevalence and natural history of LAA and explored some of the factors which might influence the selection of individuals into work. These latter themes were further developed in Chapter 5 in relation to atopy. The systematic prevention of LAA was considered in Chapter 6 and strategies of protection in Chapter 3. These studies all contributed to informing the process of management in terms of policy and practice. Chapter 7 turned to methods of diagnosis for early and difficult cases and serves as a reminder that further challenges to research remain in this field.

The work done will also be considered more broadly in this discussion. Firstly in relation to the insights which it is able to offer into the nature of occupational allergic disease generally and secondly in relation to the contributions which it has made to the advancement of understanding of more fundamental concepts such as the nature of atopy.

Case definition, epidemiology and natural history of LAA

Current authoritative texts recommend the use of questionnaires and lung function tests for the definition of cases (78, 79). Thus no definitive test exists, so that diagnosis is achieved by the cumulation of probability based largely on subjective criteria. The step decision from disease to occupational disease may be particularly problematic.

Recent research has posited bronchial airways reactivity as a diagnostic "gold standard" for asthma (80) but such techniques were not routinely available nor so validated at the time of the work here described. This recent research and other work recently published (81) has identified the very poor sensitivity of questionnaire case identification running at less than 50%. At the time of these original studies, these deficiencies were not so specifically apparent yet the risks of poor case definition were recognised and a systematic attempt was made to maximise the likelihood of obtaining good quality data (as described in Ch. 2 methodology).
Through the stepwise methodology so employed, no asthmatic case was discarded and only two rhinitis cases. Follow-up, seven to eight years later (Ch. 4) offered a further opportunity to check reliability. As stated in that chapter, amongst those traced only one rhinitic case from the first survey admitted to asthma at the time of that survey and this case was considered to be due to deliberate concealment. When rechecked in the follow-up, no asthmatic from the first survey said that he/she did not have asthma at that time. Similarly, no rhinitic volunteered a change of symptom status on resurvey except those who had developed asthma since the original survey. Again similarly, amongst people asymptomatic in the first survey, 4 of 31 reported symptoms on resurvey. All these symptoms too were identified as having developed in the interim.

It follows that in the population studied in this thesis, in contrast to some other occupational and general populations, case definition appears to have been robust. Some special factors of note may have contributed to this. Amongst these were that the population was largely derived from researchers and technicians in social classes 1-3 with high intelligence and awareness. This was enhanced, in that population by specific knowledge of lung disease generally and allergic lung disease especially. More broadly, the rigorous structured approach to case definition and validation may have contributed also.

In this particular study therefore there existed a number of procedural steps which, combined with the factors conjectured immediately above, appear to have greatly diminished the potential inaccuracies associated with case definition by symptom. It may also be argued against the use of bronchial reactivity as a gold standard that such definition (of normality or abnormality) is itself arbitrary and that its use may merely tighten sensitivity at the cost of reduced specificity especially in developing cases (see Chapter 7). This issue is further explored in Chapter 9. Thus despite the caution which must continue to be exercised in drawing inferences from questionnaire based diagnoses, the method is too universal and too useful to discard and in any case needs to be replaced only when something superior yet as easily useable is available to replace it. Recent major studies\(^{[82,83]}\) have continued to use the methodology. Nevertheless it is of some comfort in the use of the methodology that the findings of other studies, where they have replicated work reported here, have shown good concordance with that work.
The prevalence of LAA found in our cross-sectional study (Chapter 2) was 30% overall. Two-thirds of cases had rhinitis only and one third rhinitis combined with asthma. Skin prick results and the distribution of atopy were markedly different in these two groups. Among those with rhinitis only, the prevalence of atopy was no greater than in the wholly asymptomatic (32%) whereas in those where asthma was present, atopy was significantly more common (80%). Additionally, positive skin prick tests to specific animal species were found in 80% of asthmatics, 30% of rhinitics and 0% of the wholly asymptomatic.

Upon this evidence, it seemed reasonable to postulate that rhinitis-only and rhinitis combined with asthma could be looked upon as two usefully separable disorders. Further support for this view came from the timescale and progression of symptoms. Asthma was never found without rhinitis and was always preceded by it; 70% of cases of asthma developed within three years of starting animal work, whereas a substantial proportion of rhinitics had worked for longer than three years without developing asthma. The terms regional and progressive LAA were coined for these conditions. The differentiation is of considerable importance managerially since it identifies one population moving towards significant disability and one that does not. It is worthy of note that although caution should always be exercised about the validity of inferences, like these, drawn from retrospection, this observation has been a common feature of other later prevalence studies of LAA.

This study was published in 1981 contemporaneously with studies by Cockcroft (33) and Gross (84) using similar methods. Being addressed to populations in exposure, rather than to their managements, they were intrinsically superior to two earlier studies by Lutsky (19) and Taylor (18). These authors had found a lower but wider range of LAA in the institutions which they had sampled. The range was 3-18%. The three studies by Cockcroft, Gross and ourselves showed remarkable concordance despite some methodological differences. They confirmed the underestimate of prevalence derived from earlier papers as well as the features of LAA described in previous paragraphs. The many similar studies which have now been published have not served to alter the conclusions drawn (43, 85-88).

Caution must nevertheless be urged in interpreting cross-sectional studies because they examine survivor populations; and are therefore likely to underestimate the overall morbidity, both frequency and severity, associated
with an exposure. No real attempt has been made to identify the true incidence of LAA in a population at risk (including leavers) although it may increase the case burden up to 50%\(^{(39)}\). Later prospective studies carried out by Davies et al\(^{(49)}\) and Botham et al\(^{(50)}\) may well not be directly comparable as they could reflect an incidence of LAA lowered by the modified and regulated work regime and environment which had been imposed prior to these studies.

The proposal that LAA was primarily a disease of experimental workers rather than husbandrymen\(^{(30)}\) was also addressed and it proved possible to refine the observation by examining the prevalence in more closely defined work groups (Chapter 2, Table 2.1a). Asthma was confined to the three categories of workers having "experimental" contact with animals (experimenters, technicians, auxiliaries) but rhinitis was common in husbandry personnel. The prevalence of LAA was similar in both groups but husbandry personnel had less severe regional disease exclusively.

One possible reason for this contrast is differential turnover especially as husbandry attendants are drawn from the less skilled social strata. However examination of employment records showed this not to be a tenable proposition with husbandry personnel showing less movement out of job, job grade and transfer than experimental personnel. A more likely explanation of this observation is that husbandry personnel are exposed to lower levels of animal antigen than experimenters as is illustrated in the hygiene data quoted in Chapter 1 (Fig. 1.1).

A number of variables had to be considered for their potential to affect the prevalence of LAA. Among those from which an effect might have been expected were age, sex, smoking history, ethnic background, past medical history and atopy. Of these factors, only atopy, which has already been discussed, showed any significant association with LAA. Perhaps surprisingly, smoking, which has been shown to be a predisposing factor for onset and persistence of other occupational asthmases\(^{(91-93)}\) was not found to be associated in this way with LAA although this may be a function of the prevalence study methodology.
The desirability of excluding people who might be particularly susceptible to an occupational exposure is universally acknowledged and some form of exclusion is applied in occupational health practice to many categories of potential employment. The corollary, that of identifying persons especially suitable to specific occupations, is used less frequently. Two classes of discriminant exist, predisposing factors and compromising diseases (susceptibility and vulnerability).

In relation to LAA, the exclusion of atopics has been the prime discriminatory measure sanctioned by historic usage. The findings in the study described in Chapter 2, clearly identified atopy as being strongly associated with asthma due to LAA (80%) thus giving ostensible credence to the practice. However, a screening measure requires far more than strong association to be considered valid and thus the study described in Chapter 5 was carried out to test the specificity, sensitivity and predictive value of atopy as a discriminant. Because of common and customary practice, three different concepts of atopy were tested, past personal history, family history and skin prick reactivity.

The most accurate and repeatable criterion of atopy turned out to be atopy defined by skin prick reactivity. Its sensitivity and specificity for LAA asthma was good (80% and 82%) but the predictive value was still quite low at 35%. Even had sensitivity and specificity been raised to 95% each, the predictive value would still have barely exceeded 50%. For rhinitis, the predictive value of skin prick defined atopy was poor (23%) and similarly poor values were obtained for both asthma and rhinitis when using the other, subjective criteria of atopy.

Thus, despite a strong association, even the most repeatable of the atopy criteria used was not a good predictor of LAA. The conclusion to be drawn from this is that atopy, however defined, is probably not an appropriate discriminant for employment. It might be argued that even if it was a poor discriminant, it was better than nothing at all and indeed this argument has some legal interest. Scientifically, it would weigh more heavily if the predicted disease were of a more serious and less reversible nature.

The question also arises that if atopy is not a relevant discriminant, should it be tested for at all and, if so, to what use should the information generated be put. It is possible, at present, to argue that the issue of atopy and its discriminant
value is still controversial and that the recording of atopic status continues to be appropriate for research purposes, to inform the debate. Also it may be of value for the information of individuals entering employment in animal work. The discriminant value of atopy was addressed by Newill and co-workers (41) who supported this and other conclusions drawn here. Thus Newill considered a range of potential predisposing factors including possible compromising diseases (asthma and perennial rhinitis) and elevated IgE, abnormal FEV₁ but, curiously, not smoking history. She concluded that the use of any of these screening criteria as determinants for hiring persons to work with laboratory animals was unwarranted. As we will see, this entirely rational scientific judgement may require some qualification in regard to practical management considerations.

In our work, smoking was one of several potential risk factors which was not shown to be associated with LAA. In a study of data pooled from three studies, Venables et al found an association between smoking and atopy, smoking and LAA and smoking and skin wheals to urine extracts (95). Even when the data were adjusted to exclude the influence of atopy, the association with smoking persisted and in one population from which the data was drawn the association with smoking was stronger than the association with atopy. There is thus some evidence that smoking is a risk factor for the occurrence of LAA but again the discriminant value is poor and the association is not consistent in other studies. The implication of these findings will be discussed later in the chapter when they are applied to occupational allergic disease generally.

Prevention

The result of attempts to prevent LAA by improving the ventilatory arrangements in animal rooms were presented in Chapter 6. A series of variations of animal cage and baffle positions were tested to try and identify an optimal configuration. The conclusion of these studies was that the best arrangement, using existing cage systems, was to have these placed in what was essentially an enclosed, draughted system similar in principle to the concept of the microbiological cabinet. Independently, similar, but much more extensive studies were carried out at about the same time by Yamauchi (41) and co-workers.
The impulsion for the work of Yamauchi and his group of veterinarians at Kagoshima was primarily the pursuit of improved animal husbandry and only secondarily the prevention of LAA. They took as their starting point the objective of optimal elimination of all unwanted particles and substances including ammonia, bacteria, xenobiotics and allergens. In their study designs they took particular note of the work of Edwards (94) who studied the levels of LAA antigens in caging systems and the effects of operational changes, such as humidity and stocking densities:

They concluded that the essential characteristic of existing containment systems was that of turbulent airflow which maximised the likelihood of entraining contaminants and recirculating them through the breathing zones of both caged animals and the humans that attended upon them. This reasoning led to the view that a minimally turbulent, one-way airflow system would be the best theoretical model to try. A series of different ways of achieving this effect was designed and tested. The principle underlying these systems is illustrated in Fig. 8.1.

Fig. 8.1
Diagrammatic representation of the one-way-airflow animal room with sliding doors. A, supply air inlet; B, sliding doors; C, air control plate; D, adjustable air exhaust slit; E, exhaust air outlet
The Japanese group used particle counting as a surrogate for all potential exposures. Test results showed that the enclosed cabinet system which they identified as optimal in their study series was capable of reducing exposures from Class 10,000 to Class 100. When the steady state was disturbed by opening the system or carrying out animal handling procedures, there was marked leakage of contaminants into room environments. The steady state took about half an hour to be restored.

In comparison to the studies of Yamauchi et al, the methods which were used in our studies were cruder and more cursory and can be criticised on several counts. They were carried out in a mock-up and used heat-sources as surrogates for animals. In fact, only a "rabbit" mock-up was studied. Short-term smoke releases were used to draw subjective conclusions about air distribution, containment and disposal. The benefits of using these techniques were speed of assessment, speed of configuration set-up and simplicity. A similar set of experiments using real animal rooms and animals together with measurement of airborne antigen levels would have been very time-consuming and prohibitively costly and yet the conclusion reached using the simpler methods, were essentially the same as those identified by Yamauchi and his co-workers.

The benefit of this work, in positive practical terms, was somewhat limited. It certainly satisfied the very important managerial objectives of identifying "best practicable means" and "state of the art" configurations for new animal rooms but the preventative benefit to people working in the rooms must be considered quite dubious. The smoke studies showed that the introduction of workpeople, either standing still or carrying out typical animal handling manipulations, had a profound and lasting effect on the stable air movement patterns observed in the steady state, even in the "best-available" configuration. This, together with the knowledge that it is the handling of animals themselves that increases antigen exposure, would suggest that the contribution of
conventional containment and ventilation hygiene measures is unlikely to be one making a significant impact in the prevention of LAA.

One possible set of options which has not been fully considered may be termed increase of separation (as between animals and humans). For many routine operations, such as the majority of toxicological interventions, it is possible to envisage a set of semi-automated operations with much reduced exposure of personnel. Some elements of such procedures have been attempted in at least one UK pharmaceutical company\(^{39}\) where animals were moved from their holding cages to a mobile ventilated cabinet for gavage and observational procedures. This could be further automated if caging systems were so modified as to allow the detachment and transfer of individual enclosed animal boxes to an observation cabinet. However, the original attempts to develop some parts of such a system were aborted because of the time-costs associated with the extra procedures and the doubts expressed about whether any benefit for operators might be effected or demonstrated. The difficulty of getting useful results from experiments in this field should not be underestimated.

A number of other animal handling situations lend themselves even less well to standardisation. These are the procedures of experimentation (intrinsically non-routine) and pathological study. They are the activities yielding the highest antigenic burden (Ch 1, Fig. 1.1) and yet they involve the closest contact between animals and humans. Only a limited amount of cabinet work is feasible in these circumstances and it seems unlikely that any means, other than improved and rigorously enforced procedural arrangements will be available to reduce exposure in these circumstances for the foreseeable future. These will be discussed further in the chapter on management but again, the difficulty of validating alleged improvements in working practices here, cannot be underestimated.

**Protection**

If it is reasonable to predict that the contribution of preventative hygiene to the control of LAA is likely to be limited then the intrinsically inferior approach of protection assumes a more significant place. The work described in Chapter 3\(^{47}\) appears to have been the first study to assess the benefits and shortcomings of RPE usage in LAA or indeed in any occupational asthma. This should be contrasted to the more frequent theoretical studies of exposure and mask
efficacy\(^{(97,98)}\). Given the wide-spread use of masks for protection from occupational antigenic hazards, what is surprising is that further studies have not been attempted by others. The only analogous work has been that of Anderson\(^{(48)}\) who tested the protection offered by ventilated helmets amongst sensitised pigeon fanciers.

Using the diagnostic criteria extant at the time of the study, independent blinded assessors found occupational asthma in two out of the eleven cases in the study. Three other cases had some element of airways lability not amounting to overt asthma. Alternative diagnostic criteria, using variation beyond lower 95% confidence intervals (plus diurnal variation) derived from in-person control data were used subsequently. These supported the original finding that significant airways reactivity was to be found despite RPE usage; in this case in 8 out of 11 cases. The conclusion may thus be drawn that the protection obtained from RPE, whilst undoubted, is incomplete.

An attempt to test increased procedural separation of animals and workers was made as part of this study. This involved more rigorous changeroom discipline, special overclothing and the complete avoidance of non-relevant activities (e.g. writing up notes) in animal areas. In the group under study, these precautions appeared to have had no effect on improving protection; most got worse. Indeed one individual progressed from rhinitis to overt asthma in that particular part of the study period.

Alternative outcomes might have been sought and might have been more appropriate to test protective efficacy. In the newly exposed, the development of specific skin prick test positivity or rhinitis might be better, clearer indicators. Whilst such criteria were not relevant to a study of established LAA such as the one under discussion here, they could and perhaps should be used in some future study.

The findings of our study are both tantalising and discouraging and given the size of the study cannot be considered to be other than indicative of the range of possible outcomes of intervention. Nevertheless the observations show that prospect that personal protective procedures might have a contribution to make to the management of LAA which needs considerable further evaluation.
prospect that personal protective procedures might have a contribution to make to the management of LAA which needs considerable further evaluation.

Alongside the PEFR records registered during this study, a record was kept of symptoms and their relation to work. Low PEFR did not correlate well with symptomatic episodes marked on individual records. Thus the symptoms record may be of enormous benefit to the patient for indicating subjective severity but it appears relatively unhelpful in terms of sensitivity in providing an objective view of the underlying pathophysiological state. It raises the question of whether the physician should treat the symptoms or the readings.

The results of this study and the studies of Anderson upon bird fanciers suggest that the protection to be obtained from RPE is incomplete. Some caution needs to be exercised when citing this concordance of view since the two sets of studies, in a subtle way, do not compare like with like. Thus the hobbyist is free to leave his exposure whenever he wishes whereas the employee at work is more constrained. It may be that the picture obtained from studying pigeon fanciers in therefore unduly optimistic for occupational applications. Undoubtedly, if individuals are to persist with an exposure which has caused significant lung disorder, close supervision by a committed and informed physician is required.

**Persistence**

In latter years, the transience of occupational allergic disease, particularly asthma has come to be questioned. Evidence has come forward that it may persist, despite avoidance of exposure, for several years if not indefinitely. Thus follow up of sensitised isocyanate workers has suggested that they experience an accelerated decrement in lung function. In studies of platinum workers who left work because of occupational asthma high levels of persisting symptoms have been found. They have been accompanied by adverse social consequences such as increased levels of unemployment. Among azodicarbonamide workers persistence of symptoms was associated with exposure prolonged for more than three months after the onset of asthma. The situation in disease associated with higher molecular weight antigens seems similar as with Western red cedar workers and colophony.
The authority of findings in the follow-up study of LAA in this thesis is somewhat limited by the small numbers involved. Nevertheless, the subjective symptomatic experience of those with asthma who were relocated away from exposure was better than that described in the studies cited above. However, 7 out of 9 individuals still had symptoms when exposed to causal species casually although they were quite well when not exposed. It is possible then that even in regression, LAA is a milder disorder than many other occupational asthmas.

It is necessary to differentiate carefully between the inferences to be drawn from these different studies. In the isocyanate, platinum, Western red cedar and colophony studies, workers had avoided subsequent exposure to causal agents and what was being charted was recovery, or lack of it, out of exposure. In the azodicarbonamide study both the effect of persisting in exposure after asthma onset and subsequent removal were recorded. The removal from exposure in the LAA follow-up series was less complete because of the ubiquity of animal usage in a pharmaceutical research establishment and the reluctance of individuals committed to a particular set of work interests to wholly divorce themselves from them. It may be speculated that removal from exposure to other more ubiquitous agents, such as isocyanates and Western red cedar, may also not be as complete as either subjects or their investigators believe.

The rhinitic and asymptomatic cases which were followed up are of particular interest since such groups are seldom pursued in long term outcome studies. Not unnaturally a few had passed through the well-recognised stages of LAA to develop rhinitis or asthma but the vast majority remained stable. Both the original rhinitic population and those who had developed rhinitis (without asthma) showed remarkable stability of symptom levels and immune status. Similarly, the wholly asymptomatic showed no evidence of change in immune status remaining almost wholly specific skin prick and specific IgE negative (<2%). Their persistence in exposure is therefore not deleterious.

Issues Relating to Occupational Asthma Generally

The preceding pages have been concerned with the insights which the work described in this thesis has been able to offer into the nature of LAA. A wider series of inferences may be drawn too in order to enrich our understanding of occupational asthma generally. It is also timely to speculate on the clues that
the work offers on the nature of occupational asthma and to consider the areas
where further work might be directed.

The natural history of occupational asthma attributable to many different
causes has been well described over the last decade or so. With this
information, attempts have been made to differentiate between classes of
causal agents. Earlier theories related to particle size probably owe their
ancestry to the importance of such aetiology in the more historically
well-characterised occupational lung disorders. This theme was pursued by
Pepys and Hutchcroft (1975) who stated that late asthmatic reactions were
more common in work challenge situations where particulate exposures
occurred as opposed to laboratory challenges when nebulised antigenic
sources were used. Further support was offered for this idea by Wieslander et
al. (1975) whose work derived from particulate challenges to guinea-pig lung. This
view is not substantiated by experience from vapour exposures such as
isocyanates and in practical terms the idea is of limited value since
occupational exposures are usually mixed and immediate and late reactions
are of equal inconvenience to the patient. It is as likely that these observations
related to regional deposition characteristics as that they were fundamental to
the size of antigenic particles.

Another means of antigenic differentiation has been that related to molecular
weight (MW). It has been suggested that asthma caused by low MW
substances is qualitatively different from that seen in asthma caused by high MW
antigens. This hypothesis has great scientific attraction because a
potentially simple and plausible rationale is available to accommodate it. This is
the differentiation between antigens capable of inducing an allergic response
on their own and those requiring hapten attachment for allergenic expression.

It would seem that the asthma induced by low MW substances is characterised
by rapid onset, absence of regional prodrome and rapid maximisation of effect.
The asthmas caused by high MW substances on the other hand, have a slower
onset often a regional prodrome and progress more slowly to full effect. Whilst
this differentiation is clear, it is not clear whether it is important or what light it
casts upon the underlying causal mechanisms. It is certainly possible to
postulate, from experience with grass pollen and house-dust mite asthma that
high MW sensitisers may be more efficient, at much lower concentrations, than
low MW substances so that there is some sort of threshold effect for the latter.
However this idea would seem to be given the lie by experience of platinum-salt sensitisation, isocyanates and acid anhydrides at very low levels of recorded exposure. The role of intermittent or momentous "overwhelming" exposures, as in accidents or other abnormal working conditions, is unclear in this respect but has been postulated as significant for sensitisation in TDI asthma.

The progression of occupational asthma from sensitisation, through increasing airways reactivity to full blown asthma has been charted in several case histories described in this thesis as well as from the retrospective experience of the prevalence study. However the observations in these and other similar studies are insufficiently systematic to offer a detailed view of the process of disease maturation. Even less well understood are the factors which might modify the pace of development. That such studies would be difficult to do does not take away from the fact that they would be both interesting and important in order to give clues about the likely interaction of operational or therapeutic interventions.

The long term effects of getting occupational asthma have already been discussed to an extent in this chapter but are worthy of some further analysis in order to fuel later discussions of management and diagnostic concerns. Both low and less frequently high MW asthma have now been shown to carry a burden of chronicity which was previously discounted. By contrast, rhinitis, when it occurs alone and does not progress to asthma appears to carry no such prolonged effect nor, at least in LAA, are there covert effects in the assymptomatic. The factors tending to enhance chronicity have not been explored systematically although prolonged exposure after sensitisation has been identified as contributory. Other factors which might be expected to contribute, level of continuing exposure, exposure to causes of non-specific airway reactivity, smoking etc need evaluation. Similarly the detriment criteria such as persisting symptoms, poor lung function, employment etc. could benefit from being grouped into some index or indices of functional and social deprivation.

The Nature of Atopy

The prevalence of atopic status is stated to vary with age. Alternatively it may be a cohort effect. Little regard has been given to the implications of the observation in relation to occupation. It was only when our study population
was reassessed some years after our prevalence study of LAA that it became apparent that the transience of atopy did not relate solely to time. Where subjective criteria of atopy were used, past-personal or family history, the population identified shifted markedly (40%) within a relatively few years (5-7). Only the population defined by skin prick testing remained stable (95%). If these findings are confirmed by other studies then the value of atopy in epidemiological usage is likely to be low.

It is then worth asking why the concept remains so pervasive and to what use might it be put?

In the occupational setting, the idea may also be of particular appeal to those who would have a disease attributable to individual susceptibility rather than occupational exposure. The mind-set is historically powerful and has long been useful. However it is not inappropriate to ask whether it has outlived its conceptual usefulness. Certainly from the occupational viewpoint it could well be relegated to the status of a factor of personal interest about which some guidance might be offered at pre-employment screening. It is only the enshrinement of atopy as a discriminant of legal significance that should cause it to be a consideration in job-placement. The opposing, as yet presumptive right of equal opportunity of employment does not yet have any legal standing in the UK.

