Asthma and Work
The Colt Lecture, delivered at the Ninth International Symposium on Inhaled Particles, Cambridge, September 2001

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It is a great privilege to be invited to deliver the Colt lecture. The Colt Foundation, which this lecture honours, was founded by the O’Hea family to support research with the aim of reducing ill health caused by work. Their contribution provides the major charitable source of funding in the UK for investigator-initiated research into the causes and consequences of occupational disease. It is a pleasure in giving this lecture to give public recognition to the O’Hea family for their unwavering commitment to occupational health research.

I have chosen to focus on asthma and work, not only because this has been a major research interest of mine for more than two decades but, of more importance, because asthma is the most prevalent cause in the UK, and probably in the Western World, of respiratory ill health during working life. Now recognized as a chronic inflammatory disease of the bronchial airways, asthma is characterized by episodes of airway narrowing which can cause significant disability and impact on the ability to work. Increased lability of the airways, which is characteristic of asthma, allows provocation of acute airway narrowing by physical and chemical stimuli encountered at work. In addition, asthma can be induced by agents inhaled at work, both as a reaction to irritants inhaled in toxic concentrations and as the outcome of a hypersensitivity response to inhaled proteins and low molecular weight chemicals—occupational asthma.

During the past 30 yr much has been learnt of both the causes of occupational asthma and its consequences. It has become clear that the risk of development of occupational asthma is determined less by individual susceptibility (genetic or behav-

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induced asthma does not have a latent interval, but develops within hours of inhalation of the toxic chemical. Examples of some inducers and inciters of asthma encountered at work are shown in Table 1.

**ASTHMA IN WORKING LIFE**

Asthma is common during the years of working life. The European Community Respiratory Health Survey (ECRHS) estimated the prevalence of asthma in 48 countries, predominantly in Western Europe, in adults aged between 20 and 44 yr between 1988 and 1994 (Burney et al., 1996). In each centre, random samples of 1500 men and 1500 women were identified from populations of at least 150,000 people of all ages. Questionnaires asking seven main and two supplementary questions were sent by post: the overall response rate was 78%. The questionnaires were translated into 17 languages and applied after back translation, usually into English. A case of diagnosed current asthma was based on a positive answer to two questions, indicating an attack of asthma in the previous 12 months or currently receiving treatment for asthma. The median prevalence of ‘diagnosed current asthma’ was 4.5%, with considerable variation between countries. The study included samples from a number of towns outside Europe, in the USA, Australia and India. The highest prevalences were consistently found in English speaking countries, with rates of 11.9% in Melbourne, Australia, 11.3 and 11.2% in Wellington and Christchurch, New Zealand and 8.4, 8, 7.8 and 7.4% in Cambridge, Caerphilly, Ipswich and Norwich, UK. Studies in North America, Western Europe and Australasia have also indicated that the prevalence of asthma in childhood has increased during the past 20–30 yr. Two studies of schoolchildren which used identical methods of ascertainment at two time points, one in South Wales separated by 15 yr (Burr et al., 1989), the second in Aberdeen separated by 25 yr (Ninan and Russell, 1992), found increases of 2- and 2.5-fold in the prevalence of asthma, identified in both surveys by questionnaire and in South Wales also by exercise testing.

A study in Finland using national registry data, required for health costs reimbursement, for adults between 1986 and 1993 showed a 21% increase in the incidence of asthma in adults (from 15 to 64 yr) during this period (Reijula et al., 1996). The increase was greater in those aged between 15 and 49 yr, both in men and women, than in 50–64 yr olds. The prevalence of asthma in those of working age has increased, an increase which, because of the increased incidence during childhood, seems likely to continue for at least another decade. Furthermore, those children with asthma who remitted in their teenage years remain at increased risk of developing asthma during adult life. Children in the UK have been followed up at regular intervals from childhood into adult life. Asthma recurred in a proportion in adult life after a period of remission in childhood: more than half of those who had wheezed before the age of 7 yr and who reported wheezing aged 33 yr had been free of symptoms for 7 yr between the ages of 16 and 23 yr (Strachan et al., 1996).