The Nature of Asthma

The dynamic assessment of altered airways reactivity by PEFR has done much to help better understand the idea of asthma. Occupational asthma has had an important part to play in informing current perceptions because onset, progress, cause and course can be well charted. Thus asthma is now defined to encompass ideas of transience and variability as well as symptoms.

The fit between some of these ideas, particularly symptoms and physiological parameters is not good, as was evidenced by work in this thesis (Chapter 3). The current definitions of asthma are thus hybrids and perhaps even crude compromises at that, and if absolute genetic or biochemical criteria are not available, it might be more helpful to consider definitions of asthma which were based on potential (susceptibility or evidence of liability to develop disease) rather than effect.
This might help to improve understanding of the hidden transience of asthma, that is the change in reactivity related to time, exposure etc as evidenced by the lung function traces of Case 3 (Chapter 7). The question would then arise whether to treat readings or symptoms. Currently this is an uncertain area, the medical convention being mainly deeply traditional and inclining to the symptomatic. A change in the conceptual framework to dealing with anticipated effects could powerfully affect treatment criteria. Given our knowledge of the long term effects of occupational asthma such a change towards pro-active treatment and management might well be usefully considered anew.
CHAPTER 9

The surveillance of animal workers
INTRODUCTION

For the individual at risk by reason of his or her exposure to animals, the objectives of surveillance are to provide warning of that risk, to diagnose disease promptly and to avoid undesirable sequelae. For workforces, as groups, and particularly for their managements, surveillance has a broader remit. This remit incorporates pre-employment and periodic surveillance, case finding, reassurance monitoring, workplace assessment and workplace monitoring.

Pre-employment surveillance

Das et al\(^{(109)}\) have identified atopy, generalised airways hyperactivity and smoking as risk factors in LAA. Their work supports the many studies which have similarly identified atopy including that described in Chapter 2. Their work also supports the work of Venables\(^{(95)}\) with regard to smoking. From the risk management viewpoint, the possible pre-disposing or susceptibility factors must be considered alongside diseases which may be present prior to employment and which can act as potential compromising factors in LAA (although these latter are not discussed here).

As has been remarked in Chapter 5, association, however strong, may not be sufficient grounds for use of a risk factor as a discriminant. Of potential discriminants, atopy has been most intensely debated. The reasons for this are twofold. Firstly atopy is a traditional discriminant in occupational health practice and is thus retained inertially. Secondly it has a constant, strong association with asthma, the more serious end of the morbidity scale in LAA. Also, underpinning the retention of atopy as a discriminant, at least in the UK, has been the legal precept of "special duty of care".

In a cross-sectional and prospective study, Kibby et al\(^{(110)}\) examined the value of cumulating atopic markers as predictors of risk for LAA. The authors stated that the presence of three or more markers was the best predictor. They used history of hay fever, childhood rashes, other allergies, asthma and family history. However neither these, or other authors have distinguished between association and predictive value and such cumulation of criteria will have sacrificed specificity for sensitivity. Nevertheless they have agreed universally with the conclusions drawn in the study described in Chapter 5 which proposed that the predictive value of a best marker of atopy (skin prick testing), at 35%, was insufficient to indicate the use of atopy as a discriminant for employment with animals.
The implication of not using atopy as a discriminant is that on the data given above, approximately one of three atopes recruited into employment will develop asthma due to LAA. Conversely, were atopy used as a discriminant, three persons would be excluded from employment to prevent one case of asthma within those three, but other cases would arise in the non-atopic persons recruited.

At present, therefore, atopy is not used as an employment bar for LAA risk in most institutions in the UK. It may well be that this practice is reinforced by awareness of legislation in the USA prohibiting use of medical risk factors as employment discriminants and the possibility that such legislation could also find a place in European statute. It has been argued that were atopy predictive of a more irreversible or serious disorder, the balance towards its use as a bar would alter markedly. In the meanwhile, the risk that it poses needs to be articulated to atopes who do pass into employment in animal work. This practice is becoming increasingly common.

Smoking may be treated in similar view to atopy in relation to risk. Its associations with LAA appear to be similar or less than atopy. Again it seems appropriate to warn smokers of the association and to advise cessation. More radically, and in the general context of the movement towards smoke-free workplaces, it might be suggested that employment be made conditional upon cessation or at least compliance with a smoke-free policy.

Periodic surveillance

Conventional authorities\textsuperscript{[78]} propose questionnaires and lung function tests for the surveillance of exposed populations. It is necessary to see how these procedures satisfy surveillance needs in practice and how they serve different individual and group needs.

A number of authors have recently examined the performance of questionnaires in asthma, occupational and non-occupational\textsuperscript{[80,81,112,113]}. In general, questionnaires have been found to have poor sensitivity and less than complete specificity. It may be argued that this is unsatisfactory for the individual but is less so for the group. It follows thus that the purpose for which the screening instrument is used is key to its value.
individual but is less so for the group. It follows thus that the purpose for which the screening instrument is used is key to its value.

It does not appear to have been the purpose of any of the above-mentioned studies to optimise questionnaire performance. This is of particular importance in OAD because, in contrast to MRCQ, there is no standard instrument, although many of the instruments in use are very similar to each other. Optimisation, pursued pragmatically, was the process described in the early part of Chapter 7. The main objectives were to produce an instrument which firstly maximised compliance and secondly was sufficiently specific to capture most in “LAA cases” and sensitive enough not to capture too many “non-cases”. It was thus deliberately brief and aimed to err on the side of caution. It is shown in Appendix 4.

It seems self-apparent that the needs of screening and research are likely to be different. Similarly the requirements for rapidly screening an exposed population are likely to be different from those for screening concerned or anxious individuals. Questionnaires may be and are indeed becoming a part of screening in all of these circumstances but it is necessary to recognise the specific role that they will be asked to play in each of those circumstances as part of a larger process of surveillance which may involve interview, examination and tests. Investigators may thus need to go on from, or back from, sensitivity, specificity or predictive value general to fitness for exact purpose.

A number of objectives may be defined for surveillance. Among these are risk finding, case finding and reassurance monitoring. As questionnaires may be adjusted to optimise fit to purpose so also may “objective” tests be considered. Those used customarily in LAA are skin prick tests and lung function tests.

Because of regulatory considerations, the range of skin-prick solutions available for surveillance purposes is sub-optimal. In research, skin prick tests have been used to chart progress from pre-employment, through the prodrome of LAA and thence to mark the progress of disease. In more routine population surveillance, skin prick tests can be considered against the purposes outlined in the previous paragraph.
It has been argued that risk finding, in this case skin-prick testing for atopy and LAA, is a proper practice for the advice of the individual on the one hand and the protection of an employer's interest on the other. Whether it is essential or alternatively, desirable is a moot point and one dependant at present more on legal than scientific considerations. The study in Ch. 5 demonstrated that skin-prick is the most reliable marker of atopy and this may argue in favour of its use.

For case finding the study described in Ch. 2 showed a very strong association between specific skin prick tests and LAA asthma but overall, including rhinitis, only a minority of LAA cases are so associated. Das(109) found a bare majority (57%) in asthma. When considering periodic surveillance in an exposed population, it is necessary to recall that the incidence of new cases of LAA will be very small. Therefore, if there is no research purpose, the use of routine skin prick tests, an invasive procedure, seems unjustified. It appears more appropriate to use such tests as a second line diagnostic tool following on questionnaire screening and possibly, lung function tests.

Similar arguments for lung function tests may be used as for skin prick tests. However spirometry and peak flow measurement, whilst capable of causing transient discomfort, are not invasive. Challenge tests may though be considered more invasive. In screening a population, most lung function tests will be normal. It follows that such tests offer little benefit in these circumstances except for reassurance, though that is or may be an important personal and medicological objective in its own right. Again, as for skin prick testing, lung function tests may normally best be seen as a secondary measure to follow questionnaire screening. However the argument cannot be so strongly made as for skin prick testing.

If reliance is to be placed mainly on questionnaire usage for population screening, then that screening must be appropriate and timely to take account of the natural history of the disease. The screening questionnaire in Appendix 4 was used annually. Attempts to screen more frequently in atotics and new starters for the first 2 or 3 years of animal exposure foundered, as described in Chapter 7, because of complexity and poor compliance. The use of computer driven surveillance programmes and direct entry may overcome these problems and should be tested. In the meanwhile annual screening coupled with provision of hazard and action information which contains exhortations to
report suspect symptoms between monitoring periods can be argued to be adequate.

**Case Finding**

It has been argued above that in routine surveillance, preliminary case identification should be by questionnaire. It has also been suggested that this method needs to be coupled with effective exhortation to symptom reporting between screening periods. Another factor of special importance is the strong evidence now available from many occupational asthma studies relating to the long term effects of asthma particularly after prolonged exposure to the causal agent. This creates an imperative both clinical and legal, for early disease identification and early removal from exposure if the disease is confirmed.

Sufficient evidence has been adduced from prospective studies and case studies (some reported in this thesis) to state that in LAA asthma, skin prick conversion and elevated specific IgE levels have preceded overt disease have typically by some months. Indeed this may be seen by some as an argument for routine prospective skin prick testing. Further evidence from this and other studies indicates that asthma is usually associated with and preceded by rhinitis. An argument therefore exists for the relocation of the skin prick positive rhinitic especially if it can be shown that specific skin pricks have converted from negative. To this authors knowledge, this combination of risk factors has not been tested for its predictive value but by judicious combination of existing and historic cohorts perhaps could be.

Many career dedicated individuals will not eschew exposure until they must and will not accept risk based prospective advice. For them it becomes important to offer confirmatory diagnosis of asthma at the earliest opportunity. The techniques described in the case studies in Chapter 7 may be over sensitive in routine usage but when combined with other evidence such as positive specific skin pricks and a suggestive history may be sufficiently persuasive to both patient and clinician. They are worthy of further study to see how early and how reliably the onset of asthma can be identified.
Reassurance Monitoring

An issue not infrequently raised but not yet studied intensively has been the possibility of covert effects in the seemingly unaffected individual in prolonged LAA antigen exposure. In the small, follow up study reported in Ch. 4, subjective evidence of symptom stability in rhinitics and objective evidence of unchanged specific IgE levels in rhinitics and asymptomatic individuals was presented. These data offer limited reassurance to these large groups. However the size of the study and its duration precluded offering the long term definitive information on symptoms, skin prick and especially lung function which individual in such groups might reasonably seek. A prospective study addressing these “silent” groups would usefully identify both risk and those surveillance measures that could usefully be developed routinely in such populations.

Another group requiring long term monitoring are LAA asthmatics. Those who remain in any reduced level of exposure clearly require intensive monitoring of lung function including reactivity. However, as shown in Ch. 4, even those asthmatics putatively wholly relocated out of exposure, retain their immune competence and need to be reassured about the integrity of their lung function. Perhaps also, with reference to the following section, they need to be reassured that they are truly out of exposure.

Workplace surveillance

The antigens of LAA come within the remit of the COSHH Regulations yet there is a marked reluctance amongst employers and researchers to operate as if they did. The reasons for this, which have been discussed in Chapters 6, 8 and 10 in this thesis, are simple enough and relate to the absence of a hygiene standard and the ubiquity of exposures.

However it can be argued that sufficient has been known of the major LAA allergens for some time and sufficient has been known of the conditions in which high levels are encountered for COSHH assessments to be carried out in the workplace and for prioritised hygiene programmes to be established to characterise those exposures. The author is unaware of any published data discussing the operation of such a programme or its effect even though such a process has at least been envisaged\textsuperscript{(114)}. 
It seems to the author that there are practical benefits to such programmes that go beyond the basic requirement of compliance with the law. A detailed knowledge of exposure levels in different operating circumstances would permit further elucidation of the dose response relationships which has been started, so far only semi-quantitatively; by Cullinan and co-workers\(^{(83)}\). It would also permit the accurate placement of symptomatic individuals into the lower exposure levels advocated by Hendrick as sufficient relocation in some cases\(^{(115)}\).

**Summary**

In summary it may be stated that the purposes of surveillance, the requirements of different interest groups and the instruments to achieve desired goals have not yet been fully recognised or developed and thus present both research and operational challenges to those in the field.
CHAPTER 10

The organisational management
of LAA and general implications for the
management of occupational allergic disease
INTRODUCTION

This chapter complements the preceding chapter. That concentrated on individuals and populations and this targets their work environment and what occupational health measures a management should be induced to consider. The themes related to separation and protection which were discussed in Chapter 8 will be further developed alongside another organisational initiative, the provision of information.

Separation and Protection

It has been remarked already, that the first preventative option in occupational health practice, substitution, is not an available option in the management of LAA. Separation and protection therefore present as the major practicable strategies.

In Chapter 6, the most absolute form of separation, containment at source, was demonstrated to be feasible but impracticable. This was particularly so because the very activities most necessary to the work are amongst those most likely to result in high levels of antigenic exposure.

More generally, taking an overview based on experience with LAA, it can seen that containment strategies for asthmogens are likely to be of limited value. One set of reasons for this situation rests with the nature of the tasks associated with exposure and the other set relates to levels of exposure.

Very sophisticated, costly and effective containment has been deployed in a few situations where an activity involving an occupational allergen can be concentrated to a small number of locations. Where this has been possible, the results have been mixed. Thus, complete avoidance of occupational symptoms has been claimed for workers operating closed processes involving B. Subtilis enzymes\(^{45}\) even though some escape occurs. Sporadic cases of asthma are still reported in platinum salt workers despite even better levels of containment than those that are obtained in the detergent industry\(^{46}\). In many situations, as with LAA, exposures to antigens come in an infinite variety of tasks only a minority of which are amenable to any degree of containment. This is not to say that containment should not be vigorously researched but that the benefit
likely to be obtained from it should be realistically assessed and pursued only to reasonable limits.

Two inferences of interest are available from experience of containment. The first is that containment can work and that there may therefore be a threshold below which no effect is seen. The second inference is that if containment does not work fully then the threshold may be variable. This then leads to considering the value of attempting to define hygiene standards for sensitisers. The first problem here is that the nature of hygiene standards. These work best where there is a deterministic relationship between concentration (of toxicant) and effect. A safety factor, as customarily applied for hygiene standards, then reduces likely (toxic) effects practically to zero. Where the relationship is stochastic as presumed with carcinogens, there must always be considered to be some level of residual risk however low the standard is set.

With sensitisers the situation is probably even more complex. There is a deterministic element in the equation in that there are some elements of a dose-response relationship apparent in workplace and challenge experiences in those sensitised. However there are or may be some stochastic elements relating to the probability of becoming sensitised in those who are exposed but not yet sensitised. Even if the two objectives of preventing sensitisation and protecting the sensitised are separated and rationalised in this way there remains another unique set of features which relates not to the substance but to the persons and populations at risk. Whilst there exists a range of susceptibility to conventional toxicants which varies with factors such as age, genetic and biochemical profile, this range is quite small and can be accounted for by use of a conservative safety factor. In contrast, in allergic disease, variable susceptibility is inherent to the definition of the disease. Put at its simplest, an exposure level which will cause asthma one day may not do so the following week. There is thus possible a wide range of susceptibility within the person and naturally, a much wider range in any population.

In these circumstances, it is perhaps inevitable that any attempt at setting a hygiene standard will be frustrated. This is clearly the case with TDI\(^{108}\). As was hinted in Chapter 8, the best that can be obtained are a set of ranges of exposure which can be correlated to sensitisation on the one hand and effects in the sensitised on the other. It is possible with many agents causing
occupational asthma that the ranges will be wide and the absolute thresholds, if any, will be so low as to be unattainable in practical terms.

The protective efficacy of RPE, the ventilated helmet, was tested in Ch. 3 and protection was found to be incomplete. A wider range of direct and procedural protective measures has also been prescribed in LAA (see Appendix 5) and tested\(^{49,50}\). Protection in the latter set of circumstances may also be inferred to be incomplete but incidence when compared to expected (without precautions) was reported to be substantially diminished.

It is thus disappointing to record the paucity of studies addressing protective issues. Whilst acknowledging that the difficulties of doing such studies are redoubled by the very factors tending to render containment and hygiene standard ineffective, it remains that the understanding of effective protective measures will be essential to the control of LAA and other causes of OAD for the foreseeable future.

It seems plausible to propose that the benefit to be derived from a series of within person studies of RPE would be self-apparent. RPE using different theoretical protection factors could be compared and the studies could be carried out quite easily using small numbers of subjects both for LAA and other OAD. Double sampling of allergens (inside and outside RPE) might add further information about the behavioural characteristics of aeroallergens.

As well as being of benefit themselves, they might also provide information about the likely range or ranges of exposure levels where effects were diminished or abolished. More complex studies addressing the aeroallergen blocking capacity of other protective factors (e.g. gowning schedules, cage transport and cleaning regimes etc) as well as clinical effects still seem exceedingly difficult to standardise or measure effectively but might yield to a stepwise approach where individual protective measures are tested in isolation or cumulatively.

**Provision of Information**

Effective communication of the issues relating to LAA and OAD’s more generally has been, until recently, a relatively neglected area. A sample of “in-house” communication to a workforce is presented in Appendix 5. HSE have recently
issued an information card, "Breathe freely - a workers information card on respiratory sensitisers".\(^{[116]}\).

The HSE card addresses hazard whereas the "in-house" sheet attempts a broader attack and contains facets of hazard, risk and management. The complexities of providing information, a general requirement of Section 6 of the Health and Safety at Work et., Act, 1974, have only recently begun to receive the attention that they deserve. This has been crystallised by the CHIP Regulations 1994.

It is necessary to digress slightly in discussing the provision of information to the ubiquitous hazard data sheet (HDS). This, by its nature, should contain only hazard information. By so doing, it loses relevance for the particular circumstances of the individual work or workgroup. The desire to make HDS more relevant was acknowledged in an ad hoc way by many employers by the inclusion of risk information in some sheets and officially by the use of designated risk phrases under CHIP. This situation is further confused in that these so-called risk phrases are to some extent actually still hazard descriptors.

The nub of all this is that hazard information may be generally applicable, but when applied in particular circumstances, loses relevance if not combined with risk information. Similarly action information, that is the description of what to do if a risk manifests itself in effect, also needs to be specific if it is to be seen as useful. Thus a hierarchy of information needs, which involves guidance on protective and surveillance measures evolves. The pinnacle of this process which incorporates the measures previously mentioned, is policy.

In the case of LAA, those different facets of informational need are yet to be integrated. This exercise would be timely and research on the penetration and impact of such initiatives would be of great interest and great practical value.

**Policy and its implementation**

The publication of our cross-sectional study and other similar studies in 1981\(^{[33,84,103]}\) led to the identification of LAA as a frequent and significant disorder of people working with animals. As normally occurs for occupational disorders in such circumstances, this led to action on two managerial fronts. Firstly, those organisations which had animal exposed populations began to consider how
LAA might be prevented, alleviated and controlled. Secondly, prospects of prescription and compensation came into consideration.

A working party was established in the pharmaceutical industry under the auspices of the Association of the British Pharmaceutical Industry (ABPI) of which this author became a member. The remit of the working party was to produce recommended guidance on LAA management. A preliminary task of the group was to persuade parts of the membership of the ABPI, who had played no part in the research into LAA, of the fact that the condition existed, was common and could be serious. The need to share perception of hazard and risk and to obtain consensual acknowledgement of this is a critical step in the management process. Nor should the time and effort to do this be under-estimated as it often is when the issue comes to litigation. Indeed it is a particularly noteworthy feature of the history of LAA in the UK that it is only in the last few years that the majority of academic and governmental institutions have begun to apply some of the same efforts to the control of LAA as were manifested in the early 1980's in the pharmaceutical industry.

The first edition of ABPI guidance was published in 1983 and the second in 1987 (Appendix 1). The first edition was criticised for being rather vague and insufficiently prescriptive. However this must be seen as inevitable since reliance had necessarily to be placed upon a relatively narrow knowledge base and, of course, the document had, in part, the simple purpose of education and persuasion.

When comparing the two editions, a generally increased authority is detectable in the tone of advice offered in 1987. In the area of aetiology it was possible to be much more precise about causal agents\(^{(104)}\) and their distribution in the working environment\(^{(96)}\). In contrast, the guidance on prevention with regard to animal room and ventilation, had become more tentative recognising the knowledge gained from studies such as those described in this thesis (Chapter 6). However the impetus to segregate animals from people had become more definitive with regard to such procedures as transportation, animal room entry, protective clothing and the use of exhaust ventilated cabinets. The debate on protection had been informed by the study in Chapter 3 and appropriate caution was advised for the surveillance of individuals using masks and helmet respirators\(^{(47)}\). Similarly the shortcomings of atopy as a discriminant had become more clearly delineated\(^{(105)}\).
During this time, HSE involvement was maintained through a "special interest" study group of which, again, the author was a member. This group exchanged research information, set out research objectives and ultimately provided the knowledge base from which stemmed HSE guidance\(^{63}\). Other than complying to the common format of HSE guidance notes, the content and advice provided is little different from that in the ABPI document, 2nd edition.

One of the desirable objectives identified by the HSE study group, during its existence, was validation of the practical advice measures in the guidance notes. This objective was pursued boldly by Teasdale and his group who embarked on a vigorous campaign of awareness and compliance raising in the organisation in which they worked. This was given impact by transforming guidance into operating rules and the effect of these was tested by an extensive range of prospective studies. The first of these studies was published in 1983 and the second in 1987\(^{49,50}\). The earlier study, showed a fall of 75% in incidence of LAA when compared to prevalence in "pre-rules", periods. The later study demonstrated that this outcome was largely maintained for the length of the follow-up period (max. 5 years), thus precluding the possibility that the effect was due to any great delayed onset or progression of LAA.

The value of these studies is considerable since they remain the only prospective examinations of (managerial) intervention in LAA. However, they did not examine individual facets of the multiple interventions that comprised the works rules imposed and they did not measure objectively any effect of the rules on reducing exposure in those activities. Thus it remains to be shown which interventions are particularly effective in reducing LAA incidence and the levels of exposure at which sensitisation and symptom stimulus are avoided. Given the dynamic nature of the physiological process leading to LAA and its symptomatic manifestations, it seems likely that each of these will prove to be a range of values and possibly a wide one. Nevertheless, it is important that that range be identified so that effort can be concentrated on the reduction of exposures where those ranges are exceeded. This work promises likely to be complex and time-consuming.
Prescriptive and compensation

No discussion of the management of LAA is complete without mention of prescriptive and compensation issues. The prescriptive process, by which occupational disorders become recognised for the payment of industrial injury benefit is operated by the IIAC[117]. Prescription is decided using as "rule of thumb" criteria a relative risk >2 consistently to allow attribution to an occupational cause. It is then possible to offer claimants a "benefit of presumption". Payments are made on the presence of exposure and the presence of illness and, in contrast to compensation derived from common law claimancy, without any attribution of blame. The process has been criticised as laggardy since its inception, but in the case of occupational asthma due to LAA (prescribed in 1982) this is hardly so. Contrastingly the salutary dis-benefits of premature prescription can be seen in the cases of "RSI" in Australia and "painter's syndrome" in Scandinavia where doubts about the aetiology, diagnostic criteria and very existence of the conditions have subsequently been raised.

Traditionally, claimancy for compensation follows on prescription and this has been true for LAA. No case has yet come to court although there have been a number of settlements out of court. The main issues at contention, foreseeability and the adequacy of management arrangements, have been significantly informed by the work comprising this thesis. Remarks have already been made in this discussion of the often uncomfortable relationship between the scientific investigation of disease and the judicial views of causation and foreseeability. In the UK, it is still common for the judiciary to circumvent the often prolonged process of scientific consensus on causation by expressing preference for one body of evidence as compared to another. Similarly time to foreseeability tends to be telescoped to a specific, and often only sentinel scientific paper. The distortions caused by these assumptions must be a cause of concern for expert witnesses called upon to give evidence in litigation. The problems that this causes have been recognised in the USA and are the subject of medicolegal consultation and debate[118] This has yet to begin in this country.

Dissonances between scientifically justified practice and legal expectation are commonplace in medicine and are acknowledged generically as requirements of defensive medicine. The prime example in the area of occupational allergic disease is the use of atopy as a discriminant and the consideration which has to
be given to its continued use in the light of legal interest in the concept of "special duty of care" to which, perhaps unfortunately, atopy relates well. A curious characteristic of such legal precepts, taken up as they are through the precedential system, is their prolonged persistence once adopted. This may be contrasted with the situation described in the previous paragraph where the case law system often crystallises or imposes a set of parameters about an issue of scientific controversy prematurely in the interests of obtaining some sort of practical conclusion. As a result of these sort of experiences, it has been argued that the British courts are not well suited to the settlement of issues involving complex scientific controversy and that some other means, such as no-fault compensation, is more appropriate and, in the end, more equitable.
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APPENDIX 1

Guidance documentation on L.A.A.
Issued by ABPI
Advisory note on Laboratory Animal Allergy
1st Edition
1983
ADVISORY NOTE ON LABORATORY ANIMAL ALLERGY

A joint working party of the ABPI Scientific and Environmental, Health and Safety Committees has prepared this advisory note as an outline of the principles involved in laboratory animal allergy at the present time. It is hoped that this will provide employers with a basis on which to establish internal company practices appropriate to their own organisation and facilities. The note represents the views of the working party in the light of current medical knowledge and laboratory practice, and recognises that further research is necessary to achieve a fuller understanding of occupational allergy associated with exposure to laboratory animals and its management.
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I. INTRODUCTION

Allergy to laboratory animals is a common condition which may present with a variety of respiratory or cutaneous manifestations.

There have been a number of prevalence studies (Cockcroft, *et al.*, 1981, Davies, *et al.*, 1981, Dewdney, 1981 and Gross, 1980) which suggest that about 20-25% of people exposed to small laboratory animals develop symptoms of some kind. Although the great majority of individuals who become sensitised do so during their first four years of exposure, some people develop symptoms only after many years.

Symptoms may present singly or in various combinations. The most common symptom is rhinitis, i.e. blocked nose and sneezing, and this may be associated with irritation and watering of the eyes. Skin rashes are much less common and take the form of urticaria or nettle rash, or papula or vesicular erythema. Only about 3% of people develop the clinically more serious allergic asthma. This may occur on its own or in association with other symptoms and may present as an immediate or as a delayed reaction.

Different organisations have tackled the problem of animal allergy in a variety of ways and with varying degrees of success. Conclusions from recent studies have challenged the rationale of some previously accepted practices and new concepts are emerging which are based on a better understanding of the problem.

The issues which require clarification are similar to those which arise from the employment of people for any work which has been shown to carry a potential risk to health. They cover personnel matters such as recruitment policies, pre-employment selection, health screening, redeployment implications and matters relating to the work place, the standard of animal room facilities provided, and the working practices of the staff.

The employer must assure himself that he is doing everything that is reasonably practicable to reduce the incidence of new cases of sensitisation amongst his staff. In January 1981, a report was presented to Parliament by the Industrial Injuries Advisory Council on Occupational Asthma in which it was recommended that occupational asthma should become a prescribed disease in relation to exposure to, among other causative agents, "animals and insects" in laboratories. This recommendation came into force in March 1982 (S.I. No. 249, 1982, Social Security Industrial Injuries Prescribed Diseases Amendment Regulations, 1982).

This advisory note reviews the present state of knowledge about laboratory animal allergy and attempts to deal with the issues which inevitably arise within an organisation from an occupational condition of such prevalence. An employer has both common law and statutory duties to protect his employees. Legal advice has been sought to clarify certain points of possible disagreement arising between employer and employees, and these points have been clarified in the relevant part of this advisory note. However, as a general principle, an employer should take steps to protect his employee "so far as is reasonably practicable". If an employer brings a civil action based on the negligence of an employer, evidence that the employer has been convicted of an offence under the Health and Safety at Work etc. Act, 1974 which involved a negligent act or omission will support his case. Case law on this point is as yet unclear. With this in mind, the following advisory note makes recommendations which hopefully will enable the responsible employer to conduct his business in a safe manner, so far as is reasonably practicable, and thereby fulfil his legal obligation.
II. DEFINITIONS

The terms below have been defined specifically for this advisory note. Some of the terms may have wider definitions or different uses elsewhere.

Atopy—a form of immunological reactivity assessed by skin test reactions to common allergens (D. pteronyssinus; pollens; aspergillus; cladosporium; cat, dog or horse hair).

It should be noted that this immunological definition of atopy does not mean that the atopic subject has clinical symptoms of allergy, only that he is of atopic predisposition.

Allergy and hypersensitivity are used synonymously in this advisory note to describe a clinical syndrome which may include conjunctivitis, rhinitis, asthma and dermatoses induced by exposure to a specific allergen.

An allergic or hypersensitive individual may thus suffer clinical symptoms of allergic disease when exposed to the relevant allergens. This definition does not presuppose knowledge of the precise aetiology of the underlying mechanism, only that it is immunologically mediated.

Allergen—an allergen is a substance which interacts with a specific antibody to elicit a biological response, that is, a hypersensitivity reaction. The term “allergen” may also be used for a substance which elicits the production of an IgE class antibody.

Asthma—a syndrome characterised by rapidly reversible, paroxysmal dyspnea caused by mechanical obstruction of the airways and hyper-reactivity to irritant stimuli.

Chronic obstructive bronchitis—a chronic irreversible resistance to air flow in the bronchioles. The syndrome is characterised by cough and breathlessness.

RAST—the radioallergosorbent technique; a radioimmunoassay for the measurement of allergen specific IgE antibodies.

RAST inhibition—a modification of the radioallergosorbent technique used to measure allergen concentrations.
III. LABORATORY ANIMAL ALLERGY—DISEASE AND PATHOGENESIS

It has been known for more than a century that contact with certain animal species can result in the development of allergic symptoms including asthma. Most research work to date has been in rodents, i.e. rats, guinea pigs, mice and rabbits. Allergy to other species is known, although has yet to be fully researched. Only relatively recently however has laboratory animal allergy been recognised as an occupational disease of significance.

Immunological Studies

Immunological studies have shown that many individuals who develop laboratory animal allergy, and nearly all those with asthma as a clinical manifestation of the condition, have IgE antibody specific for laboratory animal derived allergens. Both the skin prick test and the radioallergosorbent test have been used in the diagnosis of asthma induced by exposure to laboratory animals and in recent studies it has been shown that a strong correlation exists between clinical history, animal exposure and both the prick test and the RAST.

Specific IgG antibodies may also be present in the serum of some individuals affected by laboratory animal allergy. These antibodies are also present in the serum of individuals exposed to animals in the work place, but who exhibit no symptoms of laboratory animal allergy. Current opinion is therefore that the presence of this class of antibody indicates exposure rather than being diagnostic of laboratory animal allergy or involved in the pathogenesis of the disease.

Laboratory animal allergy is thus an allergic syndrome which shares with the common atopic diseases, hayfever and house mite allergy, a similar clinical picture and an IgE mediated pathogenesis.

Pathogenesis

The mast cell plays a central role in the pathogenesis of the common atopic diseases and, it is assumed, in laboratory animal allergy also.

These cells, found in the mucosal and submucosal layers of the respiratory tract and in the skin, contain the biochemical apparatus necessary to initiate the characteristic response of an allergic subject to allergen.

The external membrane of the mast cell binds IgE tightly so that the cell surface is covered with molecules which recognise and combine with specific allergen. When an allergic subject is exposed to allergen, adjacent IgE molecules are cross-linked by allergen stimulating the mast cell to release substances which, depending on the route by which allergen enters the body, can induce an attack of asthma, rhinitis or urticaria.

The most characteristic structural features of mast cells are their histamine containing granules. When allergen interacts with the mast cell, histamine is released from the granules. At the same time, the mast cell is involved with other cells in making and releasing prostaglandins and leukotrienes (SRS-A). Both histamine and slow reacting substance contract smooth muscle and increase vascular permeability while the prostaglandins can enhance the permeability changes by increasing blood flow.

The products of the interaction of specific allergen with the mast cells of an allergic subject thus have all the properties required to initiate the acute bronchoconstriction and subsequent inflammation of the asthmatic attack, the congestive haemorrhage and oedema of rhinitis, and the oedema of urticaria.
The initial induction of antibody of the IgE immunoglobulin class is under complex genetic control. While it is clear that the majority of individuals can produce IgE class antibody to a wide range of allergens, one group of people do so more readily for reasons that are not fully understood. These people are called 'atopics' and they are characterised primarily by their reactivity to a range of allergens, a reactivity determined in part by the vigour with which they produce IgE antibody.

The question then arises as to whether atopic individuals are more likely to become allergic to laboratory animals if exposed to them. A priori reasoning would so indicate and, in fact, studies have shown a clear association between the development of asthma to animals and the atopic state.

Any association between atopy and other manifestations of laboratory animal allergy is less convincing, but the matter cannot be resolved until other factors are clarified. Amongst these other factors is the influence of length of exposure; it has been claimed that the majority of individuals who develop laboratory animal allergy do so in the first three to four years of exposure while in some a history of some twenty years' exposure is given. It may be that the greater responsiveness of the atopic person results in earlier manifestation of disease in comparison with the longer exposure required to sensitise the non-atopic.

**Immunoochemical Studies**

Immunoochemical studies have attempted to characterise the allergens responsible for the induction of the specific antibody response. The relative importance of animal epithelial scales (danders), saliva, serum and urine as sources of allergenic proteins has not been fully defined. Increasing attention is being paid to proteins excreted in urine following the finding that rats and mice excrete potent allergens in urine, the degree of excretion being, in part, both age (post-pubertal) and sex (male) determined. Analysis of these proteins reveals that both serum proteins, notably albumin, and urine-specific proteins are present and are potent allergens.

Work is far less advanced in defining the allergens derived from rabbits and guinea pigs. Serum albumin is known to be an important allergen with respect to allergy to dogs and cats and it is possibly these allergens which are responsible for the varying degrees of cross-allergenicity observed in individuals.

**Aeroenvironmental Studies**

It is assumed that allergy is induced by the inhalation of these allergens in the form of aerosols or as particles, or less importantly, by entry through abraded or damaged skin. Methods are now being developed for the measurement of specific allergens in the environment; a RAST-inhibition technique has been successfully used, for example, to measure urinary protein allergens in laboratories and animal rooms and to establish the influence of ventilation changes and humidity on allergen levels.

These studies are important in providing a basis for improvement of work environments by reducing exposure to allergenic substances.
IV. ANIMAL ROOM ENVIRONMENTS

With the present state of knowledge of the incidence and control of laboratory animal allergy, it is not possible to advise on the type of laboratory environment which will prevent absolutely the sensitisation of personnel. The advice which follows has as its objective the prevention or amelioration of symptoms in sensitised individuals. These measures may also have a beneficial effect in reducing the incidence of sensitisation, but there are limitations to the evidence that environmental measures will protect employees. However, there is little doubt that certain practices will reduce exposure to allergen-bearing dusts.

Monitoring

The sources of laboratory animal allergens have been considered in Section III. Allergens may be deposited onto laboratory animal food, litter or dust particles and become airborne during both animal and human activity in a laboratory animal room. Ventilation designed for the well-being of animals may contribute to the distribution of such allergen-bearing particles.

Standardised methods for measurement of allergen in air are becoming available. Typical animal room levels of allergen have been found to be in the order of a few micrograms/m³, although the range is quite wide. Given the limited information on the levels of allergen in animal room environments and their correlation with human sensitisation, the setting of hygiene standards at this stage would be inappropriate. There are a considerable number of allergens and their relative potencies and cross-reactivities are not known. There is also likely to be a degree of variation in individual susceptibility of employees. Assays of allergen in air are still being researched and validated, but could in the future find a place in assessment of animal room environments.

Working Environments

Exposure to laboratory animals during the course of work may occur in a number of different settings. It is useful to consider these different working environments separately in the categories described below. It is recognised that the facilities and practices in many existing working environments vary considerably. The advice in this section is practically based and must be adapted to the needs and individual differences of each situation, particularly with regard to practical constraints in existing facilities:

Recommended Procedures for the Working Environment

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<tr>
<th>Working Environment</th>
<th>Desirable Facilities and Suggested Procedures</th>
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<tbody>
<tr>
<td>Animal husbandry—keeping, breeding and cleaning</td>
<td>These areas should be segregated from changing rooms and uncontaminated areas. Staff should change into protective clothing and boots in a separate designated area and preferably wear a dust mask for all dry work, especially when clearing contaminated litter. Wet or absorbent methods are advised for cleaning excreta and urine.</td>
</tr>
<tr>
<td><strong>Experimental rooms—working or observation</strong></td>
<td>It is not envisaged that these rooms are used for report writing, etc. It is desirable for experimental rooms to have the minimum stocking density necessary for the studies in hand. Preferably these rooms should have entry and exit routines with a separate designated area for putting on and removing protective clothing. Ideally, dust masks, properly secured, should be worn and discarded before entering uncontaminated areas. Contaminated equipment should be cleaned before removal to uncontaminated areas.</td>
</tr>
<tr>
<td><strong>Holding and transport of animals</strong></td>
<td>The use of filtered boxes, segregated or filtered vehicles is preferable, and as far as practicable, holding areas within experimental rooms should be segregated. Flexible ordering and delivery systems are advisable to enable minimum stocking density. Separation of delivery routes from uncontaminated areas and general human contact is preferable.</td>
</tr>
<tr>
<td><strong>Handling of tissues, excretions, sera etc.</strong></td>
<td>All contamination should be kept to a minimum. Additional care is needed with allergen rich substances (e.g. the use of non-absorbent gloves, aprons etc.), particularly to avoid the formation of aerosols.</td>
</tr>
<tr>
<td><strong>Ancillary staff—(e.g. fitters, cleaners, secretaries etc.)</strong></td>
<td>Operations of ancillary staff should be planned taking into account the possibility of allergenic exposure. Information on procedures to be adopted with appropriate equipment should be provided. In certain areas, access should be restricted by special clearance permits, and limited to the minimum number of visits and personnel necessary.</td>
</tr>
<tr>
<td><strong>Uncontaminated areas—(offices, writing, rest room and eating areas)</strong></td>
<td>As far as possible there should be physical segregation of these areas and positive outward airflows. Protective working clothing and contaminated materials should not be brought into these areas.</td>
</tr>
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**Notes:**

**General** — The areas outlined above are separate environments each with their hazards and necessary precautions. It is helpful if they are clearly designated, perhaps by colour coding signs, so that staff are fully aware of the differences.

If a safe working environment can be provided by engineering means then the wearing of masks would be unnecessary. However, this is not practicable in all laboratory facilities and thus the use of personal protection, e.g. masks, is recommended. Further research on the use and effectiveness of masks may confirm the need for this measure in future.
Masks — There is as yet no validation of the efficiency of particular masks other than ventilated helmets. The following have been used:

i) For light or casual exposure for non-asthmatic personnel —
   - 3M-8500 — a light disposable dust mask for non-toxic substances
   - 3M-8800 — a heavier, longer, more durable mask
   - VigiloD — pleated and non-toxic particle masks

ii) For heavier exposure for non-asthmatic personnel —
   - 3M-8710 — a heavier mask with some re-use capacity, intended for toxic dusts
   - 3M-9920 — a heavier mask incorporating an exhalation valve, intended for welding fumes

There is anecdotal evidence that these masks may offer some protection to asthmatic personnel.

iii) For asthmatic personnel —
Where the relocation option has not been exercised (see Section V), the airstream helmet (Racal) offers good protection. Recent studies suggest that these can be very effective. Rigorous attention to usage and personal working practices may improve their effectiveness further. The final choice in any case will depend on user preference, tolerance, as well as efficacy, and should be decided on an individual basis.

Ventilation

Two alternative strategies may be deployed for ventilation: these are air dilution and allergen/dust suppression. Information based on current research is outlined below. The measures discussed below give an indication of current practice and may in any case need modification depending on the age and design of the animal facility and particular requirements for the care and maintenance of laboratory animals.

Typical air change rates found in laboratory animal facilities at present are currently about 10-15 air changes per hour with no provision for laminar flows. Even when introduced, laminar flow is often confounded by the strong thermals and eddies resulting from animal heat and activity. Experimental work has suggested that a delay in the onset of symptoms and a reduction in their severity can be obtained by increasing air change rates and reducing dust exposure. Increases in humidity levels will also suppress dust generation. Changes in either of these parameters have to take into account the well-being of the laboratory animals within the facility. Newly constructed animal room facilities with enhanced air flow rates with central roof entry and peripheral roof exhaust can overcome the thermal effects of animals at rest, but do not necessarily prevent the development of laboratory animal allergy in people working in these rooms. Roof to floor laminar flow can only be obtained with very high change rates (180 changes per hour), but this is not practicable on a routine basis because of high costs. Further research on ways of reducing atmospheric levels of antigen is necessary before any definitive view can be offered on the most effective way of reducing the exposure of employees working in these areas.
Work Stations

Difficulties experienced in controlling the presence of allergens in air in animal rooms have led to the development of work stations. These are segregated compartments or areas within animal rooms or near to them. Ventilatory protection can be achieved by blowing air across the work and away from workers or by local extraction ventilation. The former is cheaper and more efficient, but may create turbulence and contaminate the whole of a room. Again, further investigation of the optimum methods is necessary.

Considerations for New or Refurbished Facilities

Piecemeal modification of existing facilities is seldom efficient or cost effective in reducing the incidence of animal allergy. The following general principles could however be used in the design of new or extensively refurbished animal rooms when their construction is being considered:

i) Laboratory facilities should be designed as far as possible as a scientific facility dedicated to a particular use and not for any more general purpose.

ii) The principle of segregation is paramount. Ideally, animal work should be physically segregated from other areas of work insofar as is practicable. Different types of working areas should also be segregated from each other. Casual access to any laboratory area in which animals are used is undesirable.

iii) Ventilation should be planned taking into consideration the points outlined above. As more information becomes available on the optimum methods of ventilation, it may become possible to define more clearly the best type of system. However, this will always depend to some extent on the individual facility.
V. PERSONNEL ISSUES

The incidence of occupational allergy associated with exposure to laboratory animals raises a number of issues both in terms of the general company policy in relation to the handling of occupational problems, and in terms of special provisions which must be made for staff exposed to the risk of occupational allergy.

Company Employment Policy

The Health and Safety at Work etc. Act, 1974 details the responsibility of employers and employees in general terms. At common law, an employer owes his employees a duty to take reasonable care of their health and safety according to the circumstances so that an employer's business is carried out in such a way as not to expose the employees to an unnecessary risk. The fact that an employee contracts a condition or disease which is prescribed by regulations as due to the nature of his employment does not automatically make an employer liable at common law for the injury. The employee must still prove that the employer was negligent in exposing the employee to the risk of contracting such injury and proof of negligence will depend on considerations such as whether the employer maintained a safe system of work when the general practice of industry at this time will be relevant. In addition to the duty at common law, an employer has to observe a number of statutory provisions relating to the safety, health and welfare of his employees, the breach of which make him liable to prosecution under the Health and Safety at Work etc. Act, 1974 as well as to an action for damages.

Occupational asthma following exposure to laboratory animals has now been added to the list of prescribed diseases for industrial injury benefit. This makes it advisable for companies to prepare a general policy statement on this subject. Such a policy should include a statement of the company attitude to pre-employment selection and medical screening, medical surveillance during employment, relocation and dismissal. Detailed consideration of these various aspects follows below.

It is important that the subject of laboratory animal allergy is discussed with a prospective employee. This would refer to company policy and work practices. The interview should be conducted by the responsible manager or an appropriate member of the occupational health service, and the prospective employee should, depending on company practice, confirm that the communication has taken place while understanding that this does not in any way absolve the employer from liability.

Pre-employment Selection and Medical Screening

All candidates who are to work with laboratory animals should be medically assessed as part of the pre-employment selection before commencing their duties. Medical staff, as a result, would make a recommendation to management regarding the candidate's medical suitability. Refusal to employ an individual on the grounds of medical evidence is not a basis for discrimination in law, and therefore an employer is free not to employ staff on the basis of a medical recommendation with regard to likely susceptibility to laboratory animal allergy. On occasion, a prospective member of staff may be employed contrary to medical advice (for example, a career scientist involved in animal research). In such cases, the employer could be liable under common law unless it was reasonable to ignore the medical advice that was given. It is possible that an employer could be prosecuted under Section 2 of the Health and Safety at Work etc. Act, 1974, but if the injury was minor, risk of prosecution is low. Therefore the basis of the medical advice given is very important.
Medical Assessment

The content of the medical assessment may vary from company to company. It should always include a detailed occupational history with dates plus a questionnaire on medical history including details of any allergic conditions which have occurred with the time of occurrence, results of investigations and treatment past and present (see Appendix A). Consideration should be given to recommending rejection where there is a history of allergy to small animals or where candidates are suffering from active asthma or chronic skin disease.

Supplementary Pre-employment Screening

There are a number of investigations whose value in pre-employment screening is not yet fully defined. Investigations such as pulmonary function tests and skin prick tests which are being carried out by some companies may usefully contribute to the pre-employment medical assessment. Companies undertaking pulmonary function testing, e.g. vitalograph studies, at pre-employment, find them of value in confirming the respiratory state of the candidate. They also provide base-line figures against which any future changes may be assessed whatever the cause. Prick testing is being carried out by a few companies as an integral part of the pre-employment scheme to try to identify atopic individuals. Others use it more as part of prospective research to provide information on the usefulness of prick testing as a supplement to data from questionnaires and interviews. If it is validated, prick testing would provide a useful additional base-line and could be of assistance in identifying candidates who are at a higher risk of developing clinical symptoms at a later date.

Health Monitoring of Staff

Monitoring of exposed staff is advisable at annual intervals. The employee is constrained to comply with an employer's requirements (Health and Safety at Work etc. Act, 1974, Section 7, b). Employees should be asked to give their consent for invasive testing, but precedents are established for the use of invasive testing if related to a potential hazard. If an employee refuses a test which is a contractual requirement, this may constitute an act which terminates a contract (and this may be of importance in dismissal procedures). Even if the test is not a contractual requirement, the employee's refusal to co-operate in respect of protecting his own health gives grounds for employers to move or dismiss him. If an employee refuses to submit to invasive testing (regardless of contract), the employer still has a common law responsibility to protect him. In any event, the employee's refusal to co-operate would be contributory negligence and reduce the employer's liability.

The following monitoring of exposed staff is recommended:

a) An annual questionnaire similar to that in Appendix A

b) An abnormal pattern of sickness absence records should be taken into consideration

c) It is important to emphasise to all employees the need to report any untoward symptoms which may be of allergic origin to the occupational health staff.
The following supplementary tests may be considered to provide additional information (see also Supplementary Pre-employment Screening above).

i) Respiratory function testing; e.g. spirometry (FEV₁/FVC) or the use of peak flow measurement carried out by the employee over a period of time (throughout a shift in the workplace).

ii) Prick testing (see also Supplementary Pre-employment Screening above) is still being evaluated as a predictive test to identify atopic individuals. In the future its use with specific antigens (when they become generally available) may provide a useful diagnostic aid.

iii) Research is being carried out into the use of serum samples to serialise immunoglobulins and the identification of specific antibodies. These procedures may be of assistance in monitoring employees in the future.

**Policy on Identification of Occupational Allergy**

Where, on assessment, the symptoms are considered to be allergic, the following actions should be instigated immediately. A full relevant history should be taken and a clinical examination carried out with additional tests as is considered appropriate.

When the diagnosis of laboratory animal allergy is confirmed in an employee, an employer would be regarded as negligent if he kept that employee in the same work without ensuring his reasonable safety. Where minor symptoms are concerned, it is not the normal practice for companies to require employees to relocate, and the introduction of additional protective measures should make it possible for most individuals to continue in the same work. If the employee wishes to stay in a particular job with additional protection, the employer must ensure that the protection is used and institute procedures to confirm that this is the case.