The impact of asthma on productive work is the consequence of its frequency and severity. It is a chronic disease characterized by exacerbations which may be provoked by viral respiratory tract infections and exposure to allergens such as pollens, mites and domestic animals, but which often are of unknown cause. Exacerbations can induce prolonged episodes of airway narrowing with associated disability and time lost from work. A study by Blanc and Toren (1999) of the ECRHS sample of 20–44 yr olds in Goteborg, Sweden found that 13% of those with asthma identified by questionnaire and 22% of those who had work-related symptoms and airway hyper-responsiveness had lost or changed their job because of ‘breathing affected by a job’. The major risk factors identified were contact with ‘vapour, gases, dusts or fumes’ [prevalence ratio (PR) 4.3] and with environmental tobacco smoke (PR 1.8), particularly in atopics (PR 6). A study of young adults in the UK found that those with asthma in the past but not the previous year were half and those with asthma during the previous year one-third more likely to be unemployed than contemporaries without asthma. In addition, they were more likely than those without a history of asthma to have had more periods and more time out of work (Sibbald et al., 1992).

**Table 1. Inducers and inciters of asthma**

<table>
<thead>
<tr>
<th>Inducers</th>
<th>Inciters</th>
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<tbody>
<tr>
<td>Irritant</td>
<td>Exercise</td>
</tr>
<tr>
<td>Chlorine</td>
<td>Cold air</td>
</tr>
<tr>
<td>Ammonia</td>
<td>Sulphur dioxide</td>
</tr>
<tr>
<td>Toluene di-isocyanate</td>
<td></td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td></td>
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<tr>
<td>Proteins</td>
<td></td>
</tr>
<tr>
<td>Enzymes</td>
<td></td>
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<tr>
<td>Animal urine proteins</td>
<td></td>
</tr>
<tr>
<td>Flour</td>
<td></td>
</tr>
<tr>
<td>Latex</td>
<td></td>
</tr>
<tr>
<td>Low molecular weight chemicals</td>
<td></td>
</tr>
<tr>
<td>Isocyanates</td>
<td></td>
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<tr>
<td>Platinum salts</td>
<td></td>
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<tr>
<td>Acid anhydrides</td>
<td></td>
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<tr>
<td>Reactive dyes</td>
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</table>
THE INTER-RELATIONSHIP OF ASTHMA AND WORK

Work can combine with asthma in several ways to increase disability and the associated economic consequences.

Inducers of asthma encountered at work, both irritants and sensitizers, initiate asthma: inciters of asthma provoke episodes of acute airway narrowing in those with pre-existing asthma. In both cases the physical or chemical environment of work causes functional impairment and associated disability. The nature of work can also increase the disability of asthma without directly provoking functional impairment: the demands of heavy physical work may not be achievable; the characteristics of asthma, the diurnal pattern of airway narrowing, worse at night and in the early morning, and the tendency to exacerbations of disabling airway narrowing, can require control over the pace and timing of work and acceptance by employers of absences from work at times of exacerbations.

Those of lower educational attainment and socioeconomic status are least likely to be employed in occupations which permit flexibility and autonomy at work. They are also more likely to be engaged in work which will be the most physically demanding and which brings them into contact with agents which induce and incite asthma (Blanc, 2000).

ASTHMA INDUCED BY WORK

Asthma induced by agents inhaled at work has been a major subject of research during the past 30 yr. The outbreaks of asthma in the early 1970s, which followed the introduction of proteolytic enzymes into detergent manufacture, a commercially important and expanding market in the UK, Scandinavia, Australia and the USA, stimulated considerable research interest in allergic occupational asthma. Asthma induced by irritant chemicals inhaled in toxic concentrations, which was first described in 10 patients in 1985 as reactive airways dysfunction syndrome (RADS) (Brooks et al., 1985), has been increasingly recognized as an entity during the past 10 yr. However, the more prevalent hypersensitivity-induced asthma has remained the major focus of investigation: a clear picture has emerged of its incidence by occupation and by agent and of its major determinants, with evidence for exposure–response relationships for several of its causes and for modifying host factors, in particular atopy, cigarette smoking and HLA phenotype, for some of its causes.