The precautionary measures may include:

i) limiting the hours of exposure

ii) withdrawing the individual from those procedures most likely to put him at risk

iii) use of respiratory protection or such other protective measures as may seem appropriate which will be provided by the company

iv) working, where possible, using a work station or other safety cabinet

v) increased monitoring of individuals to assess the efficacy of protective measures and any possible progression of disease.

**Relocation**—It may become necessary to recommend relocation following a diagnosis of laboratory animal allergy in the following circumstances:

i) immediately following diagnosis where management, having received the recommendations of a medical advisor, believes that protective measures would not be sufficient to protect the individual from the risk of serious harm to his health or

ii) protective measures have been tried and proved ineffective for any reason, or

iii) where the individual requests relocation.
An employer owes a duty both in common law and under the Health and Safety at Work etc. Act, 1974 to remove an employee to a safer job or even to terminate his employment if the risk is too great. (This should be regarded as a fair dismissal provided there is no other alternative work available, and the employee's incapacity goes to the root of his employment contract, i.e. he is incapable of safely performing the work. Therefore to prevent an action being brought on these grounds, the medical evidence must be significant).

Considerations Relating to Relocation

i) When considered desirable, the opinion of an outside consultant to the company may be sought. Additionally, employees may seek a second opinion from a medical practitioner of their own choice which will be considered by the company's medical officer when making recommendations to the management.

ii) The company should make all reasonable endeavours to relocate the individual appropriately in full and proper consultation with the employee. In the event of an employee refusing to co-operate, a reasonable employer cannot permit him to remain exposed to the hazard. Section 2 of the Health and Safety at Work etc. Act, 1974 places a duty of care on the employer who, when presented with circumstances outlined above, has very little option but to insist on moving the employee. However, if relocation cannot be implemented successfully, there may be no alternative but to terminate the employment of the individual, if the risk is too great, on grounds of occupational ill health. Under these circumstances, normal procedures for the termination of employment in liaison with the company legal department should be implemented.

While the possible options for management of staff who develop occupational allergy are fairly clear-cut as outlined above, it is frequently less easy to resolve individual problems in practice. The advice outlined in this Section and Section IV on the control of animal room environments and the protection of sensitised individuals exposed to laboratory animals is intended to help to resolve some of these practical issues. It is, however, clear from a legal assessment of the problem that protection of the health of the individual is as important as protection of his employment.
Advisory note on Allergy to Laboratory Animals
2nd edition
1987
SUMMARY

This Advisory note outlines the pathogenesis and control of allergy to laboratory animals. Information is given on the responsibilities of employers and employees under the 1982 Prescribed Diseases Amendment Regulations and the Reporting of Injuries, Diseases and Dangerous Occurrences Regulations 1985.

The recommendation is made that companies should prepare, and discuss with managers, a company policy on allergy to laboratory animals and prepare a statement of working practices for issue to all staff working with animals.

The adoption of these measures should reduce the prevalence and severity of allergy to laboratory animals and should ensure that managers and staff fulfil their legal obligations with respect to this Prescribed Disease.

The advice given is based on currently available information. Clinical and experimental research is still in progress and this Advisory Note will be reviewed from time to time to ensure that statements made remain in line with the outcome of that research.
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1. INTRODUCTION

Allergy to laboratory animals is a common condition which may present with a variety of respiratory or cutaneous manifestations.

There have been a number of prevalence studies which suggest that about 20–30% of people exposed to small laboratory animals develop symptoms of some kind (1–9). Although the great majority of individuals who become sensitised do so during their first few years of exposure (4, 5), some people develop symptoms only after many years (6).

Symptoms may present singly or in various combinations. The most common symptom is rhinitis, i.e. blocked nose and sneezing, and this may be associated with irritation and watering of the eyes. Skin rashes are also common and take the form of urticaria or nettle rash, or papula or vesicular erythema (10). Wheals may develop on the skin around bites or scratches especially if the area is contaminated with urine or saliva from the animal (11). Some 3–12% of people develop the clinically more serious condition, allergic asthma (1–9). This may occur on its own or more usually in association with other symptoms and may present as an immediate or as a delayed reaction (5). The severity of these symptoms is variable depending on the sensitivity of the individual and the degree of exposure. It has been estimated that 48% of those with symptoms (9% of total exposed population) may have to cease working at least temporarily with animals (4). Systemic reactions, involving hypotension and bronchoconstriction, have been recorded but this anaphylactic type of reactivity seems to be an extremely rare manifestation of allergy to laboratory animals (12).

Different organisations have tackled the problem of animal allergy in a variety of ways and with varying degrees of success. The health and safety issues which require clarification are similar to those which arise from the employment of people for any work which has been shown to carry a potential risk to health. They cover personnel matters such as recruitment policies, pre-employment selection, health screening, redeployment implications and matters relating to the workplace, the standard of animal room facilities provided, and the working practices of the staff.

The employer must assure himself that he is doing everything that is reasonably practicable to reduce the incidence of new cases of sensitisation amongst his staff. In January 1981, a report was presented to Parliament by the Industrial Injuries Advisory Council on Occupational Asthma in which it was recommended that occupational asthma should become a prescribed disease in relation to exposure to, among other causative agents, ‘animals and insects’ in laboratories. This recommendation came into force in March 1982 (S.I. No. 249, 1982, Social Security Industrial Injuries Prescribed Diseases Amendment Regulations, 1982).

This Advisory Note reviews the present state of knowledge about allergy to laboratory animals and attempts to deal with the issues which inevitably arise within an organisation from an occupational condition of such prevalence. An employer has both statutory and common law duties to protect his employees. Legal advice has been sought to clarify certain points of possible disagreement arising between employer and employees, and these points have been clarified in the relevant part of this Advisory Note. However, as a general principle, an employer should take steps to protect his employee ‘so far as is reasonably practicable’. If an employee brings a civil action based on the negligence of an employer, evidence that the employer has been convicted of an offence under the Health and Safety at Work etc. Act, 1974, which involved a negligent act or omission will support his case. Case law on this point is as yet unclear. With this in mind, the following Advisory Note makes recommendations which should enable the responsible employer to conduct his business in a safe manner, so far as is reasonably practicable, and thereby fulfill both his legal obligation, and his wish to ensure safer working conditions for his staff.
In addition, the employer is now required to report formally to the Health and Safety Executive any new case of occupational asthma when the work involves exposure to animals bred and used for the purposes of research or education in laboratories. This obligation is detailed in the Reporting of Injuries, Diseases and Dangerous Occurrences Regulations (Riddor) 1985 [HSE 18 Occupational Disease Reporting] which came into force on 1 April 1986. The new system firmly places responsibility for reporting on employers.

II. DEFINITIONS

The terms below have been defined specifically for this Advisory Note. Some of the terms may have wider definitions or different uses elsewhere.

Allergen – an allergen is a substance which interacts with a specific antibody to elicit a biological response, that is, a hypersensitivity reaction. The term ‘allergen’ may also be used for a substance which elicits the production of an IgE class antibody.

Allergy and hypersensitivity – are used synonymously in this Advisory Note to describe a clinical syndrome which may include conjunctivitis, rhinitis, asthma and dermatoses induced by exposure to a specific allergen.

An allergic or hypersensitive individual may thus suffer clinical symptoms of allergic disease when exposed to the relevant allergens. This definition does not presuppose knowledge of the precise aetiology of the underlying mechanism, only that it is immunologically mediated.

Asthma – a syndrome characterised by rapidly reversible, paroxysmal dyspnoea caused by mechanical obstruction of the airways and hyper-reactivity to irritant stimuli.

Atopy – a form of immunological reactivity assessed by skin test reactions to common allergens (D. pteronyssinus; pollens; aspergillus; cladosporium; cat, dog or horse hair).

It should be noted that this immunological definition of atopy does not mean that the atopic subject has clinical symptoms of allergy, only that he is of atopic predisposition.

Chronic obstructive bronchitis – a chronic irreversible resistance to air flow in the bronchioles. The syndrome is characterised by cough and breathlessness.

ELISA – the enzyme-linked immunoabsorbent assay; an immunoassay using an enzyme label to measure antibody or antigen.

RAST – the radioallergosorbent technique; a radioimmunoassay for the measurement of allergen specific IgE antibodies.

RAST inhibition – a modification of the radioallergosorbent technique used to measure allergen concentrations.
III. ALLERGY TO LABORATORY ANIMALS - DISEASE AND PATHOGENESIS

It has been known for more than a century that contact with certain animal species can result in the development of allergic symptoms including asthma. The syndrome which develops in response to exposure to rodents (rats, mice and guinea-pigs) and rabbits has been well studied and the underlying immunological changes have been established. Formal recognition in the U.K. of allergy to laboratory animals as an occupational disease has been more recent culminating in its prescription in 1982.

Allergy to other animal species for example, monkeys (13) cats (1) and poultry (14), through occupational exposure is recognised but research studies are less advanced.

III.1 Immunological Studies

Allergy to laboratory animals is an allergic syndrome which shares with the common atopic diseases, hayfever and house dust mite allergy, a similar clinical picture and an IgE mediated pathogenesis.

Immunological studies have shown that over half the individuals who develop allergy to laboratory animals have IgE antibody specific for laboratory animal derived allergens which can be detected either by skin prick tests using appropriate reagents, or by immunoassay (2, 3, 8, 9, 15, 16, 17, 18, 19).

Neither technique will identify all individuals who are diagnosed as laboratory animal allergics; studies indicate that some 55% will be positive by skin test; 62% by immunoassay. However, for the asthmatic individuals, almost all give positive results in these two assays and the correlation between them is excellent.

Specific IgG antibodies are present in the serum of the majority of individuals affected by allergy to laboratory animals but also in a significant proportion of workers exposed to animal-derived allergens but exhibiting no clinical signs of allergy (3, 20). It is unlikely therefore that this class of antibody plays a role in the pathogenesis of allergy to laboratory animals and in fact, there is only one report in the literature of extrinsic allergic alveolitis due to exposure to laboratory animals (21). However, because this class of antibody reflects exposure, sequential serum IgG assays using radioimmunoassays or ELISA can be of value in monitoring the effectiveness of measures taken to reduce or eliminate exposure to animal-derived allergens.

III.2 Pathogenesis

The mast cell plays a central role in the pathogenesis of the common atopic diseases and, it is assumed, in allergy to laboratory animals also (22). These cells, found in the pulmonary lumen, in the mucosal and submucosal layers of the respiratory tract and in other target tissues such as skin and intestinal mucosa, contain the biochemical apparatus necessary to initiate the characteristic responses of an allergic subject to allergen.

The external membrane of the mast cell binds IgE tightly so that the cell surface is covered with molecules which recognise and combine with specific allergen. When an allergic subject is exposed to allergen adjacent IgE molecules are cross-linked by allergen stimulating the mast cell to release substances which, depending on the route by which allergen enters the body, can induce an attack of asthma, rhinitis or urticaria.
One of the fundamental characteristics of asthma and to some extent rhinitis is the hyper-responsiveness or hyper-reactivity of the airways to both specific (i.e. allergenic) and non-specific (irritant) stimuli (23). Particularly in asthmatic subjects the responsiveness of the airways to physical, chemical and pharmacological stimuli can be very much greater than that of non-asthmatics. This can be observed both as increased response to a stimulus and as a lowering of the threshold of sensitivity to the stimulus.

The pathological basis of this is not clear. However, hyper-reactivity correlates well with the severity of the disease and with frequency and extent of exposure to stimuli. Thus any measures that successfully reduce the exposure of subjects to allergen will tend to lower not only the frequency but also the severity of the response.

### III.3 Role of Atopy

The initial induction of antibody of the IgE immunoglobulin class is under complex genetic control. While it is clear that the majority of individuals can produce IgE class antibody to a wide range of allergens, one group of people do so more readily for reasons that are not fully understood. These people are called ‘atopics’ and they are characterised primarily by their reactivity to a range of allergens, a reactivity determined in part by the vigour with which they produce IgE antibody. This reactivity is utilized by skin testing to natural environmental allergens as a means of defining atopic predisposition (24).

The question then arises as to whether atopic individuals are more likely to become allergic to laboratory animals if exposed to them. A priori reasoning would indicate that this would be so, and, in fact, it now seems clear that an association does exist between the atopic state and the likelihood of an individual developing allergy to laboratory animals (2, 5, 25, 26), although not all studies support this conclusion (4).

Atopy is not however a sufficient determinant of the development of allergy to laboratory animals to justify exclusion of atopics from work which involves exposure to animals. Pre-employment medical examinations of individuals who may be exposed to animals (or animal-derived products) to identify atopy should, as indicated later in this document, be undertaken with a view to giving appropriate advice to an atopic person but not as a reason per se for exclusion from employment.

The rationale for this recommendation is based on the fact that some 33% of individuals will be deemed to be of atopic predisposition judged by family history and skin testing. Based on current knowledge, although up to 30% of these individuals may develop allergy to laboratory animals and 3–12% of them may experience asthmatic symptoms, 70% will not.

Exclusion of atopics from work with animals would impose a considerable and unjustified penalty upon this group.

Other factors probably influence the development of allergy to laboratory animals. These include exposure, both in terms of concentration and the length of time involved but it has not proved possible to quantify these influences yet. As noted earlier, several studies now indicate that the majority of individuals who develop allergy to laboratory animals do so in the first few years of exposure (4, 5), although rarely allergy may develop over a period which may be as long as 20 years (6).
III.4 Characterisation of allergens

Immunochemical studies have been reported which attempt to characterise the allergens responsible for the induction of the specific antibody response (11, 17, 27, 28, 29).

Epithelial cells (furs, hairs and dander) have long been recognised as important allergens (18, 19) but more recent studies stress the importance of urine as a primary source of allergenic protein derived from mice, rats and guinea pigs. The presence of allergens in the saliva of rats and in particular of guinea pigs has also been highlighted (19, 30, 31, 32).

The degree of excretion of allergenic proteins in the urine of rodents has been shown to be both age and sex determined. The highest concentrations of allergenic protein are to be found in the urine of post-pubertal male animals although allergens are also present in pre-pubertal males and females (11, 17).

Definition of the allergens derived from the rabbit is less well advanced. Studies in progress indicate that urine may not be the major source of allergens in this species; it seems likely that saliva is the source of a major allergen (33), and dander is also important (19).

III.5 Exposure to allergens

It is assumed that allergy is induced by the inhalation of allergens in the form of aerosols or as particles. Particles in excess of 30 microns are likely to be trapped in the nose and then swallowed, whereas those of less than 10 microns will be distributed throughout the respiratory tract.

Recommendations on the control of the working environment through engineering control or through the introduction of good working practices (Section IV.1 and IV.2) and for systems of personal protection (Section IV.3) are based on the assumption that these are the major routes of entry of allergen into the body.

Less is known about the importance of the skin as a route of entry of allergen but it seems appropriate to recommend (see Section VB) the use of protective gloves especially if skin is inflamed or abraded.
IV. ANIMAL ROOM ENVIRONMENTS

With the present state of knowledge of the incidence and control of allergy to laboratory animals, it is not possible to advise on the type of laboratory environment which will prevent absolutely the sensitisation of personnel. The advice which follows has as its objective the prevention of symptoms or amelioration in sensitised individuals. These measures may also have a beneficial effect in reducing the incidence of sensitisation and some data are available which indicate that this may be so. However, although the evidence that environmental measures will protect employees is still incomplete, there is little doubt that certain practices will reduce exposure to allergen-bearing dusts.

IV.1 Engineering Control

Exposure to allergens may be minimised by implementing engineering control systems. The most effective control is by containing animals within enclosures such as isolators or cage boxes with filter tops. If this is not practical adequate ventilation should be installed.

Experimental work has shown that general room ventilation without directed laminar flow is not effective in controlling exposures of people carrying out specific operations involving allergens but will lower the general background level in the area. This can be assisted by increasing the humidity but this must be compatible with the needs of the animals and the comfort of operators.

Effective control of specific operations can only be maintained by the use of laminar flows of the order of 0.5 metres per second. This level of air flow is necessary to overcome eddies and other air currents caused by thermals and movement within the area. It is usually not practical to provide this level of air flow over the whole area of an animal room because of the high costs involved, but an alternative is the provision of local work stations. These are segregated areas in part of the animal accommodation or adjacent to it. They should be designed to be large enough for the operations to be carried out but not overlarge to minimise the quantity of air required for adequate control.

Air flows may either be horizontal with air moving from the worker over the animal and into the extract with a velocity of about 0.5 metres per second or vertical with extraction through the work surface.

Whichever system is considered, expert advice should be obtained on the detail of design to maximise the efficacy of the control system. It must be compatible with the procedures which are being carried out in the area.

Piecemeal modification of existing facilities is unlikely to be efficient or cost effective in reducing the incidence of allergy to laboratory animals and therefore ventilation control, the principle of segregation of working areas from animal housing areas, and personal protective measures must be considered together.

In considering new or extensively refurbished facilities the following general principles apply.

i) Laboratory facilities should be designed as far as possible as a scientific facility dedicated to a particular use and not for any more general purpose.
ii) The principle of segregation is paramount. Ideally, animal work should be physically segregated from other areas of work insofar as is practicable. Different types of working areas should also be segregated from each other. Casual access to any laboratory area in which animals are used is undesirable.

iii) Ventilation should be planned taking into consideration the points outlined above.

IV.2 Working Environments

Exposure to laboratory animals during the course of work may occur in a number of different settings. It is useful to consider these different working environments separately in the categories described below. It is recognised that the facilities and practices in many existing working environments vary considerably. The advice in this section is practically based and must be adapted to the needs and individual differences of each situation, particularly with regard to practical constraints in existing facilities.

Recommended Procedures for the Working Environment

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<td>These areas should be segregated from changing rooms and uncontaminated areas. Staff should change into protective clothing and boots/footwear in a separate designated area and wear a dust mask for all dry work, especially when cleaning contaminated litter. Wet or absorbent methods are advised for cleaning excreta and urine. Some form of hair covering is recommended.</td>
</tr>
<tr>
<td>Experimental rooms - working or observation.</td>
<td>These rooms should not be used for report writing. It is desirable that the minimum stocking density for the studies in hand is maintained. Preferably these rooms should have entry and exit routines with a separate designated area for putting on and removing protective clothing. Ideally, dust masks, properly secured, should be worn and discarded before entering uncontaminated areas. Contaminated equipment should be cleaned before removal to uncontaminated areas.</td>
</tr>
<tr>
<td>Holding and transport of animals.</td>
<td>The use of filtered boxes and segregated or filtered vehicles is preferable. Flexible ordering and delivery systems are advisable to enable minimum stocking density. Separation of delivery routes from uncontaminated areas is advised. Only staff authorised to work in such areas should be allowed to be in the vicinity.</td>
</tr>
<tr>
<td>Handling of tissues, excreta and body fluids.</td>
<td>All contamination should be kept to a minimum. Additional care is needed with allergen rich material to avoid unnecessary spread (i.e. avoid dust clouds and aerosol formation). When there is a risk of heavy contamination of clothing by faeces or body fluids, a disposable absorbent faced plastic apron should be worn.</td>
</tr>
<tr>
<td>Working Environment</td>
<td>Desirable Facilities &amp; Suggested Procedures</td>
</tr>
<tr>
<td>---------------------</td>
<td>---------------------------------------------</td>
</tr>
<tr>
<td>Ancillary staff e.g.</td>
<td>Operations of ancillary staff should be planned taking into account the possibility of exposure to allergens. In certain areas, access should be restricted by special clearance permits, and limited to the minimum number of visits and personnel necessary.</td>
</tr>
<tr>
<td>maintenance, cleaners, secretaries.</td>
<td></td>
</tr>
<tr>
<td>Uncontaminated areas</td>
<td>As far as possible there should be physical segregation of these areas and positive outward airflows. Protective clothing and contaminated materials (including paperwork) should not be brought into these areas.</td>
</tr>
<tr>
<td>(offices, writing, rest room and eating areas).</td>
<td></td>
</tr>
</tbody>
</table>

### IV.3 Personal Protection

Whenever practical engineering control methods should be used to minimise the exposure of personnel to allergens. However in some circumstances it will also be necessary to provide personal respiratory protection.

Respiratory protection should be of a type which is designated for use with toxic dusts i.e. one of those listed in Part 6 of the H.S.E. Certificate of Approval (Respiratory Protective Equipment). In practice it is found that disposable masks (e.g. 3M 8800 or 8810) are the most comfortable to wear and acceptable to the workforce.

Alternatively high efficiency ventilated visors and helmets, as listed in part 8 of the Certificate of Approval can be recommended. These have been found to be readily accepted and very effective in practice, even with sensitised personnel (34).

Dust masks which do not meet these specifications e.g. surgeons masks and nuisance dust masks should not be recommended.

Whenever respiratory protection is issued arrangements should be made to store the equipment, when not in use, in a clean area away from contamination with allergens. If powered helmets are recommended there should be appropriate systems to ensure adequate maintenance. These must include regular checks on the efficiency of the batteries and the adoption of a procedure for changing the filters at appropriate intervals. These measures, correctly used, can be helpful in the management of allergy to laboratory animals.

### IV.4 Air Sampling

Exposure to animal-derived allergens can be minimised by attention to engineering control of facilities in which animals are housed and used, by the introduction of good working practices and by personal protection as outlined in Section IV.1-3 above.

An important advance in relation to control of the working environment has been the development of methods by which air may be sampled and assayed for concentrations of animal-derived allergens. These methods may be used to monitor the effectiveness of control procedures introduced.
The source of laboratory animal derived allergens have been considered in Section III. Allergens may be deposited on to laboratory animal food, litter or dust particles and become airborne during both animal and human activity in a laboratory animal room. Ventilation designed for the well-being of animals may contribute to the distribution of such allergen-bearing particles. Methods are now available for measurement of allergen levels in the air (35, 36, 37, 38). These are based on the use of the ELISA technique or RAST inhibition to estimate levels of allergen collected using various types of filters or impactors.

Results indicate that wide ranging variations in concentrations of allergens will occur, depending on stocking densities, diurnal variation in animal activity, the entry of staff into the rooms, as well as by more fundamental differences in air control engineering.

Information is lacking on the quantitative relationships between levels of allergens and sensitisation of individuals or provocation of symptoms in the previously sensitised. The setting of hygiene standards is therefore neither appropriate nor possible at this time.

Immunoassay data show that a more relevant estimate of individual exposure to animal-derived allergens may be made by estimation of levels based on personal sampling monitors. Results indicate wide variations in exposure concentrations but in general estimated concentrations are significantly higher than those recorded from room samplers (35).
V. PERSONNEL ISSUES

The incidence of occupational allergy associated with exposure to laboratory animals raises a number of issues both in terms of the general company policy in relation to the handling of occupational problems, and in terms of special provisions which must be made for staff exposed to the risk of occupational allergy.

It would seem appropriate for companies to prepare a general policy statement on this subject for the guidance of managers and to draw up a statement outlining recommended working practices which if adopted, would serve to minimize risk to employees. The latter documentation should be made available to all new staff and to those already employed in areas where there might be exposure to animals. Staff should also be made aware that the company has a policy on this topic and managers should be prepared to discuss the main policy issues with them. A continuing education programme would be advisable and serve to re-enforce the need for both managers and staff to adopt safe working practices. This section gives guidance on these matters.

A. Policy Documents

A1. Company Employment Policy

The Health and Safety at Work etc. Act, 1974, details the responsibility of employers and employees in general terms. At common law, an employer owes his employees a duty to take reasonable care of their health and safety according to the circumstances so that an employer's business is carried out in such a way as not to expose the employees to an unnecessary risk. The fact that an employee contracts a condition or disease which is prescribed by regulations as due to the nature of his employment does not automatically make the employer liable at common law for the injury. The employee must still prove that the employer was negligent in exposing the employee to the risk of contracting such injury and proof of negligence will depend on considerations such as whether the employer maintained a safe system of work. The general practice of industry at the appropriate time will be relevant to judgement in these matters. In addition to his duty at common law, an employer has to observe a number of statutory provisions relating to the safety, health and welfare of his employees, the breach of which make him liable to prosecution under the Health and Safety at Work etc. Act, 1974 as well as to an action for damages.