The proportion of adult asthma attributable to an occupational cause has also been the subject of recent studies. Kojevinas et al. (1996) estimated the population attributable risk (PAR) in the ECRHS sample in Barcelona as 7.5%. The Finnish registry study, on the other hand, estimated that 4.8% of new cases of asthma, 6% in men and 3.9% in women, were attributable to occupation (Reijula et al., 1996). Blanc and Toren (1999) undertook a systematic analysis of relevant publications and estimated a median attributable risk of 9% (25th–75th interquartile range 5–19%), with the 12 highest rated studies yielding a median risk estimate of 15%, implying that some 10–15% of new or recurrent cases of asthma in adult life are attributable to occupation.

ESTIMATED INCIDENCE

The incidence of occupational asthma in different occupations and the relative importance of the different agents which cause it have been provided for the UK since 1989 by the Surveillance of Work and Occupational Respiratory Disease (SWORD). The scheme depends on voluntary reporting of new cases of occupational respiratory disease seen by specialist chest and occupational physicians; it is, therefore, more likely to under- than overestimate the true incidence of occupational asthma. During the first year of the scheme (1989) it achieved comprehensive coverage of chest physicians with reports from 350, representing 90% of chest clinics in the UK. Since 1992, a core group of some 30 chest physicians, with a particular interest in occupational lung disease, have continued to report monthly, while the remainder (some 400), grouped into 12 random samples, report cases seen in one selected month each year.

The relative importance of the different agents identified and the estimated incidence in different occupations have remained remarkably stable during the decade of reporting, except for some reduction in the proportion of cases attributed to isocyanates and an increase in the cases attributed to latex (Fig. 1; McDonald et al., 2000). Organic agents (such as flour/grain, wood dust and laboratory animals) and chemical agents (such as isocyanates and glutaralde-
(hyde) together account for some two-thirds of reported cases and a miscellaneous group (which includes glues, resins, hardening agents and paints) for a further 20% (Table 2).

The estimated annual incidence by occupational group ranged from 1380 per million/yr in coach and spray painters to 12 per million/yr for transport and storage workers. The occupational groups with an estimated incidence of more than 100 per million/yr, with the exception of laboratory technicians and assistants, were engaged in manufacture or processing of chemicals or metals or of organic materials such as foodstuffs and wood. The occupations associated with agents causing more than 100 cases between 1992 and 1997 are shown in Table 3.

Table 2. Estimated annual incidence rate per million employed persons in selected high risk occupations 1989–97 (after McDonald et al., 2000)

<table>
<thead>
<tr>
<th>Occupational group</th>
<th>Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coach and spray painters</td>
<td>1324</td>
</tr>
<tr>
<td>Bakers</td>
<td>518</td>
</tr>
<tr>
<td>Chemical processors</td>
<td>604</td>
</tr>
<tr>
<td>Metal treatment</td>
<td>369</td>
</tr>
<tr>
<td>Plastics workers</td>
<td>833</td>
</tr>
<tr>
<td>Welding, soldering, electronics assembly</td>
<td>282</td>
</tr>
<tr>
<td>Laboratory technicians and assistants</td>
<td>399</td>
</tr>
<tr>
<td>Food processing (excluding bakers)</td>
<td>164</td>
</tr>
<tr>
<td>Woodworkers</td>
<td>90</td>
</tr>
</tbody>
</table>

Table 3. Occupations associated with agents causing >100 cases reported to SWORD between 1992 and 1997 (after McDonald et al., 2000)

<table>
<thead>
<tr>
<th>Agent</th>
<th>Occupation</th>
<th>Number</th>
<th>Percentage of cases in this occupation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isocyanates</td>
<td>Spray painter</td>
<td>286</td>
<td>34</td>
</tr>
<tr>
<td>Flour and grain</td>
<td>Baker</td>
<td>317</td>
<td>62</td>
</tr>
<tr>
<td>Wood</td>
<td>Woodworker</td>
<td>251</td>
<td>82</td>
</tr>
<tr>
<td>Glutaraldehyde</td>
<td>Nurse</td>
<td>189</td>
<td>72</td>
</tr>
<tr>
<td>Laboratory animals</td>
<td>Laboratory technician or assistant</td>
<td>184</td>
<td>74</td>
</tr>
<tr>
<td>Solder/colophony</td>
<td>Welder, solderer or electronic assembler</td>
<td>161</td>
<td>69</td>
</tr>
</tbody>
</table>

The estimated annual incidence by occupational group ranged from 1380 per million/yr in coach and spray painters to 12 per million/yr for transport and storage workers. The occupational groups with an estimated incidence of more than 100 per million/yr, with the exception of laboratory technicians and assistants, were engaged in manufacture or processing of chemicals or metals or of organic materials such as foodstuffs and wood. The occupations associated with agents causing more than 100 cases between 1992 and 1997 are shown in Table 3.

Three comparisons, one internal and two external, are informative. The proportion of total cases of occupational asthma and mesothelioma reported to SWORD are shown in Fig. 2. While occupational asthma has remained the most frequently reported category, it has remained stable throughout the decade, whereas the frequency of malignant mesothelioma has steadily increased, which it is anticipated will continue until 2020. Table 4 contrasts the proportion of cases reported to SWORD with those of a similar scheme in South Africa (SORDSA). The differences in reported diseases reflect the predominance in South Africa of mining and associated ill health (pneumoconiosis, TB and COPD) as opposed to manufacturing and service industries in the UK (Huijdo et al., 2001). The small proportion of cases of mesothelioma in South Africa seems likely to reflect incomplete ascertainment. Figure 3 shows the progressive increase in occupational asthma reported to the Finnish register of occupational disease between 1986 and 1993 (Reijula et al., 1996). The Finnish register, which probably has a more complete ascertainment than SWORD, suggests a 70% increase in the incidence of occupational asthma during this period.

IRRITANT-INDUCED ASTHMA (RADS)

Irritant-induced asthma (or RADS) is chronic asthma which persists after a single inhalation, usually of short duration, of a respiratory irritant chemical in a toxic concentration. The development of respiratory symptoms and measurable airway hyperresponsiveness within a few hours of an identifiable exposure distinguishes irritant- from hypersensitivity-induced asthma. Most reports of irritant-induced asthma have been case series. The original report in 1985 described 10 patients none of whom had evidence of pre-existing respiratory disease (Brooks et al., 1985). All developed persistent asthma after a single exposure, usually of a few minutes, but in one
A case of 12 h, to a variety of irritants which included spray paint containing ammonia, heated acid, floor sealant, uranium hexafluoride and smoke. The onset of symptoms was immediate in three, with an average interval of 9 h in the others. The duration of symptoms to the time of follow-up ranged from 1 to 12 yr, at which time all 10 had increased airway responsiveness to inhaled methacholine and seven had evidence of airflow limitation. Subsequent case reports have identified several different chemical causes, including sulphur dioxide (Harkonen et al., 1983), toluene di-isocyanate (Luo et al., 1988), anhydrous ammonia fumes (Bernstein et al., 1989) and smoke (Moisan, 1991).

In general, case reports of irritant-induced asthma have been highly selected and without information about lung function prior to the inhalation accident. One study of hospital employees (Kern, 1991) exposed to 100% acetic acid after a spill in a hospital laboratory overcame many of these problems by:

1. studying a random sample of the population exposed to the spilt chemical;
2. demonstrating an exposure–response relationship between the estimated intensity of exposure and attack rate of acute irritant symptoms and prevalence of airway hyper-responsiveness, the risk of developing irritant-induced asthma being some 13-fold greater in those most, as compared to least, exposed to acetic acid;
3. partial validation of respiratory health before the accident by examination of pre-employment questionnaires.

An investigation of 623 inhalation accidents reported to SWORD between 1990 and 1993 sug-
ggested that symptoms persisted for >1 month in 142, which included 50 new cases of asthma (Sallie and McDonald, 1996). A follow-up questionnaire in 1995 indicated that new asthma following an inhalation accident was present in 34/50 original cases, of whom 28 had continuing symptoms (Ross and McDonald, 1996). Interestingly, the most frequent causes were chemical sensitizers (particularly isocyanates) inhaled in toxic concentrations, together with chlorine, sulphur dioxide and ammonia. Spills, leaks and faulty processes accounted for one-third of these inhalation accidents and failure to observe safety guidelines, including failure to use respiratory protection and inappropriate procedures when mixing chemicals, for a further third.