Occupational asthma following exposure to laboratory animals has now been added to the list of prescribed diseases for industrial injury benefit. This makes it advisable for companies to prepare a general policy statement on this subject. Such a policy should include a statement of the company attitude to pre-employment selection and medical screening, medical surveillance during employment, relocation and dismissal. Detailed consideration of these various aspects follows below.

It is important that the subject of allergy to laboratory animals is discussed with a prospective employee. This would refer to company policy and work practices. The interview should be conducted by the responsible manager or an appropriate member of the occupational health service, and the prospective employee should, depending on company practice, confirm that the communication has taken place while understanding that this does not in any way absolve the employer from liability.
A2. Pre-employment Selection and Medical Screening

All candidates who are to work with laboratory animals should be medically assessed as part of the pre-employment selection before commencing their duties. Medical staff, as a result, would make a recommendation to management regarding the candidate’s medical suitability. Refusal to employ an individual on the grounds of medical evidence is not a basis for discrimination in law, and therefore an employer is free not to employ staff on the basis of a medical recommendation with regard to likely susceptibility to allergy to laboratory animals. Occasionally, a prospective member of staff may be employed contrary to medical advice (for example, a career scientist involved in animal research). In such cases, the employer could be liable under common law (provided that the requirements for negligence with respect to working conditions were fulfilled) unless it was reasonable to ignore the medical advice that was given. It is possible that an employer could be prosecuted under Section 2 of the Health and Safety at Work etc. Act, 1974, but if the injury were minor, risk of prosecution is low. Therefore the basis of the medical advice given is very important.

Existing members of staff who transfer to jobs working with animals should be assessed before exposure to animals commences in a similar fashion to those first joining the company.

A3. Medical Assessment

The content of the medical assessment may vary from company to company. It should always include a detailed occupational history with dates plus a questionnaire on medical history including details of any allergic conditions which have occurred, with the time of occurrence, results of investigations and treatment past and present (see Appendix).

Consideration should be given to recommending rejection where there is a history of allergy to small laboratory animals or where candidates are suffering from chronic skin disease, asthma or other cardio-respiratory disorders likely to make the candidate more susceptible to the induction or the consequences of allergy to laboratory animals (39, 40).

A4. Supplementary Pre-employment Screening

There are a number of investigations the value of which in pre-employment screening is not yet fully defined. Investigations such as pulmonary function tests and skin prick tests which are being carried out by some companies may usefully contribute to the pre-employment medical assessment. Atopics identified by skin prick testing should be warned of the increased chance of developing the disease early in their work with animals. Companies undertaking pulmonary function testing, e.g. vitalograph studies, at pre-employment, find them of value in confirming the respiratory state of the candidate. They also provide base-line figures against which any future changes may be assessed whatever the cause. Skin prick testing is being carried out by a few companies as an integral part of the pre-employment scheme to try to identify atopic individuals.

Taken together with a full family and personal history record, skin prick tests using common environmental allergens are of value in identifying atopic individuals. Preliminary evidence indicates that the majority of those with symptoms due to animals are also atopic as shown by skin tests to either grass pollen or house dust mite.
Prick testing using specific allergens derived from laboratory animals serves to identify candidates who are already allergic to these species. Skin test reagents utilising epithelial allergens derived from laboratory animals are available and are being used by some companies. These reagents serve to identify candidates who are already allergic to these species and it would seem inadvisable for such persons to be employed in positions which necessarily involve contact with animals.

A5. Health Monitoring of Staff

Monitoring of exposed staff is advisable at annual intervals. The following should be considered.

a) An annual questionnaire similar to that outlined in the Appendix to this Advisory Note.

b) An abnormal pattern of sickness absence records (duration and/or frequency) should be taken into consideration.

c) It is important to emphasise to all employees the need to report any untoward symptoms which may be of allergic origin to the occupational health staff.

Supplementary tests and investigations provide additional information and are being used by a number of companies. Although helpful in the diagnosis of allergy to laboratory animals and in staff monitoring, these tests should not be regarded as mandatory.

i) Skin Prick Testing

The use of diagnostic skin prick testing has been established as a routine in several companies. Allergen solutions derived from epithelial tissues, hair or fur which are of value for the diagnosis of allergy to laboratory animals are available. There is no commercial supplier in the UK of urinary allergen skin test reagents.

ii) Antibody Assays

The RAST is of value in the monitoring of staff for the development of allergy to laboratory animals. It measures IgE antibody and results correlate well both with appropriate skin tests (i) above and with clinical history.

Assays are also available for the measurement of IgG antibody in the serum of staff who are exposed to animals. The general view at the present time is that monitoring staff for IgG antibody can be of value in assessing exposure and evaluating the effect of control procedures which might have been introduced to limit staff exposure.

iii) Respiratory function

Peak flow measurements carried out by the employee over a period of time (for example, through a shift in the workplace) have been found to be of value in monitoring the relationship between exposure and symptoms.

Some companies assess respiratory function by spirometry (FEV₁/FVC) to give an indication of any decline in overall respiratory performance.
The decision as to whether the above tests are essential for the care of the individual and for the management of his condition rests with the medical advisor. The employee is constrained to comply with an employer's requirements (Health and Safety at Work etc. Act, 1974, Section 7, b). Employees should be asked to give their consent for invasive testing, but precedents are established for the use of invasive testing if related to a potential hazard. If an employee refuses a test which is a contractual requirement, this may constitute an act which terminates a contract (and this may be of importance in dismissal procedures). Even if the test is not a contractual requirement, the employee's refusal to co-operate in respect of protecting his own health gives grounds for employers to move or dismiss him. If an employee refuses to submit to invasive testing (regardless of contract), the employer still has a common law responsibility to protect him. In any event, the employee's refusal to co-operate would be contributory negligence and reduces the employer's liability.

A6. Policy on Identification of Occupational Allergy

Where, on assessment, the symptoms are considered to be allergic, the following actions should be instigated immediately. A full relevant history should be taken and a clinical examination carried out with additional tests as is considered appropriate.

When the diagnosis of allergy to laboratory animals is confirmed in an employee, an employer would be regarded as negligent if he kept that employee in the same work without ensuring his reasonable safety. Where minor symptoms are concerned, it is not the normal practice for companies to require employees to relocate, and the introduction of additional protective measures should make it possible for most individuals to continue in the same work. If the employee wishes to stay in a particular job with additional protection, the employer must ensure that the protection is used and institute procedures to confirm that this is the case.

The precautionary measures should include one or more of the following:

i) limiting the hours of exposure
ii) withdrawing the individual from those procedures most likely to put him at risk
iii) use of respiratory protection or such other protective measures as may seem appropriate which will be provided by the company
iv) working, where possible, using a work station or other safety cabinet
v) increased monitoring of individuals to assess the efficacy of protective measures and any possible progression of disease.

It may become necessary to recommend relocation following a diagnosis of allergy to laboratory animals in the following circumstances:

i) immediately following diagnosis where management, having received the recommendations of a medical advisor, believes that protective measures would not be sufficient to protect the individual from the risk of serious harm to his health, or
ii) protective measures have been tried and proved ineffective for any reason, or
iii) where the individual requests relocation.

An employer owes a duty both in common law and under the Health and Safety at Work etc. Act, 1974, to remove an employee to a safer job or even to terminate his employment if the risk is too great. (This should be regarded as a fair dismissal provided there is no other alternative work available, and the employee's incapacity goes to the root of his employment contract, i.e. he is incapable of safely performing the work. Therefore to prevent an action being brought on these grounds, the medical evidence must be significant.)
A7. Considerations Relating to Relocation

i) When considered desirable, the opinion of an outside consultant to the company may be sought. Additionally, employees may seek a second opinion from a medical practitioner of their own choice which will be considered by the company’s medical advisor when making recommendations to the management.

ii) The company should make all reasonable endeavours to relocate the individual appropriately in full and proper consultation with the employee. In the event of an employee refusing to co-operate, a reasonable employer cannot permit him to remain exposed to the hazard. Section 2 of the Health and Safety at Work etc. Act, 1974 places a duty of care on the employer who, when presented with circumstances outlined above, has very little option but to insist on moving the employee. However, if relocation cannot be implemented successfully, there may be no alternative but to terminate the employment of the individual, if the risk is to great, on grounds of occupational ill health.

Under these circumstances, normal procedures for the termination of employment in liaison with the company legal department should be implemented.

While the possible options for management of staff who develop occupational allergy are fairly clear-cut as outlined above, it is frequently less easy to resolve individual problems in practice. The advice outlined in this Section and Section IV on the control of animal room environments and the protection of sensitised individuals exposed to laboratory animals is intended to help to resolve some of these practical issues. It is, however, clear from a legal assessment of the problem that protection of the health of the individual is as important as protection of his employment.
B. STATEMENT OF WORKING PRACTICES

A practical statement on working practices should be drawn up by the company and made available to all staff working with animals.

An example of such a statement follows but details and emphasis will have to be modified by each company in accordance with its facilities and organisational structure.

PROCEDURES FOR THE PROTECTION OF STAFF AGAINST ALLERGY TO LABORATORY ANIMALS

Introduction

This document lays out the procedures for the personal protection which will be adopted by personnel working in or visiting animal areas where rodents or rabbits are present. Animal areas are defined as any room or laboratory where live animals are housed, transported in open containers, handled, or used for experimental procedures.

Special adaptation of these procedures may be necessary in areas where other animals are housed. Normally, these procedures will apply to all personnel in a defined area. However, if the activity has been shown only to affect those personnel directly concerned with animals, these procedures may be modified by local written instructions.

Procedures

1. Laboratory coats and other outer clothing must be removed before entering the area. Eating, drinking, smoking and the application of cosmetics are not permitted in animal areas.

2. On entering the area all personnel shall:
   2.1. Put on protective clothing which has been approved for use in that area. The type of clothing will vary and may include long sleeved gowns, laboratory coats, boiler suits etc. but will be clearly distinguishable from similar garments worn elsewhere on site, usually by colour. Where there is a risk of heavy contamination of clothing by faeces or body fluids, a disposable absorbent faced plastic apron shall be worn. (NB The absorbent side should be worn outwards.) Hair cover is recommended.
   2.2. Wear approved respiratory protection. If masks are worn they should be well fitted.
   2.3. Put on surgical gloves if the animals are to be handled.

3. All protective clothing and respiratory protection equipment should be stored outside the area, or kept in such a manner that contamination with allergens is minimised.

4. When working with animals, staff should make every effort to minimise the generation of allergens and contain any allergens which may have been generated during the procedure. Where possible all procedures should take place in a suitably ventilated area. Animals should be handled quietly and gently. Where animals are being clipped or shaved, the fur should first be dampened and/or the clippings collected by a vacuum.
Whenever possible dissection should take place in a designated area in the animal facility and tissues transported in covered containers.

5. On leaving the area, personnel should remove all protective clothing, respiratory protection and then wash their hands. Disposable garments and masks should be placed in a polythene bag for disposal. Where clothing is to be re-used, it should be stored separately from fresh clothing in such a manner as to minimise contamination. Suitable arrangements should be made for the regular collection and laundering of contaminated clothing.

6. Normally animals should not be transported outside designated areas. Whenever intact animals have to be transported, approved "filter top" boxes should be used.
APPENDIX OF SAMPLE QUESTIONNAIRES

This Appendix gives information on the type of questionnaires suitable for use for pre-employment and in-employment staff. The questionnaires are designed to elicit information on the individual's susceptibility to clinical allergic conditions involving the respiratory tract and skin and more specifically, to symptoms relating to exposure to animals.
ALLERGY TO LABORATORY ANIMALS

PRE-EMPLOYMENT QUESTIONNAIRE

Name: Date of Birth:

PLEASE ANSWER ALL THE QUESTIONS EITHER YES OR NO

1. Have you ever suffered from any of these symptoms (except when you had a cold or other respiratory infection)?

   (i) Tightness of chest/wheezing/difficulty in breathing
       If YES, have you suffered from any of these symptoms in the last 12 months?

   (ii) Eczema or allergic skin rashes
       If YES, have you suffered from either of these symptoms in the last 12 months?

   (iii) Repeated attacks of sneezing, running or blocked nose
       If YES, have you suffered from any of these symptoms in the last 12 months?

   (iv) Watery or itchy eyes
       If YES, have you suffered from either of these symptoms in the last 12 months?

2. Did you experience any of the symptoms mentioned in question 1 when in contact with animals at home or at work?

Comments
(re species etc)
3. Do you suffer from:

(i) Hay Fever

(ii) Asthma

(iii) Other Allergic Diseases

This individual has allergy to laboratory animals

(To be completed by Medical Officer)

NOTE
If immunological measurements or lung function tests have been performed as part of the medical assessment (see Section V, A4, A5) a record of findings should be made and filed with each questionnaire.
3. Since the last interview have you experienced any of the following symptoms when exposed to animals (except when you had a cold or other respiratory infection)?

(i) Tightness of chest/wheezing/difficulty in breathing  □ □

(ii) Eczema or allergic skin rashes  □ □

(iii) Repeated attacks of sneezing, running/blocked nose  □ □

(iv) Watery, itchy eyes  □ □

4. Do you wear respiratory protection when working with animals

<table>
<thead>
<tr>
<th></th>
<th>NEVER</th>
<th>SOMETIMES</th>
<th>EVERY TIME</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paper Mask</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Air fed purification</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Helmet or hood</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>eg one of the type</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>produced by ‘Racal’</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
</tbody>
</table>

5. If you no longer work with animals when did you stop and why?

<table>
<thead>
<tr>
<th>DATE</th>
<th>REASON</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

6. Do you suffer from:

(i) Hay fever  □ □

(ii) Asthma  □ □

   ) not due  □ □

   ) to exposure  □ □

(iii) Other allergic diseases  □ □

   ) to animals  □ □

This individual has allergy to laboratory animals  □ □

(To be completed by Medical Officer)

NOTE
If immunological measurements or lung function tests have been performed as part of the medical assessment (see Section V, A4, A5) a record of findings should be made and filed with each questionnaire.
ALLERGY TO LABORATORY ANIMALS

FOLLOW-UP QUESTIONNAIRE

Name: Date of Birth:

Dept: Date of starting with company:

IF YOU HAVE NOT BEEN EXPOSED TO GUINEA PIGS, HAMSTERS, MICE, RABBITS, RATS, CATS OR DOGS SINCE YOUR LAST INTERVIEW, PLEASE GO STRAIGHT TO QUESTION 5

1. How often have you been in contact with guinea pigs, hamsters, mice, rabbits, rats, cats or dogs?

   YES  NO

   Daily (continuously)

   Daily (intermittently)

   Weekly (once/twice a week)

   Monthly (once/twice a month)

   Less than once a month

2. Since your last interview what activities have you performed?

   YES  NO

   Feeding and cleaning

   Weighing

   Dosing (by any route)

   Examination

   Clipping and shaving

   Surgery

   Bleeding

   Post-Mortem
APPENDIX 2

In-house LAA - specific questionnaire
LABORATORY ANIMAL DANDER ALLERGY

<table>
<thead>
<tr>
<th>Question</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Department:</td>
<td></td>
</tr>
<tr>
<td>2. Serial number</td>
<td></td>
</tr>
<tr>
<td>3. Age (Years)</td>
<td></td>
</tr>
<tr>
<td>4. Sex (M=1, F=2)</td>
<td></td>
</tr>
<tr>
<td>5. Date started with Fisons</td>
<td></td>
</tr>
<tr>
<td>2. Animal Experimental worker - graduate/or equivalent</td>
<td></td>
</tr>
<tr>
<td>3. - assistant</td>
<td></td>
</tr>
<tr>
<td>4. Auxiliary</td>
<td></td>
</tr>
<tr>
<td>5. Other (please specify: __________________)</td>
<td></td>
</tr>
<tr>
<td>6. Work unconnected with animals (please specify: __________________)</td>
<td></td>
</tr>
<tr>
<td>7. Has the patient had any significant medical history previous to Fisons? 1=Yes, 2=No</td>
<td></td>
</tr>
<tr>
<td>8. Is the patient atopic? 1=Yes, 2=No</td>
<td></td>
</tr>
</tbody>
</table>
| 9. Has the patient any significant family history of allergy? 1=Yes, 2=No  
  (i.e. grandparents, parents, aunts/uncles, siblings, children) |         |
| 10. Previous occupation (with dates)                                                        |         |
| 1. __________________________________________________________________                   |         |
| 2. __________________________________________________________________                   |         |
| 3. __________________________________________________________________                   |         |
| 4. __________________________________________________________________                   |         |
| 11. Have you ever developed any symptoms due to an allergy? 1=Yes, 2=No  
  If so, when: _________________________                                                  |         |
| 12. What animals/birds have you kept?                                                       |         |
| 13. Were any allergic symptoms related to these pets? 1=Yes, 2=No                           |         |
| 14. Did this occur before contact with experimental animals? 1=Yes, 2=No                    |         |
14. Have you ever entered animal areas regularly? 1=Yes, 2=No

15. Has your work brought you into physical contact with experimental animals or their tissues? 1=Yes, 2=No

16. If so, were you concerned with:

1. Caring for animals
2. Carrying out experiments on animals
3. Handling animal tissues or fluids
4. Laboratory auxiliary
5. Other (specify: _____________________)

17. Date of first contact with experimental animals/tissues

18. Which animals have you worked with: (1=Yes, 2=No)

A 01 Cat
B 02 Rat
C 03 Rabbit
D 04 Goat
E 05 Guinea pig
F 06 Horse
G 07 Dog
H 08 Mouse
I 09 Ferret
J 10 Sheep
K 11 Pig
L 12 Other, specify: _____________________

19. Did you ever have any of these symptoms? 1=Yes, 2=No

1. Eye irritation
2. Nose running or sneezing
3. Palate itching
4. Chest wheezing
5. Skin reaction

20. Have any of these symptoms been associated with your work? 1=Yes, 2=No

1. Eye irritation
2. Nose running or sneezing
3. Palate itching
4. Chest wheezing
5. Skin reaction

IF NO SYMPTOMS OCCUR PROCEED TO QUESTION 32
If symptoms do occur, how long is it before they show:

1. Eye irritation
2. Nose running or sneezing
3. Palate itching
4. Chest wheezing
5. Skin reaction

Which symptom(s) first appeared and when:

1. Eye irritation
2. Nose running or sneezing
3. Palate itching
4. Chest wheezing
5. Skin reaction

Which animal(s) first appeared to cause symptom(s)?

What occupation/department were you in:

Have subsequent symptoms appeared due to contact with animals? 1=Yes, 2=No

If 'No', go to Question 30

If 'Yes', what symptoms? (Put '1' in box number corresponding to symptom numbers in question 21)

Which animals appeared to cause these symptoms?

When did these symptoms first occur: (date)

What occupation/department were you in:

Have you changed job/department due to your symptoms? 1=Yes, 2=No

If so, when did you change your job
12. Do you use any of the following protective equipment regularly?

<table>
<thead>
<tr>
<th>Equipment</th>
<th>1=Yes</th>
<th>2=No</th>
<th>Is it effective?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laminar flow cabinets</td>
<td>7</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Dri-nasal dust mask</td>
<td></td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Airstream helmet</td>
<td></td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Gloves</td>
<td></td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Other (specify: ___________</td>
<td></td>
<td>16</td>
<td></td>
</tr>
</tbody>
</table>

33. Do you take any drugs before work to prevent symptoms? 1=Yes, 2=No

Please specify: ____________________________

34. Skin Test Data

<table>
<thead>
<tr>
<th>Substance</th>
<th>Pre-emp.</th>
<th>Previous</th>
<th>Now</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>25</td>
<td>31</td>
<td>37</td>
</tr>
<tr>
<td>G/Saline</td>
<td>38</td>
<td>39</td>
<td>40</td>
</tr>
<tr>
<td>Grass mix</td>
<td></td>
<td></td>
<td>43</td>
</tr>
<tr>
<td>House Dust Mite</td>
<td></td>
<td></td>
<td>46</td>
</tr>
<tr>
<td>House Dust</td>
<td></td>
<td></td>
<td>49</td>
</tr>
<tr>
<td>Guinea pig</td>
<td></td>
<td></td>
<td>52</td>
</tr>
<tr>
<td>Mouse</td>
<td></td>
<td></td>
<td>55</td>
</tr>
<tr>
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<tr>
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<td>Horse</td>
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<td>Rabbit</td>
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<td>Histamine</td>
<td></td>
<td></td>
<td>73</td>
</tr>
<tr>
<td>Other: (specify)</td>
<td>B 9 10</td>
<td>11 16 21</td>
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35. Lung Function Data

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<th>Pre-emp.</th>
<th>Previous</th>
<th>Now</th>
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</table>

<table>
<thead>
<tr>
<th>F.E.V.(_1) (l)</th>
<th>Actual</th>
<th>Expected</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>*</td>
<td>28</td>
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<table>
<thead>
<tr>
<th>F.V.C. (l)</th>
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<thead>
<tr>
<th>F.E.V.(_1)/F.V.C. %</th>
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<th></th>
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<tbody>
<tr>
<td></td>
<td>9</td>
<td>12</td>
<td>15</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>T(_1) (mmol/min/kPa)</th>
<th>Actual</th>
<th>Expected</th>
</tr>
</thead>
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<tr>
<td></td>
<td>*</td>
<td>20</td>
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<tr>
<td></td>
<td>*</td>
<td>45</td>
</tr>
</tbody>
</table>
APPENDIX 3

Follow-up questionnaire
(Ch. 4)
**SUPPLEMENTARY QUESTIONNAIRE**

1. Since the start of 1980 have you developed any allergies?  
   Ring as appropriate  
   
   Y/N

2. Do you think any of these allergies are due to your work with animals?  
   Ring as appropriate  
   
   Y/N

If you have developed any symptoms at all, only since the start of 1980 you should have answered the appropriate questions in the previous questionnaire and you do not need to continue here. **THE NEXT SECTION IS ONLY FOR THOSE WHO ALREADY HAD SYMPTOMS BEFORE 1980 WHICH THEY ASCRIBED TO LABORATORY ANIMALS.**

3. Since 1980 what new symptoms have appeared?
   
   1. Eye irritation  
      Ring as appropriate  
      
      Y/N  
   
   2. Nose running or sneezing  
      Ring as appropriate  
      
      Y/N  
   
   3. Palate itching  
      Ring as appropriate  
      
      Y/N  
   
   4. Chest wheezing  
      Ring as appropriate  
      
      Y/N  
   
   5. Cough  
      Ring as appropriate  
      
      Y/N  
   
   6. Skin reaction  
      Ring as appropriate  
      
      Y/N  

4. What symptoms did you have before 1980?
   
   1. Eye irritation  
      Ring as appropriate  
      
      Y/N  
   
   2. Nose running or sneezing  
      Ring as appropriate  
      
      Y/N  
   
   3. Palate itching  
      Ring as appropriate  
      
      Y/N  
   
   4. Chest wheezing  
      Ring as appropriate  
      
      Y/N  
   
   5. Cough  
      Ring as appropriate  
      
      Y/N  
   
   6. Skin reaction  
      Ring as appropriate  
      
      Y/N  

5. Did you change or modify your work because of these problems since 1980?  
   Ring as appropriate  
   
   Y/N

   if YES when?  
   
<table>
<thead>
<tr>
<th>d</th>
<th>m</th>
<th>y</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
6. Have the symptoms generally got worse since 1980 in terms of severity? Y/N
7. Have the symptoms generally got better since 1980 in terms of severity? Y/N
8. Have the symptoms got better since 1980 in terms of frequency? Y/N
9. Have the symptoms got worse since 1980 in terms of frequency? Y/N
APPENDIX 4

Screening questionnaire for periodic surveillance
LAA - Annual Surveillance Questionnaire

Please answer these questions for the last 12 months or since you were last screened.

1. Have you developed any of these symptoms?
   1. Eye irritation Y/N
   2. Nose running or sneezing Y/N
   3. Palate itching Y/N
   4. Chest wheezing Y/N
   5. Cough Y/N
   6. Skin irritation Y/N

2. Do you attribute any of these symptoms to your work? Y/N

   If YES, insert here number or numbers above ........................................

3. If YES to question 2, do you remember when the symptoms started

<table>
<thead>
<tr>
<th>DAY</th>
<th>MONTH</th>
<th>YEAR</th>
</tr>
</thead>
</table>

   If YES to question 2, have the symptoms worsened Y/N

Thank you for completing the questionnaire. Your answers will be reviewed and you will be contacted automatically for further investigations if necessary. If you wish to discuss your health or LAA with O.H. staff anyway please indicate here Y/N
APPENDIX 5
Internal policy and information document
LAA Division Policy

This policy outlines the actions undertaken and the guidance provided by the Division to discharge its responsibilities for the Health and Safety of personnel working with Laboratory animals, including the requirements of the Control of Substances Hazardous to health Regulations 1989 (C.O.S.H.H).

1. **General Policy**

1.1 **Recruitment**

Persons with a previous history of allergic disease to animals or current history of asthma are excluded from jobs involving exposure to animals or their tissues. It does not seem reasonable at present, to discriminate against people because they are atopic*. However they are advised that they are at some increased risk of developing the more severe manifestations of LAA as compared with non-atopic people.

1.2 **Relocation**

Persons who develop symptoms of laboratory animal allergy at work, which materially disturb their good health or ability to work efficiently, will be transferred to other jobs when practicable. Other persons, who may be asymptomatic, may need to be transferred if they show deterioration in lung function tests taken at work that can be reasonably ascribed to animal exposure.

Whilst a sympathetic relocation policy is the preferred method of handling this problem, it is difficult to require of the patient whose career is in animal work, (e.g. a specialist biologist, particularly if his career is well advanced). It is therefore acceptable to have a trial of the use of effective personal protection combined with job modification as outlined in the next section. If good protection is obtained on trial, relocation may be deferred indefinitely.

1.3 **Personal Protection (PPE) and Job Modification**

The present state of knowledge of science in this field does not permit full reliance to be placed upon general or local ventilation for the suppression of LAA although such ventilation is, in theory, inherently superior to personal protective equipment (PPE). Therefore reliance must be placed on personal protection to a considerable extent. For sensitised personnel, who express a wish to have a trial of PPE, protection using a

* allergic to grass pollen, house dust mite etc.
ventilated helmet may be attempted. This measure may be combined with job modification to reduce exposure. The level of protection must be carefully assessed and relocation enforced if protection is not substantially complete. For all other animal exposed personnel (including fitters and others with intermittent animal contact) a mask or helmet must be worn in areas where animal exposure is likely to occur. Gloves and suitable overclothing must be worn.

Dispensation from these requirements may be given by departmental managers in consultation with the O.H. department for particular tasks considered to carry low risk. However such dispensation will not be given lightly.

1.4 Information and Education

The results of surveys will be made available to staff generally and specifically to staff representatives in Health and Safety Committees.

2. Medical Policy

2.1 Surveillance

A surveillance programme has been developed and maintained. The purpose of this continued monitoring is to identify new cases of LAA and to ensure that the animal exposed workforce show no significant long term or permanent decrease in lung function when compared with non-exposed personnel. The technical aspects of this surveillance, particularly in regard of significant sub-groups of the exposed population is fairly complex and will not be discussed further here.

3. Systems Control of Laboratory Animal Allergy

3.1 Nature of Antigens

The primary allergens are proteins derived from the rat, mouse, rabbit and guinea pig. These are present in urine, serum and saliva or may be deposited on pelts and animal house dust.

Cross-reactivities and the relevant importance of different antigens have yet to be researched in any detail.

3.1.1 Measurement

It is now experimentally possible to measure antigens-in-air by using conventional dust-capturing techniques and ELISA. This will need to be developed further before being available as a robust and reliable
methodology which can be used to measure working conditions and guide improvements scientifically. Research continues on this subject.

3.2 **Animal Handling Operations**

The different animal handling operations in F.P.D. may be divided into the following groupings:

1. Husbandry
2. Transport and storage
3. Observation
4. Experimental activities

Each of these operations has different types and levels of exposure to animals. The important factors are time of exposure, volume of animals, type of activity and animal response to that activity. The measures set down in Section 1.3 apply to all the above activities.

3.2.1 **Animal Husbandry**

Antigens levels in animal husbandry are usually low because of the low stress impact on animal populations in these circumstances. However antigen rich atmospheres may be generated in specific cases such as cage-cleaning, sweeping-out etc. Wet methods very effectively suppress antigen levels in such circumstances and should be used whenever possible.

3.2.2 **Transport and storage**

Small animals must be transported in filtered cages. Transport movements and stocking levels must be kept as low as reasonably practicable. Animals or dirty cages must not be kept in corridors or other temporary storage where unprotected persons may encounter them. Whilst awaiting observations or other procedures, animals should be stored in designated areas: where practicable these should be physically separated from casual human contact.

3.2.3 **Observation**

These activities can yield high antigen exposure levels especially if traumatic procedures are necessary. Animals should be handled firmly, gently and securely as this helps to reduce antigen exposure. rooms used for keeping animals under study should, where practicable, have a separate ante-room for the keeping and donning of protective clothing.
3.2.4 **Experimental Activities**

Shaving, bleeding, dosing and anaesthetisation all lead to high exposure levels of antigen. Where practicable, such procedures should be carried out in a fume cupboard or laminar flow cabinet or in a system otherwise equipped with local exhaust ventilation (LEV). Wet shaving methods must be used. Where LEV is impracticable, the wearing of PPE must be strictly enforced.

Experimental work under anaesthesia, dissection, post mortems and tissue preparation present lesser risks but can still generate antigen rich environments. RPE and good general ventilation is usually sufficient.

4. **Basic Principles in Design of Animal Areas**

Animal densities should be kept to the minimum as should animal movements. Animal work should be segregated from other work. This implies that persons not having business in animal areas should not be permitted to enter them. Exposure time of individuals working with animals should be kept to the minimum. Facilities should be available to don and remove PPE in isolation from animals and from general working environments by the designation of ante-rooms or other specified areas. LEV must be supplied where practicable i.e., procedure cabinets, fume cupboards, down draught work surfaces. Consideration should be given to the protection of fitters and other service personnel by the design of easily removable and self contained equipment where contaminated items require handling or servicing (e.g., filters).

There is a commitment to ongoing research into various aspects of LAA prevention and management.

5. **C.O.S.H.H.**

This policy may be seen as an expression of the outcome of continuous assessment of activities associated with laboratory animal exposures. As such it is deemed to fulfil the requirements of C.O.S.H.H. in relation to assessment. It will be reviewed at the end of one year and thereafter at less frequent intervals as seems appropriate.

To comply with the spirit of C.O.S.H.H. requirements, precautions and procedures related to the risk of LAA must be written into departmental operating and other procedural documents. Compliance must be checked periodically and those checks recorded and records kept in the department for five years.
6. **Interpretation**

In order to assist those needing to interpret this policy, guidance on some common applications is given as an appendix to this policy. The examples given should not be seen as anything other than general guidance and specific cases should be dealt with on their merits in consultation with O.H. or safety personnel as appropriate.
Appendix to LAA Division Policy

Guidance on Interpretation of Policy

1. **Use of local exhaust ventilation (L.E.V)**

The ranking order of risk in relation to antigen exposure has been measured and is generally as follows:

shaving > bleeding/dosing/induction of anaesthesia > post-mortems/tissue preparation > work under anaesthesia. L.E.V, which may be procedure cabinet, laminar flow cabinet, fume cupboard or downdraught work surfaces must be provided, where practicable, wherever the more hazardous activities are undertaken. L.E.V. is inherently superior to personal protective equipment in such situations.

2. **Use of personal protective equipment**

There is little controversy over the use of special external clothing. There is appreciable controversy over the use of gloves and masks/helmets. With regard to the use of gloves, managers must make a balanced judgement in relation to protection vs ease of handling in the instructions which they issue on particular procedures. The argument that animals gain reassurance from direct contact with human skin cannot be generally accepted since it is anecdotal. It is as likely that animals will get used to glove contact if gloves are regularly used.

The policy specifies the use of mask or ventilated helmets. Ventilated helmets provide superior protection to masks and are the first choice. They may be specified exclusively in departmental rules. In low risk activities, the use of a toxic particle dust mask (having at least 99% theoretical protection factor e.g., 3M-8810) may be allowed.

From time to time persons may seek dispensation from the use of personal protection and this is permitted by the policy at management discretion and with appropriate consultation. Exemption should not be lightly given. The usual reasons given are low likelihood of developing LAA because of long animal exposure (3-5 years +) and claustrophobia. It is true that LAA incidence after more than 3 years animal exposure does fall to quite a low level but it is still there. Therefore compliance with P.P.E. is still generally required and non-compliance may be interpreted as a disciplinary issue to be commented on in assessment of individual performance. Persons claiming to be claustrophobic will need to have this diagnosis confirmed in the O.H. department. They may be asked to take treatment for the condition or to return to use of P.P.E. after an interval of time.
3. **Transient and casual contact**

Persons only occasionally visiting animal areas (e.g. secretarial staff, maintenance staff, Q.C., etc.,) must use the same protection as those regularly in animal contact. To discourage casual contact and to regularise it, entry into animal handling areas should be restricted by card access whenever possible.

Dr A J M Slovak

5th July 1989
Laboratory Animal Allergy - Fact Sheet

A number of people who work with laboratory animals develop Laboratory Animal Allergy (LAA). This may take the form of skin rashes, running eyes and nose or wheezing. It is caused by rats, mice, guinea pigs, rabbits and some insects. These symptoms may be indistinguishable from hay-fever and asthma caused by outside agents when away from work.

The prevalence among established animal workers is 20-30%. It usually develops over the first 2-3 years of exposure but occasionally much later. The condition stops at the hay-fever stage in many people but in some, especially atopic people, it progresses to asthma.

If you are interested, please ask Sister for a copy of the Division's policy which explains what we do to control the condition.

Part of the policy is to screen animal workers regularly on an annual basis to find new cases and assess the health of established cases. The information gained during this screening is also important in improving medical understanding of allergies and LAA in particular, so that your co-operation is important for the benefit of others as well as yourself.

If symptoms become obtrusive it is Divisional policy to help with relocation of affected persons if possible. However some people with career commitments to animal work may prefer to be offered protective equipment which is fairly reliable for prevention and this option is also available to them. It is worth noting that at present there appears to be no good way of preventing this condition from starting. It should also be noted that LAA asthma is now a prescribed disease and those who have it may be eligible for State benefits. The O.H. department will provide advice and supporting evidence from test results for those who may be eligible.

The Occupational Health Department will contact you automatically when your screening becomes due. You will be advised whether any more tests are needed and the meaning of the results.
LABORATORY ANIMAL ALLERGY:
A Clinical Survey of an exposed population

A J M Slovak
&
R N Hill
LABORATORY ANIMAL ALLERGY:
A Clinical Survey of an Exposed Population

ABSTRACT

A clinical survey of workers exposed to laboratory animals in a pharmaceutical company was designed to discover the prevalence and severity of symptoms of laboratory animal allergy (LAA). The overall prevalence of the condition was 30%, and two distinguishable LAA syndromes, termed regional and progressive LAA, were found. The first is characterised by rhinitis with negative skin prick tests. The second consists of rhinitis leading progressively to asthma with positive prick tests. Prick tests were useful diagnostically only in the latter. Atopes were shown not to be at special risk of developing LAA, but if they did so were more likely to progress to asthma. The implications for selection and management policy are outlined and specific measures for the further study of LAA are proposed.

The development and safety evaluation of new therapeutic agents has resulted in the exposure of human populations in industry to experimental animals and the consequent possibility of developing allergy during the course of work. Lincoln et al. and Lutsky and Neuman in the United States have reviewed large populations handling laboratory animals and have described the associated symptoms. Perception of the true nature of allergens in laboratory animal allergy (LAA) has been refined by the observation of Newman-Taylor et al. of the sensitising potential of low molecular weight urinary proteins in the rat. Our survey, which was carried out in a pharmaceutical company in the summer and autumn of 1978, was designed to discover the prevalence and the clinical characteristics of LAA in a population exposed to laboratory animals in Britain.

METHODS

The population studied was located at two sites and was engaged in animal husbandry and experimental studies. Working conditions were similar to those obtaining in animal-handling facilities in other companies in Britain. The total exposed population was identified by reference to job descriptions and subdivided into work categories.

The MRC respiratory questionnaire, an in-house LAA questionnaire designed specifically for this study, and lung function and prick tests were all administered on the same occasion. The LAA questionnaire examined family and personal histories of atopy and pre-employment exposure to animals, and then sought information on symptoms due to allergy. The possibility of symptoms being work-related was then explored. Questions about correlation to animal exposure were left to last. Details of time sequence and progression of symptoms were also recorded. All procedures were performed on a Friday, thus allowing lung function tests to act as possible indicators of work-week effect. The entire
population of 146 people currently exposed to animals took part in the survey voluntarily.

Standard skin prick tests were performed using commercially available preparations of common environmental allergens and dander extracts of animals used in research (Bencard for guinea pig, mouse, and rat extracts, Dome Labs for remainder). One person from the index population refused prick tests. Lung function tests were performed on the Vitalograph spirometer according to standard techniques. Records were made of FEV₁, FVC, and FEV₁/FVC ratio. One trained operator performed all the tests, and there were no refusals of lung function tests.

Atopy was defined according to Pepy's criteria as any skin-positive reaction with wheal and flare to one or more of the following - grass mixture, house-dust extract or house-dust mite, or Aspergillus fumigatus. Asthma due to LAA was understood, in terms of the in-house questionnaire, as a positive subjective correlation between work, exposure to certain specific animal species, and chest wheezing. Conjunctivitis and rhinitis were defined in similar terms.

**RESULTS**

**Prevalence**

Table 1 shows the number of cases of LAA and its prevalence in each work category. These results show asthma to have been confined to experimental workers but indicate that those engaged in animal husbandry include an appreciable proportion of people with rhinitis.

<table>
<thead>
<tr>
<th>Work Category</th>
<th>No. exposed</th>
<th>No. with LAA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Animal handler (husbandry)</td>
<td>19</td>
<td>8 (42)</td>
</tr>
<tr>
<td>Graduate or equivalent</td>
<td>62</td>
<td>18 (29)</td>
</tr>
<tr>
<td>experimental workers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Experimental technicians</td>
<td>39</td>
<td>16 (41)</td>
</tr>
<tr>
<td>Auxiliaries (cleaners, helpers, etc)</td>
<td>11</td>
<td>4 (36)</td>
</tr>
<tr>
<td>Others (fitters, etc)</td>
<td>15</td>
<td>2 (13)</td>
</tr>
<tr>
<td>TOTAL</td>
<td>146</td>
<td>48 (30)</td>
</tr>
</tbody>
</table>

*Table 1 - Prevalence of LAA in the population currently exposed (1978). subdivision by work category (Percentage in parentheses)*
DISTRIBUTION OF ATOPY

Tables 2a and 2b show the distribution of atopy within the exposed population and the number of atopes with asthma contrasted with atopy in those with rhinitis only.

<table>
<thead>
<tr>
<th>Subjects with LAA</th>
<th>Asymptomatic subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atopes</td>
<td>20</td>
</tr>
<tr>
<td>Non-atopes</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>83</td>
</tr>
</tbody>
</table>

\[ \chi^2 = 2.00. \text{ Not significant} \]

**Table 2a** - Distribution of atopy in the exposed population

<table>
<thead>
<tr>
<th>Rhinitics</th>
<th>Asthmatics (progressive)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atopes</td>
<td>8</td>
</tr>
<tr>
<td>Non-atopes</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>3</td>
</tr>
</tbody>
</table>

\[ \chi^2 = 14.7. \text{ Significant at } p = 0.001 \]

**Table 2b** - Distribution of atopy within the LAA group. Rhinitis vs progressive disease

LATENCY

Table 3 compares the latency of onset of symptoms in rhinitis-only and in asthmatic (progressive) cases. There is little difference in time to onset of first symptoms, but 66% of those with progression to asthma who responded positively to the question developed their asthma within three years of their first symptom. This rapid acquisition of further symptoms, however, is not pronounced enough to be useful in setting a cut-off point for predicting who will or will not develop asthma.

<table>
<thead>
<tr>
<th></th>
<th>&lt;1 year</th>
<th>1-3 years</th>
<th>&gt;3 years</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time from first exposure to onset of first symptom</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rhinitics</td>
<td>9%</td>
<td>39%</td>
<td>36%</td>
<td>16%</td>
</tr>
<tr>
<td>Asthmatics (progressive)</td>
<td>20%</td>
<td>27%</td>
<td>40%</td>
<td>13%</td>
</tr>
<tr>
<td>Time from first to subsequent symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthmatics (progressive)</td>
<td>46%</td>
<td>20%</td>
<td>20%</td>
<td>14%</td>
</tr>
</tbody>
</table>

**Table 3** - Latency from first exposure to first and subsequent symptoms, rhinitics v progressive cases
SKIN PRICK TESTS TO ANIMAL ALLERGENS

The distribution of positive prick tests within the total animal-exposed population (Table 4a) shows that positive prick tests are confined to the population with LAA. This result may be refined by comparison of syndrome subgroups within the LAA population (Table 4b). There is a strong correlation between positive prick tests and asthma (progressive) disease but poor correlation for rhinitis-only LAA.

<table>
<thead>
<tr>
<th>Prick Tests</th>
<th>Subjects with LAA</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive (1 or more)</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td>Negative</td>
<td>26</td>
<td>98</td>
</tr>
</tbody>
</table>

**Table 4a** - Distribution of positive prick tests to animals in the exposed population

<table>
<thead>
<tr>
<th>Prick Tests</th>
<th>Rhinitics</th>
<th>Progressives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>8</td>
<td>13</td>
</tr>
<tr>
<td>Negative</td>
<td>25</td>
<td>2</td>
</tr>
</tbody>
</table>

\[ X^2 = 15.64 \text{ Significant at } p = 0.001 \]

**Table 4b** - Animal prick test results, rhinitics v progressive cases

LUNG FUNCTION TESTS

Table 5 shows the significant findings from these tests. The asthmatic cases show a decrease in FEV₁/FVC ratio, which may be a work-week effect; there is no such decrease in controls or in cases with rhinitis-only.

<table>
<thead>
<tr>
<th>FEV₁/FVC ratio</th>
<th>Mean ± SE</th>
<th>t value</th>
<th>2-tail significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actual ratio</td>
<td>Predicted ratio</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthma cases v rhinitic cases</td>
<td>77.1 ± 2.39</td>
<td>82.3 ± 1.20</td>
<td>-2.194</td>
</tr>
<tr>
<td>Asthma cases v controls</td>
<td>77.1 ± 2.39</td>
<td>83.3 ± 0.90</td>
<td>-2.800</td>
</tr>
</tbody>
</table>

**Table 5** - Student t test on FEV₁/FVC ratio
AGE, SEX, ETHNIC GROUPING, SMOKING AND OWNING OF PETS

The data were analysed for the effect of these factors on all results, but no significant differences were noted within the LAA groups or in controls.

DISCUSSION

Previous surveys have shown the prevalence of LAA to be between 11.3% and 14.7% in laboratory animal-exposed populations. The prevalence in this study was 30%. Previous studies, like the one described here, have been cross-sectional and therefore, by their nature, deal with survivor populations. If an entire working population were traced the prevalence might be over 50% (A. Newman-Taylor, personal communication). The under-reporting of prevalence in earlier surveys may be due to differences in working conditions in laboratories in the United States and Britain but is more possibly due to variations in method. Thus one study relied on obtaining prevalence rates by sending a questionnaire to many institutions handling laboratory animals, and it is unlikely that the respondents from these institutions would all use the same criteria for the definition of LAA or the same energy in seeking out cases. Also the amount and type of animal exposure was relatively imprecisely quantified, so that the populations were likely to show dilution by including those administratively ascribed to a particular department but not actually having contact with animals. This survey has attempted to define its animal-exposed population much more closely. The definition, however, of an animal-exposed population in absolute terms can only be consequent on a properly constituted occupational hygiene survey correlated to work patterns and clinical manifestations of illness.

While our LAA questionnaire was specifically designed to avoid leading questions whenever possible, our acceptance of patients' correlation between symptoms and work-exposure is clearly subjective and cannot avoid memory bias. We consider, however, that our reliance on this method is vindicated by the high level of agreement between the results of the prick test and the subjective finding of symptoms in the asthmatic group with LAA. We did not perform any type of challenge test as we were not satisfied that any set of standardised conditions could evoke the true range of responses in the population studied.

There appear to be two syndromes associated with LAA. The first, which includes most cases, comprises patients who have rhinitis with or without skin sensitivity. In terms of the results of the prick test and prevalence of atopy this group cannot be separated from a positive control group (the animal-exposed population without LAA) except by the manifestation of their symptoms. The minority group contains those who develop asthma due to LAA. They are characterised by an illness that usually begins as rhinitis and progresses to asthma, usually over a period of a year or two. This group may be clearly
differentiated from the exposed population without LAA and from the rhinitis-only group in terms of relevance of atopy (80%) and prick and lung function test results. Possibly, therefore, two separate groups with LAA can be defined on clinical grounds. For these groups we proposed the terms regional and progressive LAA.

This differentiation improves our perception of LAA, particularly with regard to the prognostic significance, since the rhinitis-only group consists of people who are unlikely to progress to asthma. They may therefore be allowed, if they wish, to continue working with animals in the reasonable belief that there is a low risk of any serious consequences. A few of the group will progress to asthma, but these can easily be identified at any early stage by follow-up, which is clearly an important part of their health supervision.

The survey results indicate that atopy by itself is not associated with a higher prevalence of LAA but that the distribution of atopes is concentrated among those with progression to asthma. It appears, therefore, that while atopes are no more likely than others to get LAA, if they do it tends to be progressive. This has clear implications for employment selection policies. The distribution of atopy in the population under study was 33%, which is similar to that of the general population,

It has been suggested that LAA is a disease of animal experimenters and not of animal handlers, but this is refuted by the results presented in Table 1. The absence of progressive cases in animal handlers in this study is noteworthy but, bearing in mind the small numbers surveyed, could also be due to job transfer or to chance. The fact remains that LAA clearly occurs among animal handlers, as indeed it does in those supposedly more casually concerned with animals in auxiliary jobs and maintenance.

Prick test results to animal dander extracts showed a good correlation with symptoms in the progressive LAA group. Moreover, the people in this group were able to identify accurately those animals to which they were allergic, and their prediction was confirmed by subsequent prick testing. This was in direct contrast to the regional LAA group, where positive prick tests to animals were relatively uncommon and correlated poorly with patient claimed allergy. The prick test is therefore a useful tool in diagnosing established, progressive LAA. It appears to be of no value in rhinitis, however, and its usefulness in predicting progression from rhinitis to asthma awaits a larger scale prospective study.

Our knowledge of the antigens in LAA is sketchy. Most studies have examined allergy to the Wistar rat, and work is currently under way to identify the antigenic role of animal hair and scales. Although the rat poses the largest problem of LAA since so many are used in laboratories, other animals may be most efficient sensitisers. Rudolph has noted the high antigenicity of the guinea pig and we
have also observed this to be the case. The rabbit is also a highly antigenic animal. To gain a better understanding of LAA, it is important that this area of comparative antigenicity be explored further.

We have touched on the difficulties inherent in using a cross-sectional survey to establish “true” incidence and prevalence of an occupational disease. There is a clear need for a prospective study of recent entrants to laboratory animal work to establish the incidence and prevalence of LAA and to chart its development. Such a study could be definitive, especially if it were designed to run alongside a properly constituted occupational hygiene survey, so that some quantitative correlation could be made with incidence and prevalence. Only then would it be possible to offer an opinion on the establishment of hygiene standards. Meanwhile we consider it premature to make any other than the most general recommendations about the protective efficacy of specific designs for cages, animal rooms, experimental rooms, ventilation systems, and other protective equipment.

We thank Sister L A Hyde, SRN, for her clinical work and her resolution in achieving 100% compliance within the survey.

References


IMMUNOLOGICAL DIFFERENCES BETWEEN ASTHMA
AND OTHER ALLERGIC REACTIONS IN LABORATORY ANIMAL WORKERS

A J Newman-Taylor
J R Myers
J L Longbottom
D Spackman
A J M Slovak
IMMUNOLOGICAL DIFFERENCES BETWEEN ASTHMA AND OTHER ALLERGIC REACTIONS IN LABORATORY ANIMAL WORKERS

We surveyed 145 pharmaceutical research employees, working in direct or close indirect contact with laboratory animals, to examine the association between immunological reactions to animal antigens and allergic symptoms. Symptoms were recorded by objective questionnaire and from clinical history; skin prick testing was carried out using common inhalant allergens (grass, house-dust mite, A. fumigatus) and preparations of urine, serum and hair from laboratory animals. In 27 employees, allergic asthmatic and nasal symptoms and urticaria, singly or in combination, were recorded as being provoked by exposure to small mammals (rats, mice, rabbits, guinea pigs). Using skin test criteria, atopy was associated most with asthmatic symptoms, being present in nine out of 11 asthmatic patients compared with seven out of 16 with other allergic symptoms and 37 out of 114 with no symptoms (p<0.01). Skin test reactions to rat, mouse, and guinea pig urines were closely associated with symptoms of asthma, but not with those of rhinitis or urticaria. Urine skin tests were positive in eight out of nine with asthmatic symptoms to rats, in all of three for mice, and in three out of four for guinea pigs. In those with nasal symptoms or urticaria, urine skin tests were positive in three out of eight for rats, one out of four for mice, and in none out of three for guinea pigs. In relation to specific IgE to urine antigens, mean RAST scores were also higher in those complaining of asthma than in those with other symptoms: 2700 versus 1740 for rats, 2100 versus 1200 for mice, and 5810 versus 910 for guinea pigs. These findings suggest that the immunological mechanisms responsible for asthmatic reactions to laboratory animals are different from those involved in rhinitis and urticaria.
ANAPHYLAXIS FOLLOWING BITES BY RODENTS

E L Teasdale
G E Davies
A J M Slovak
ANALYPHYLLAXIS FOLLOWING BITES BY RODENTS

We report two cases of analphylaxis in laboratory workers following rodent bites.

Case Reports

Case 1

Male, aged 23 with no history of allergy until April 1981, after working with animals for 5 years, when he complained of sneezing, itching and irritation of his nasal passages. In December 1981 he complained of severe rhinorrhea present within 5 min. of exposure to animals. In September 1982, during weekend work, he was moving rats from one cage to another and was bitten. When questioned later he reported that within a few minutes he felt tightness of the chest; a colleague observed that his skin became ‘bright red’ and he complained of ‘tingling’; his eyes became bloodshot, his nasal passages became congested and he expectorated mucus. The acute respiratory distress persisted and an ambulance was summoned to take him to a local hospital. Within 4 hours the effect had worn off but 2½ hours later he again experienced tightness of his chest and inflammation of his skin returned. These later symptoms subsided when a nurse removed his pillow containing feathers. He has now been given work which does not involve contact with animals.

Case 2

Male, aged 30. He had worked with rodents for 8 years without experiencing any symptoms of allergy; he was not atopic. In September 1982 whilst working with mice, he was bitten on the hand. The bite drew blood. Within 5 minutes he felt a warm flush in his hand which gradually spread to his arm and body over the next 10 minutes; 20 minutes after the bite his eyes and nose began to run profusely and he developed chest tightness. There was no upper respiratory obstruction. He was given chlorpheniramine maleate, 10mg iv and salbutomol in inhaler. The chest symptoms subsided within 10 minutes and the other symptoms over the next few hours during which he experienced a headache. Six hours after the bite he was perfectly well.

Investigations

Skin prick tests and estimation of specific IgE antibodies by standard RAST procedures were carried out with the results shown in the Table. Case 1 showed a marked increase in reactivity, principally to rat and mouse allergens, but also to guinea pig serum over an 8 month period, the latter tests being carried out 9 months before the anaphylactic reaction. Specific IgE antibodies to these allergens were also raised. The immunological tests in Case 2 were less positive.
but more specific; the high levels of IgE antibody to mouse urine and dander are noteworthy.

**Dander**

Both cases present some common features. Both had worked for some years with rodents before developing allergy; one of the subjects was atopic, as judged by skin testing, both had positive skin prick tests and high levels of specific IgE to the offending species were found. The nature of the actual provoking allergen is not, at present, known: there would seem to be two possibilities: (i) a specific salivary protein or (ii) urinary and/or serum proteins present in saliva.

Published accounts of anaphylaxis following animal bites are exceedingly rare, the only report we have been able to find is that of an incident caused by a Slow Loris in Thailand¹. However, it is likely that the event is more common than the literature suggests and there may be at least anecdotal evidence of other such episodes. We think it important, though, to emphasise that although bites from rodents are common this severe reaction is extremely rare. It might be prudent that the management's of institutions with large numbers of animals should review their medical arrangements for dealing with such emergencies.

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## IMMUNOLOGICAL FINDINGS

<table>
<thead>
<tr>
<th>Allergen</th>
<th>IgE Antibodies (% binding of 1125 rabbit anti-human (IgE))</th>
<th>Skin prick test (diameter of response in mm)</th>
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<tbody>
<tr>
<td></td>
<td>Case 1 (4/81)</td>
<td>Case 2 (12/81)</td>
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<tr>
<td>Rat - urine</td>
<td>11</td>
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<tr>
<td></td>
<td>23</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>28</td>
<td>2</td>
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<tr>
<td>Mouse - urine</td>
<td>21</td>
<td>15</td>
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<td></td>
<td>14</td>
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<td>21</td>
<td>4</td>
</tr>
<tr>
<td>Rabbit - urine</td>
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<td>0</td>
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<td>1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>5</td>
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<tr>
<td>Guinea Pig - urine</td>
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<td></td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>Grass Pollens</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>D.pteronyssinus</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Cat dander</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>Dog dander</td>
<td>3</td>
<td>9</td>
</tr>
</tbody>
</table>
EFFICACY OF THE HELMET RESPIRATOR IN OCCUPATIONAL ASTHMA DUE TO LABORATORY ANIMAL ALLERGY (LAA)

A J M Slovak
R G Orr
E L Teasdale
EFFICACY OF THE HELMET RESPIRATOR IN OCCUPATIONAL ASTHMA DUE TO LABORATORY ANIMAL ALLERGY (LAA)

The efficacy of the Racal Airstream helmet respirator in preventing symptoms due to Laboratory Animal Allergy (LAA) was assessed in ten patients. Eight of these were established cases of asthma and two had severe rhinitis. Peak expiratory flow rate (PEFR) readings, recorded every two hours, were kept for seven weeks (six in exposure), together with a diary of subjective symptoms. Objective evidence of good protection was obtained in six out of the eight asthmatic patients; overt asthma was seen in the other two. The helmet respirator would appear to be a valuable adjunct in the management of occupational asthma in those who opt to remain in exposure. Those asthmatics who use a helmet respirator need to be monitored carefully and regularly to ensure that their respiratory function has not deteriorated. Persons with severe local symptoms of rhinitis and conjunctivitis also benefit subjectively from the use of the helmet although symptoms are not completely suppressed nor may progression towards asthma be prevented. The findings may well be applicable to the management of other types of occupational asthma but any inferences should be drawn with caution.

INTRODUCTION

Occupational asthma due to Laboratory Animal Allergy (LAA) is a well established and widespread phenomenon among those engaged in animal husbandry and experimentation. The prevalence of LAA has been estimated by a number of cross-sectional surveys in the UK and USA as being between 11 and 30% of the exposed population of which between one-quarter and one-fifth suffer from asthma.  

The UK Safety of Mines Research Establishment (SMRE) has produced a helmet respirator, developed and marketed as the Racal Airstream helmet, that has won widespread acceptance as an efficient and comfortable way of avoiding dust exposure in many workplace environments. In the last two or three years it has become increasingly popular with people engaged in work with small mammals. It has been used for two purposes; as a prophylactic against the development of Laboratory Animal Allergy (LAA) in asymptomatic personnel and to prevent symptoms in those with established LAA. Although subjective reports have been very favourable, no objective evidence of their efficacy in either of these roles has been reported. The helmet respirator has become something of a panacea for problems in the prevention and control of LAA, and it seemed timely to assess the value and limitation of this type of equipment before indiscriminate and perhaps inappropriate usage became widespread.
METHODS

Most people who develop the more serious symptoms of LAA, such as asthma, choose to have their disease managed by relocation. It was therefore quite difficult to find people to study who had developed LAA and were still in exposure. However ten such persons with LAA, identified during previous prevalence studies, were observed in this study. Eight of these were established cases of asthma and two were severe rhinitics without known asthma. All had opted to remain in exposure to animals for career reasons and all were regular helmet users. Current disease status was established by a questionnaire at the beginning of the study.

All persons used the standard AH1 (nearest US equivalent - AH5, MSHA-NIOSH approved TC-21C-197) helmet respirator and standard AS60023 (US-AS-23-3) filter. This is a helmet-mounted, powered, air purifying respirator that, when fitted with the AS-23-3 filter, is claimed to exclude 95% of dust particles down to 0.5 microns. In order to obtain type approval, the qualities of helmet respirator have been well validated with regard to inter-helmet and inter-personal performance variability, and these were not considered further in this study.

Peak expiratory flow rate (PEFR) measurements were obtained using Wright mini-flow meters, the readings being recorded by the patient. Readings were taken every two hours throughout working hours during a seven-week period outside the hay fever season. Details of working conditions and precautions taken during the seven-week period are listed in Table. 1.

<table>
<thead>
<tr>
<th>Weeks</th>
<th>Working Conditions</th>
<th>Precautions Taken</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No animal exposure</td>
<td>None</td>
</tr>
<tr>
<td>2-5</td>
<td>Normal work</td>
<td>Helmet worn according to normal custom, no attempt at uniformity of precautions</td>
</tr>
<tr>
<td>6-7</td>
<td>Normal work</td>
<td>Helmet work whenever at work, filter changed daily, outer protective clothing worn</td>
</tr>
</tbody>
</table>

Table 1 - Subdivisions of 7-week study period according to working conditions and precautions taken

The records were computer analysed and interpreted blindly by independent assessors. According to standard internal criteria, asthma was diagnosed as >15% variability between maximum and minimum daily PEFR readings. This was considered to be work-related if it occurred during all of one or more workweeks. While it would have been useful for the study to include a period of exposure without protection to obtain within-person positive controls, such a
procedure was rejected as being unethical and unnecessary since all subjects had a past history of severe symptomatology on unprotected exposure.

Skin prick tests were performed in order to assess atopic status and confirm reactivity to specific antigens of LAA. For the purposes of this study atopy was defined as skin prick reactivity to grass pollen, house dust mite or aspergillus. Skin pricks were considered positive if a wheal of 2mm or more was observed after 10 mins. Commercial test solutions were used for grass pollen, house dust mite, aspergillus and mouse, rat and rabbit danders (Bencard or Dome). Urine extracts (1mg/mL) from mouse, rat, rabbit and guinea pig were produced for research purposes by Bencard and are not yet commercially available.

One subject had completed a course of grass pollen desensitising injections just before this study began and another completed a similar course at the end of the study. One of these had LAA asthma, the other only rhinitis. No other subjects were on any medical treatment.

No attempt was made to measure airborne levels of allergens. Although techniques do now exist for such measurement(7-8) they are experimental and laborious and insufficient work has been done to establish symptomatic levels of exposure. It is important to note that the setting of hygiene standards for allergens is difficult because there are two separate objectives. One is the prevention of the development of allergy, and the other is the prevention of symptoms in the allergic. The issue is further complicated with LAA in that each causal animal (principally the rat, mouse, rabbit and guinea pig) produces several immunologically discreet allergenic entities, and it is not known yet which of these is important in the aetiology of human illness. Suffice it to say that, in terms of exposure through this study (weeks 2-7) all persons in the study worked in conditions know to cause them severe symptoms if they entered unprotected.

RESULTS

Skin Prick Reactivity

The results in Table 11 show that all ten subjects were atopic and all had positive skin prick reactivity to one or more specific antigens of LAA. These results are valid even when using alternative criteria of positive (i.e. 3 or 4mm wheal or wheal 2mm larger than negative control).

Disease Status and Activity

All ten subjects had had work-related symptoms, ascribed to LAA, within twelve months of the start of the study. Both rhinitics and two asthmatics considered that their symptoms had worsened in severity, frequency or duration or in a combination of these qualities.
### Table 11 - Skin Prick Test results for Asthmatics and Rhinitics(a)

(a) Numbers in table represent positive allergic responses by skin prick testing.

(b) Numbers responding positively in asthmatics column are out of 8.

(c) Numbers responding in rhinitis column are out of 2.

**PEFR Records**

There was no asthma in any patient during week 1 nor was there any evidence of any change which might suggest recovery from acute or chronic depression of lung function due to previous exposure. Therefore any subsequent change observed in weeks 2-7 could be considered a consequence of the test exposure and the effect of the helmet in ameliorating that exposure.

Out of the eight asthmatics, two showed overt asthma on their PEFR records during weeks 2-7 and six did not. One of the cases with overt asthma was judged by the independent assessors not to be occupationally related, but this person's subjective symptoms correlated well with work. One of the two rhinitics also developed occupationally related asthma in week 7 during an upper respiratory tract infection. Figure 1 shows individual examples of typical individual asthmatic and non-asthmatic records for illustrative purposes.
Only one person showed any visible improvement on his PEFR record in weeks 6 and 7 when compared with weeks 2-5 but this difference proved not to be statistically significant.

Subjective Records

Both asthmatics with PEFR records of overt asthma experienced subjective work-related symptoms of wheezing or shortness of breath at least once during the study period, as did two other asthmatics. Five asthmatics also had episodes of rhinitis usually, but not always, followed by prodromal chest symptoms falling short of overt asthma (i.e. cough, throat tightness). Both rhinitics had episodes of work-related nasal and prodromal chest symptoms.
Discussion

It might be argued that the best way of managing occupational allergic disease, other than prevention at source, is by rapid relocation of the affected individual to work where there is no risk of exposure to the offending antigen. Such a policy is relatively easy to practice when jobs are plentiful and labour turnover high or when a career does not depend on continuing in a particular type of work; however, with animal work many people are career dedicated and those who are not see few alternative job opportunities at present. Under these circumstances, many workpeople will be tempted to stay in exposure and conceal their symptoms, thereby risking the development of generalised airways hyperactivity and prolonged respiratory disturbance even if they belatedly change their work. Alternative and acceptable strategies have to be offered to prevent this happening and these fall into two groups, preventative and palliative. Preventative measures include the use of systems and personal protection and prophylactic treatment. Palliative measures consist essentially of symptomatic treatment.

In this study we have examined the contribution which may be made by helmet respirators to the management of LAA. We have shown that a good level of protection was obtained in the majority of asthmatics (75%) when measured objectively by PEFR recording. Even in these people, subjective symptoms were not totally suppressed, however.

The first week of the study period, during which there was no animal exposure, was necessary in order to permit any recovery of depressed lung function so that a true baseline could be obtained. More importantly in this study is that, perhaps, the absence of any such pattern in any case is strongly supportive of the opinion that regular use of helmet respirators prevents chronic depression of lung function or has done so in these subjects.

There was little or no difference between the results from PEFR records obtained during weeks 2-5 and weeks 6-7. This is a somewhat surprising finding since the regimen imposed upon the patients in the last two weeks of the study was the strictest and most painstaking that it was believed they could tolerate reasonably. It might be speculated that the amount of antigen bearing dust deposited on clothing during the normal course of work was insufficient to later affect the lung when the helmet was removed. Alternatively, it might be that the dust in clothing was insufficiently disturbed to get into the breathing zone in these subjects or that dust from this source was not allergenically important. Whatever speculation may be placed upon this finding, it does suggest that elaborate procedural precautions do not contribute much to protection.
A number of factors affecting the performance of helmet respirators have to be taken into account in trying to improve the protection offered to people with LAA. Among the most important of these are those listed below (some of them are being further explored by one of us (ELT):

1. Personal, wearer factors.
2. Inter-helmet variation.
3. Alternative filter/battery specifications.
4. Wearer compliance.
5. Effect of maintenance schedules.
6. Level of exposure.

The first two factors listed have been assessed extensively by the manufacturers of these and other helmet respirators and the products are manufactured to MSHA/NIOSH type approval specifications. To a large extent they may be described as variable of known power that are likely to have a relatively small impact on the protection obtained by most people. The last factor was referred to in the methodology section. The contribution of other factors is less easy to quantify.

This study did not examine the efficacy of other helmets. This is clearly necessary but may be difficult to obtain because of the relative scarcity of available subjects and the demanding nature of the lung function surveillance routines. The filter tests (AS-23-3) is claimed to offer a twentyfold protection factor in terms of dust penetrance down to a 0.5 micron lower limit. Higher specification filters are available and need to be tested, perhaps in those asthmatics who are overtly symptomatic. The effect of higher demand upon battery and motor output when using more efficient filters needs to be taken into consideration in such studies. This is less of a problem with standard industrial tasks involving shifts of known length. Many animal workers, however, have an irregular or prolonged work pattern so that battery life may become the crucial factor in respirator performance.

Perhaps even more important to take into account when assessing the efficacy of these respirators are wearer compliance and maintenance schedules. Here human nature and fallibility have the widest scope for reducing the protective value of equipment. In this study we attempted to diminish the impact of these potentially serious confounding factors by insisting on standardised wearing and cleaning conditions. This is a discipline which is difficult to obtain in everyday life. Mention has already been made of the irregular nature of the work of many animal exposed personnel. They habitually move in and out of animal rooms during any working day. Helmet respirators are rather heavy and socially isolating so that there is a tendency to remove them when no in animal exposure and sometimes to risk a short exposure to animals without putting them back on again. Observation of everyday work practice leads us to conclude
that this may be an important problem in relation to respirator efficacy shortfall in animal workers.

Scrupulous attention was paid to cleaning the helmet respirators of persons involved in this study. Again, this is more difficult to obtain in normal workpractice than during a special study. This is particularly a problem when dealing with allergens when one is using non-allergic people to clean the helmets. Naturally enough, as they are wholly unaffected by the allergens, they tend to underestimate the exquisite sensitivity of allergic individuals to minute exposures and tend not to clean as thoroughly as they should. A radical approach to this problem is to consider asking the users themselves to clean their own helmets while wearing another helmet. This ensures thoroughness and should be safe.

A more subtle maintenance problem relates to battery changing and cycling. Some preliminary work by one of us (ELT) suggests that batteries need to be regularly used and fully discharged before recharging to obtain maximal performance and that premature deterioration in battery power during the workday may result from recharging partially discharged or stored batteries.

Previous work has shown that LAA asthma is a progressively developing condition\(^4\). After a symptom-free period, rhinitis and conjunctivitis develop, worsen and then merge into asthma over a period of months or years. Atopic people are most at risk in completing this progression to asthma\(^\text{4,5}\). The two rhinitics in this study were both atopic and had positive skin prick tests to specific LAA allergens. Both were thus well on the path of progression; indeed, in one case overt asthma was unmasked by a cold. The evidence of these cases suggests it is possible that the helmet respirator does not do much to prevent or delay progression. Therefore, the case for the prophylactic use of helmets by the asymptotic or those with mild symptoms may not be strong, even if they were willing to put up with the inconvenience of wearing helmets, which oftentimes they are not.

Our findings in this study lead us to proffer some tentative suggestions for the management of those asthmatics who prefer to stay exposed to animals to which they have become allergic. It is important to review with the patient the technical factors which affect the reliability of the respirator.

Someone else should change the filters and clean the helmet unless the patient is willing to accept the radical alternative previously described. The early period of exposure should be monitored by PEFR recording, including a week or two before re-exposure. Such recording needs to be kept up for two or three months and we have found this is acceptable to well motivated patients. The every-two-hours routine is preferable, but one of us (AJMS) has found a four-times daily schedule (morning, noon, late afternoon, late night) nearly as useful after the first month. Those patients who continue to produce a non-asthmatic
record over the initial study period can probably be allowed to continue their work without further intervention other than a month's monitoring spell each year (which should be outside the hay fever season). Patients who produce a doubtful record or overt asthma are probably candidates for the reassessment of their protection, including a more efficient respirator, and perhaps for prophylactic medical treatment. The combination of respirator and treatment protection requires continued monitoring until a stable and satisfactory condition has been achieved. Failure of this combined management leads logically to symptomatic treatment, but relocation is more sensible.

A heavy responsibility is undertaken by those who accept the management of asthmatics who choose to remain in exposure to substances which provoke their symptoms. While we have no reason to believe that the experience obtained from this work is not applicable to other occupational asthmatics, great care should be taken to ensure that monitoring schedules are tailored carefully to the needs of the individual patient so that any shortcomings in the protection offered to him are quickly detected and effectively remedied.

Acknowledgements

We should like to thank Drs A Newman-Taylor and K Venables of the Brompton Hospital for their analysis of PEFR records and Dr J Dewdney for scientific advice. Thanks also to Sisters L A Hyde, D A Phillips and J Critchley for their clinical work and Miss D G Podevyn for secretarial help.

References


(4th February 1984; Revised 18 March 1985).
DOES ATOPY HAVE ANY PREDICTIVE VALUE FOR LABORATORY ANIMAL ALLERGY?

A COMPARISON OF DIFFERENT CONCEPTS OF ATOPY

A J M Slovak
R N Hill
DOES ATOPY HAVE ANY PREDICTIVE VALUE FOR LABORATORY ANIMAL ALLERGY? A COMPARISON OF DIFFERENT CONCEPTS OF ATOPY

ABSTRACT

Atopy is widely used as a discriminant in selection for employment involving exposure to allergenic substances. The validity of this has been tested in a population with a known burden of what is largely considered to be an IgE mediated disease, laboratory animal allergy. The findings suggest that atopy is insufficiently sensitive and specific for this purpose and that this is probably true for other occupational allergic diseases. The relation between different concepts of atopy - namely, atopy defined by family history, by personal history, and by skin prick tests with common allergens - has also been examined. The sub-populations identified by these criteria differed appreciably. Different concepts of atopy should not be used synonymously as they often are at present.

Atopy is a useful and widespread concept in clinical medicine describing a tendency to develop allergic disease. In occupational medicine it has traditionally been used as a discriminant in selecting those who are to work with substances capable of causing allergic disorders. Several studies have sought to assess the importance of atopy as a marker of susceptibility to disease, usually by using skin prick tests as the criterion of atopy \(^{(1-7)}\). In clinical practice, however, it is still much more common to use family or personal history as indicators of atopy. Thus at least three different concepts of atopy have evolved. To assess their value as discriminants, we have studied the sensitivity, specificity, predictive value, and correlation of these different concepts in a population with a known burden of an IgE mediated, occupational allergic disease - laboratory animal allergy. Our findings were derived from data generated in our cross sectional study of laboratory animal allergy (LAA) \(^{(5)}\) but not previously analysed.

METHODS

In an exposed population of 146 individuals, surveyed to assess the prevalence of laboratory animal allergy, a standardised questionnaire was developed and used to obtain evidence of family history (parents, grandparents, siblings) and personal history of allergy. The questionnaire was administered by one nurse interviewer. Family and personal history of allergy were accepted as positive if such had been diagnosed at any time by a clinician, although not necessarily confirmed by objective tests. It is easy to criticise this definition but looser definitions are commonplace as discriminants in occupational health practice. Tighter definitions, especially those requiring objective confirmation, would have seriously underestimated the true rates.
Standard skin prick tests to grass mixture, house dust and Aspergillus (Bencard) were also carried out, atopy being defined as the presence of a 3mm wheal to any one of the three tests at 10 minutes.(5) Skin tests for cat, dog and horse hair were also performed but not included as criteria for atopy because of the possibility of cross reactivity with LAA antigens. The standardised questionnaire was used in an attempt to minimise ascertainment bias, a fault to which this type of study is prone. Memory bias is more difficult to avoid but this population was in secure employment and was not to be the subject of any discriminatory action where atopy to be found. Additionally, previously presented evidence suggested that there was no preferential wastage of atopic individuals from the population studied.(5) A diagnosis of LAA was made solely on the symptoms reported by patients. The questionnaire was so designed that it was necessary for patients to ascribe their symptoms positively to their work and then identify the species of animals which had caused to effect before the diagnosis was accepted. The subjects were divided into three groups according to their symptoms. The first group consisted of those who had LAA asthma (with rhinitis). All but two of these had positive skin prick tests to specific animal antigens (rat, mouse, guinea pig, rabbit), indicating IgE mediated disease. The second group comprised people with LAA rhinitis only but who had a much lower prevalence of specific animal antigen skin prick positively (8 out of 33). The third group comprised the remainder of the population, having no evidence of laboratory animal allergy. No one in this last group had positive skinprick tests to specific LAA antigens.

**RESULTS**

The basic numerical data (Table 1) were examined in terms of allergic disease to provide sensitivity, specificity, and predictive values for the different concepts of atopy (Table 2).

Atopy defined by skin prick tests with common allergens was a sensitive (80%) and quite specific (82%) test for LAA asthma. Atopy defined by personal or family history was less discriminant. For LAA rhinitis all three definitions of atopy were insensitive (24-39%). Even for skin prick test atopy, the predictive value of atopy for disease was low (34% for LAA asthma, 23% for LAA rhinitis) and only 75% of non-atopics were without symptoms. Of those people classified as atopic by personal history, 65% would have been so classified by family history. Similarly for atopy classified by personal history as against skin prick test and atopy classified by family history as against skin prick test, the percentages were 72% and 64% respectively. This is low for supposedly identical parameters.

Pre-employment data on skin prick reactivity to common allergens was available in 46 of the 146 individuals in the study (32%). There was no evidence that these 46 were in any way an unrepresentative sample of the population. The atopic status of individuals had not altered between pre-employment
examination and the period of the survey (mean 2-6 years, range 1-6). The theoretical consideration that the development of LAA might itself alter atopic status is therefore unlikely in this particular population but cannot be completely ruled out. Six people were skin test positive to cat fur, three to dog, and one to horse hair. Of these, only one, who responded to cat, dog and horse was not also responsive to grass or house dust mite. The exclusion of cat fur in the skin prick definition of atopy therefore had an insignificant effect of the number defined by that criterion.

DISCUSSION

The conceptual value and ubiquity of the idea of atopy has served to conceal its ambiguities. Many occupational physicians consider the three different concepts of atopy we tested as synonymous, yet our study shows that they are not. Our evaluation of these concepts of atopy has identified three substantially different, albeit overlapping, populations. The inference we have drawn from this finding is that great caution must be exercised in the way that these concepts are used as discriminants or predictors of allergy.

In prevalence studies of occupational allergic disease the issue of atopy has usually been discussed only with regard to its sensitivity as a marker of various occupational allergic states. In some cases there has been no positive association at all, as with epoxy adhesives, azodicarbonamide, and piperazine. In other cases, such as animal allergies, some degree of
association with atopy has been noted. These findings may be used to infer two main types of conclusion relating to specific immune mechanisms on the one hand and to predictive hypotheses on the other. It is the latter with which we are concerned here for the traditional popular, and seldom denied inference from positive associations is that sensitivity and predictive value are directly linked. This is not necessarily so. To complete an assessment of such results the prevalence of the condition must be considered as well as the sensitivity and specificity of the screening test (8).

The relation between positive predictive value and prevalence is derived from the equation.

\[
\text{PV} = \frac{P \times SE}{P \times SE + (1-P) \times (1-Sp)}
\]

(\text{where PV} = \text{positive predictive value}
\text{P} = \text{prevalence}
\text{SE} = \text{sensitivity}
\text{Sp} = \text{specificity})

From this formula a series of curves may be drawn for different combinations of sensitivity and specificity. For atopy related to LAA the figure shows the curves for the best and worst sensitivity/specificity combinations in this study. The curve for 95% sensitivity and specificity is also drawn for illustrative purposes. The results of several studies have placed the prevalence of LAA in the range 11-33% with asthma accounting for between 25% and 33% of all disease (4,5,9-12). In the particular population considered in this study the prevalence of LAA was 33% with asthma at 10%. The prevalence intercepts for these findings have been presented in the figure. They show clearly the shortcomings of any of the concepts of atopy as indicators of disease. For asthma, perhaps the most serious manifestation of LAA, a sensitivity and specificity of about 95% would be necessary to justify the use of atopy as a pre-employment screen in order to eliminate a simple majority of potential cases correctly.

Comparing the three concepts of atopy, we have shown that personal history and skinprick test results have statistically significant associations with LAA asthma but not with rhinitis; the best association is with atopy defined by skin prick tests with common allergens. Although we have shown that atopy is not a convincing marker of an individual's risk of developing LAA, the association shown does serve to indicate increased relative risk, at least for asthma. It seems reasonable that, whereas these relative risks should not be used as job discriminants, they may be used positively to give atopic individuals an informed view of their chances of developing LAA if they take up a job in exposure. Additionally, atopy may be used as an indication for more frequent or more searching monitoring in periodic medical surveillance.
The screening out of atopic individuals (by whatever criteria) from work in certain occupations remains a widespread occupational health practice. Our findings support the views put forward by Cockcroft et al (13) and Newman Taylor (14) whose studies in laboratory animal workers, despite some methodological differences, reached essentially the same conclusion. This was that the practice of excluding people found to be atopic at pre-employment medical examinations framework with laboratory animals should be abandoned. Though unlikely on present evidence, some forms of occupational asthma may possibly be more closely associated with atopy that is LAA asthma. In this situation, particularly in workplaces with a high rate of occupational asthma, such exclusion might be justified.

We thank M T Stevens for statistical advice and Mrs I Ball for secretarial work.
References


ACHIEVED OBJECTIVES IN LABORATORY ANIMAL ALLERGY RESEARCH:
THEIR SIGNIFICANCE FOR POLICY AND PRACTICE

A J M Slovak
ACHIEVED OBJECTIVES IN LABORATORY ANIMAL ALLERGY RESEARCH:
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ABSTRACT

The state of the art, so far as laboratory animal allergy (LAA) is concerned, has been significantly advanced by the research which I have described. The clinical patterns of LAA and their medical management can be reasonably confidently set out. Even so, I would expect some of the views, so confidently asserted here, to be overturned by future work. The advent of practicable, accurate hygiene methodology opens up the opportunity to develop credible protective strategies. In this area, I have refrained almost completely from offering detailed opinions on the grounds that, at present, they would be correct only by chance.

The paper describes the research work done on the characterisation and management of laboratory animal allergy (LAA) in the last ten years. It attempts to identify those goals that have been achieved and those which need to be reached before LAA can be managed in an entirely objective way.

For a number of serendipitous reasons, much of this work was done in the United Kingdom where, in the 1970's there existed a most exciting and supportive atmosphere for work in allergy and clinical immunology in the wake of such as Altounyan and Pepys. In 1973, contemporaneously with Lincoln and Lutsky², members of the British Society of Allergy and Clinical Immunology set up a survey which resulted in a brief publication in Nature in 1976³. After this, a number of interested people formed themselves into a loose cooperative association to exchange views, identify problems and to share out the work that needed to be done. In 1980 this association received some official backing and became a Study Group under the auspices of the UK Health and Safety Executive. Much of the work described in this paper has been performed under the hegemony of this Study Group.

EPIDEMIOLOGY AND CLINICAL HISTORY

Until very recently, the epidemiology of LAA has consisted exclusively of cross-sectional prevalence studies. These have fallen into two groups. The first of these [2,4] sampled exposed populations at multiple institutions using questionnaires to obtain subjective clinical histories. The second group of studies[1,5,6,7,8] considered the occurrence of LAA in discrete and more closely defined populations at one or a few institutions and, to a greater or lesser extent, attempted to validate subjective evidence by clinical follow-up and immunological studies. It is a consequence of the methodology of these studies that the first group painted an outline canvas and the second group filled in the details and sharpened the clarity of the picture.
Before 1974 it was believed that LAA was a relatively rare and only occasionally serious phenomenon. Now, it is clear that it is common and frequently causes severe symptoms and enforced job change. In the UK, prevalence has been reported as varying between 23-30%\(^{[4,6,7]}\) with the USA consistently reporting lower (range 11-15%)\(^{[1,2,5]}\) it is not clear whether this reflects a genuine difference. LAA develops in the majority of cases over the first three years of exposure especially between six and 36 months. The most common form of the disease is rhinitis, often with associated conjunctivitis and palate itching. This may be termed the regional form of LAA. A proportion of rhinitic cases go on to develop asthma and this proportion is between one-half and one-quarter of rhinitic cases. This latter group contains a preponderance of atopic people and may be termed the progressive group. Both regional and progressive cases can have symptoms severe enough to necessitate job relocation or treatment. It is important to note that the disease pattern described here is very different from the occupational allergies caused by low molecular weight (M.W) chemicals such as isocyanates where the predominant symptom is early, severe and universal asthma.

It would be useful to have comparative information from other prospective studies particularly with regard to incidence and prevalence rates in Europe and North America. However, those contemplating the design of new studies should seek to include specific new objectives. Thus the measurement of airborne antigen levels in relation to sensitisation as well as symptoms in established cases would be an important advance as would be the establishment of studies comparing incidence in different job categories and with different work routines.

Little is know about the long-terms effects of LAA or of laboratory animal exposure in the asymptotic. What little evidence there is about occupational asthma relates to disability after removal from exposure in the low M.W. "chemical" asthmatics. Here, there is evidence of frequent, substantial long-term disability\(^{[10,11]}\). While LAA seems in many ways a different type of acute disease, it does not follow that the prognosis is necessarily different too. Work on this subject is difficult but sorely needed.

**ETIOLOGY**

Post-war work on animal allergies, especially pets like cats, dogs and horses, identified the major sources of antigen as being of dermal origin. In 1977, Newman-Taylor, Longbottom and Pepys\(^{[12]}\) published results from a study of five asthmatic laboratory workers. They had been particularly impressed by reports from these people that they developed skin precautions when animals urinated on and then ran across the skin and wondered whether these in fact represented inadvertent skin prick tests. Their study showed that mouse and rat
urine derived proteins were indeed stronger and more specific antigens than dander extracts, both by skin prick and on bronchial challenge.

Since 1977, Longbottom has carried out a series of further studies which have identified a number of rat and mouse derived proteins which have antigenic potential\(^{13}\) some of these proteins, in varying concentrations, occur in dander extracts, urine, serum and saliva; some occur predominantly only in one of these sources. These findings imply that each of these sources has antigenic potential, but it is only now that some clues are forthcoming from industrial hygiene work which suggest which of these sources are of practical importance. It may yet be that each is important in different working circumstances and it is likely that this will be a profitable area for future study.

While most work on antigen identification has concentrated on the rat and mouse,\(^{13,14,15}\) we gained a strong impression in our study\(^{7}\) that the other commonly allergenic laboratory mammals, the guinea pig and the rabbit, were much more effective sensitisers than the rat and mouse. This view is supported by Rudolph.\(^{16}\) It would be useful to have the allergenic potential of the guinea pig and rabbit more fully explored both clinically and immunologically.

**PREDICTIVITY AND IMMUNOLOGICAL DIAGNOSTICS**

If a particular sub-group in a population can be identified as being unduly susceptible to the development of an occupational condition then this finding has both clinical and medicolegal significance. In relation to LAA, atopy was strongly cited as a predisposing factor in early papers,\(^{1,2}\). In later studies, Gross, Cockcroft et al and Slovak and Hill\(^{5,6,7}\) all specifically examined aspects of the possible correlation of atopy to LAA. This analysis was and is complicated by the existence of at least three main criteria or concepts for defining atopy - family history of allergy, past personal history of allergy and skin prick reactivity to common environmental allergens. From a plethora of conflicting data and inferences there was one area of remarkable concordance from the two British studies. Both reported a high correlation between LAA asthma and atopy defined by skin prick tests to common environmental allergens.

As a consequence of these reports the desirability of screening out atopic persons from employment with laboratory animals has been called in question. The evidence is that atopy is a universal and very useful clinical concept but its epidemiological applicability as a screening tool in LAA is highly questionable. This is shown in Table 1 which displays data derived from a further analysis of findings from the Slovak and Hill study.\(^{7}\) The diagram illustrates the sensitivity of atopy as a marker of LAA asthma (which is good) and its predictive value for LAA asthma or rhinitis (which is poor).
<table>
<thead>
<tr>
<th>Sensitivity</th>
<th>Predictive Value</th>
</tr>
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<tbody>
<tr>
<td><strong>Past History</strong></td>
<td><strong>Family History</strong></td>
</tr>
<tr>
<td>0.13</td>
<td>0.30</td>
</tr>
<tr>
<td>0.55*</td>
<td>0.43</td>
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</tbody>
</table>

* = significant at 95% confidence limits

**Table 1 - Sensitivity and Predictive Value of Atopy in LAA**

The common clinical pattern of immediate onset asthma in LAA suggests a predominantly IgE mediated response and this has been confirmed by the work of Newman-Taylor, Longbottom and Davies. IgE appears to be a somewhat indifferent marker of exposure. The value and place of immunological measurements in the diagnosis of LAA has been the subject of some debate. Skin prick tests, using serum and urine derived protein material not commercially available, were used in the Cockcroft and Slovak studies. Both of these studies showed a very strong correlation between positive skin prick tests and LAA asthma but no correlation between prick test positivity and LAA rhinitis. In the latter study, we also attempted to compare these experimental skin prick test solutions with those dander extracts that are commercially available. An improvement in diagnostic precision was noticeable but not statistically significant with the relatively small number of cases in our study. However these test solutions are now used exclusively in our Study Group and have proved reliable. A substantive comparative trial with existing commercial test antigens would be helpful in validating these clinical impressions.

Newman-Taylor et al restudied a large part of the population of our study some 18 months later. As well as confirming the original findings, they looked at specific IgE to urinary antigens by RAST. Their findings suggesting a RAST score gradient, asthma > rhinitis > asymptomatics, led them to conclude that the immunological mechanisms responsible for "progressive" LAA (asthma) might be different from those involved in regional LAA (rhinitis and urticaria). This suggestion has been challenged in studies performed by Orr and Davies et al. The question of whether there are separable populations who "progress" or do not, has important implications for management and would repay further study.

**LUNG FUNCTION TESTS**

For occupational asthma, spirometric recording of FEV₁/FVC is a cumbersome technique for assessing lung function except in specially set up challenge studies such as that described by Gross. While challenge studies are an
important part of the early investigations of new causes of occupational asthma, they offer an essentially artificial situation and do not reflect the actual day to day pattern of disability imposed by an occupational or environmental agent. The development of portable mini-peak-flow-meters now allows many asthmatics to monitor their lung function regularly each day. In the field of occupational asthma, their use has been pioneered by Burge who has contributed a substantial volume of work on the various patterns of occupational asthma including LAA\(^{(20)}\).

Peak expiratory flow records (PEFR) kept over a period of months not only provide an accurate record of the severity and pattern of disease but allow the effect of various protective and therapeutic measures to be assessed. Thus we have studied the efficacy of ventilated helmet respirators in LAA asthmatics who opted for career reasons to maintain some animal exposure. Two out of eight asthmatics studied over a six week exposure period had episodes of over work-related asthma despite rigorous adherence to helmet usage routines, four achieved a substantial degree of protection and two were totally protected. These findings suggest that these helmets are a substantial contribution to protection but no panacea. A further refinement which may be added to peak-flow recording is to obtain concurrent recording of symptoms. This provides further information on the intrusiveness of the disease process and the correlation between subjective symptomatology and objective lung function deficits. These are often people in the early stages of progression to full-blown LAA asthma. We have begun to study them using periodic histamine challenge and skin prick tests. As yet, too few patients have been studied in this way to draw definite conclusions but it would appear that the process of unfolding of this disease is a relatively leisurely affair of several months development marked by increasing skin prick and histamine reactivity. Those having access to large occupationally exposed populations would be amply repaid for their effects in studying the early progress of LAA by these techniques.

**MEASUREMENT AND PROTECTION**

It is conventional occupational health practice to identify exposure levels below which most people are deemed safe to work. This is the rationale of hygiene standards. With occupational allergens, the setting of exposure limits is complicated by the fact that there are two separate objectives, the prevention of sensitisation and the prevention of symptoms in the sensitised. With most causes of occupational asthma only the latter objective is worth attempting currently.

To do this, the essential requirement is for a system which will capture airborne antigens and measure them quantitatively and qualitatively. In animal rooms, early attempts were made to approach this objective indirectly by measuring total dust or protein in dust. At that time, antigen assay techniques were too insensitive to deal with the minute quantities involved. The temptation to
assume that there was some sort of universal correlation between these parameters and actual antigen levels was difficult to resist and the technique of total dust measurement was used by Burrows et al in experimental work on animal room design\cite{21}. In the indirect approach it has been shown that antigen levels do correlate when diurnal activity is measured in particular animal rooms; this relationship does not hold between different rooms or, more importantly, when human beings intrude into the situation. In this latter case, increased antigen levels are not merely derived from increased dust generation by the animals but also produced de novo by fear associated urinary voiding. The antigen released into air by urination is quantitatively important and is naturally independent of existing dust levels. Thus Davies et al\cite{22} reported a ranking of antigen exposure levels according to activities performed in animal rooms. In this ranking, feeding weighing operations were low but experimentation and observation were high. This means that dust suppression systems, such as cage ventilation, wet litter clearance, etc., are likely to be ineffective in preventing LAA because the antigens, even if effectively removed are not those to which humans, working in those environments, are actually exposed. Both Twiggs\cite{15} and Davies et al\cite{22} have now described reliable techniques for measuring airborne antigens so the way is clear to mapping animal room activities in terms of exposure. A considerable amount of work is necessary to document antigen levels in the various exposure situations involved in animal work. From these findings it should be possible to modify work routines and establish protective systems which will demonstrably prevent or minimise antigen challenges to workpeople. The simplest protective systems are personal equipment such as masks and ventilated helmet respirators. There is plenty of anecdotal evidence that they have some efficacy in preventing symptoms of LAA; however, other than the work referred to in the previous section (Lung Function Tests), there is no objective published evidence of the limitations of this efficacy. Since they are currently available and relatively cheap, they merit further serious evaluation.

**MANAGEMENT POLICIES**

It is worth noting that LAA, as it is seen in hospital clinics, is not representative of the overall pattern of the disease in working populations. It is therefore prudent for clinicians to be cautious in deriving conclusions about the management of LAA from the skewed samples of severe and clinically problematic cases from which they are likely to have drawn their experience. In the majority of cases LAA is more of a nuisance than a problem and neither affected individuals nor their employers will thank us if we seek to lay down unnecessarily rigid guidance for them to follow.

The management considerations presented below are discussed at greater length in the Association of the British Pharmaceutical Industry Advisory Note on LAA\cite{23} and more generally elsewhere\cite{25}. They take account of a medicolegal situation which is somewhat different from that prevailing in North America. It is
worth stating briefly what that situation is. Firstly, in UK law, actions taken to secure health and safety take primacy over anti-discriminatory, employment protection and other allied legal precepts. Secondly, asthma due to LAA is a prescribed disease attracting State compensation. Prescription by time honoured practice has always been a signal to Labour Unions to attempt common law claims against employers. In order to win these the plaintiff must prove negligence. That is, that an employer should have been aware of a risk but had not taken reasonable and appropriate action to ameliorate it.

RECRUITMENT

Even if legally excused from penalty for discriminative policies, it is sensible in simple equity to discriminate medically against as few persons as possible. However some people are likely to be severely embarrassed with regard to their health, if they develop LAA. At special risk are those with pre-existing severe chest or heart disease. Also it is plainly foolish to employ someone with serious established LAA or active and frequent asthma if they are to work directly with or near animals. From the evidence presented earlier in this paper, supported by findings of Cockcroft et al[6] it seems unhelpful to exclude atopic persons, representing, as they do, some 30% of potential recruits and knowing that a large proportion of them will not develop LAA at all. Conversely, atopics are at special risk of progressing to asthma if they do develop LAA and I consider there to be a duty to inform them of this fact so that they can decide individually if they wish to take up animal work.

INFORMATION

As well as the duty of special care to atopics there is a general responsibility, well recognised in statute and common law, to provide information to all relevant workpeople about any common condition that they might be expected to develop as a consequence of work. This information should cover the basic facts about prevalence, symptoms, protection, reporting procedures, screening, investigation and management and may also refer to an organisational policy on such issues as relocation.

SCREENING AND INVESTIGATION

Occupational diseases are generally underreported. Even with severe asthma we have found this to be true, with less than 50% of patients reporting their symptoms to any medical authority[25]. Such findings suggest a clear need for protective screening and this we do annually by the use of a simply self-completed questionnaire. This is followed by interview and such investigations as are deemed necessary.

The diagnosis of LAA is made on clinical history. Immunological and lung function tests are only consistently positive in asthma but usually serve for
exclusion in rhinitis. Where there is asthma, with positive, specific, skin prick tests (and/or RAST) and a characteristic dipping PEFR record, the diagnosis is easy to make. However even with asthma, not all cases are straightforward and practical work challenge, (rather than clinic or laboratory simulation), is useful in both rhinitis and asthma where there are doubts about the diagnosis. Obviously, this should only be done where the severity of the likely response does not preclude such a procedure.

Lack of knowledge of long-term effects has already been mentioned both in those with LAA and those without but in exposure. It seems timely to begin considering the storage of simple periodic spirometric records from animal workers.

RELOCATION

If a disease can be prevented from manifesting by the avoidance of an exposure then the management is obvious. Persons developing serious LAA rhinitis or asthma should be offered the opportunity for relocation away from animal work; however many persons will opt to remain in exposure for career, employment or other reasons. If this course of action is decided on then temporary relocation, for a period of 6-12 months, may be helpful to allow the diminution of airways hyperactivity before re-exposure occurs. In any case, such people require additional counselling, special care with protection and periodic lung function screening.

In practice, the best protection currently available is the helmet respirator and this can be worn all day although it is heavy and socially isolating. A lighter version is becoming available. A reliable system of helmet filter changing, cleaning and battery care is essential. Counselling will consist of general advice on protection, management and minimisation of exposure and the identification of specific tasks causing severe symptoms which can then be avoided. PEFR needs to be performed periodically to assess the level of protection afforded by the various measure undertaken. Ours is carried out annually for a minimum of one month outside the hay fever season. Interreactons between specific occupational airways hyperactivity and seasonal disease are a problem from time to time\textsuperscript{23}, and may need to be investigated in detail in some patients.

PROTECTION

The evidence needed to set exposure limits (hygiene standards) to prevent sensitisation is not currently available nor will it be for some time. Therefore any advice offered on systems of protection, however elaborate, is mere conjecture; no faith should be placed in any of them. In very general terms though, it does not seem unreasonable to aim at reducing casual exposure whenever this is relatively easy to do. Thus many animal facilities propagate
their miasma well beyond their own confines. This may be remedied by segregating animal facilities physically or by ventilatory means. Only persons needing access should be allowed to enter animal areas. Animal transport movements should be rationalised and kept to the minimum needed, as should animal stocks in laboratory areas.

If no trust is to be put in elaborate static protective systems, than what of personal protection? Again, there is no evidence of efficacy in preventing sensitisation, only of preventing or delaying symptoms in the sensitised. If mask wearing were to be put forward as a prophylactic protective measure for the asymptomatic it would meet resistance on a number of grounds. Firstly it is not common custom and practice among animal workers, secondly there is no proof that it works and thirdly only a minority of workers will get LAA, so many of them will be asked to wear masks for no palpable benefit to themselves at all; however, a minority of people are apprehensive of developing LAA and request protection. Although it is somewhat illogical to provide something which may not work and may not even to needed, it is difficult to resist such a request.

CONCLUSION

The state of the art, so far as laboratory animal allergy (LAA) is concerned, has been significantly advanced by the research which I have described. the clinical patterns of LAA and their medical management can be reasonably confidently set out. Even so, I would expect some of the views, so confidently asserted here, to be overturned by future work. The advent of practicable, accurate hygiene methodology opens up the opportunity to develop credible protective strategies. In this area, I have refrained almost completely from offering detailed opinions on the grounds that, at present, they would be correct only by chance.
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