**HYPERSENSITIVITY-INDUCED ASTHMA: EXPOSURE–RESPONSE RELATIONSHIPS**

The initial reaction to the epidemic of occupational allergy and asthma which followed the introduction of a proteolytic enzyme, Alcalase, into detergents was to find the means to reduce airborne enzyme concentration and to exclude from employment atopics, who were considered constitutionally susceptible. Contemporary studies had found that atopics, those with immediate skin test responses to common inhalant allergens, were at increased risk of developing immediate skin test responses to Alcalase (Newhouse et al., 1970); a later report of a 7 yr follow-up from 1968 of employees of one enzyme detergent factory demonstrated that atopy increased the risk of developing a skin test reaction to Alcalase at all levels of exposure (Juniper et al., 1977).

This emphasis on the importance of host susceptibility reflected contemporary scientific understanding of the immunopathogenesis of asthma, as an IgE-mediated reaction to inhaled allergens, determined primarily by individual susceptibility. The greater influence of the level of exposure to the relevant allergen or low molecular weight sensitizer on the induction of hypersensitivity-induced occupational asthma has been a major advance of the past decade. By implication, improved control of exposure, not exclusion of an identifiable susceptible minority, is the more effective means to reduce disease incidence. In part this shift in understanding, and practice, has depended on appropriate analysis of longitudinal, rather than cross-sectional, studies of working populations exposed to the causes of asthma.

The well-recognized problem of survivor bias in cross-sectional studies is a particular problem in studying a disease such as occupational asthma, which is characterized by recurrent acute reactions, which individuals can relate to their place of work and avoid further exposure by leaving or by relocation: those who accumulate exposure are those who survive to do so. Similarly, exposure measured at the time of the study may differ considerably from an earlier period when asthma developed. While cross-sectional studies can provide an estimate of the prevalence of disease and its relationship to contemporary, or estimates, of past exposures, these together will attenuate exposure–response relationships.

We have observed this in studies we have undertaken of laboratory animal allergy. The first (Venables et al., 1988) was a cross-sectional survey of the employees of a UK pharmaceutical company. Forty-four per cent of the 138 in contact with laboratory animals at work reported, in a self-completed questionnaire, symptoms of laboratory animal allergy (LAA); 15 (11%) had chest symptoms. As observed in previous studies (Cockcroft et al., 1981; Slovak and Hill, 1981). LAA chest, but not nose, eye or skin, symptoms were associated with an immediate skin test response to extracts of animal urine proteins and to atopy. Atopics were five times as likely as non-atopics to have LAA chest symptoms. Of particular interest, however, the duration of employment was inversely related to LAA chest, but not other, symptoms, suggesting that those with chest symptoms were more likely to leave employment.

In the early 1990s we embarked on a cohort study of populations working with laboratory animals in four separate institutions in the UK specializing in small animal research. The study, which included both measurements of airborne animal urinary protein concentrations and surveys of the workforces at 6 monthly intervals, was undertaken over 5 yr. In the initial phase of the study we undertook a cross-sectional survey of the cohort, defined as those employed within the 4 yr (i.e. from 1 January 1986) before our initial visits in 1990, who were in employment in the same institution in 1990 (Cullinan et al., 1994). We found a gradient of increased prevalence of skin prick test responses to rat urinary protein, which was steeper in atopics, with increasing intensity of exposure to rat urinary aero-allergen. There was, however, no consistent relationship between new work-related symptoms (chest, eye and nose or

**Fig. 3.** Cases of occupational asthma reported to the Finnish register of occupational disease (1986–93).
skin) and exposure intensity at the time of the survey. In contrast, there was a trend of increasing prevalence of new work-related symptoms, which was strongest for skin symptoms (contact urticaria), with the level of exposure at the time of onset of symptoms. This difference seemed likely to reflect movement of employees between different jobs, as well as out of employment. We found that the movement of employees after the onset of symptoms was invariably to a job with lower exposure and was most frequent for those with new work-related chest symptoms, 24% of whom had changed job. Sixteen per cent of those with new work-related eye and nose symptoms and 12% of those with new work-related skin symptoms had moved to a job of lower exposure intensity. In contrast, only 4% of the workforce without symptoms had moved to jobs of different exposure intensity, in many cases to jobs of higher intensity of exposure to rat urinary protein.

The results of the 5 yr cohort study showed clear evidence of an exposure–response relationship, particularly for those cases, the great majority, who had developed symptoms within 2 yr of starting employment (Cullinan et al., 1999). The risk of developing any new work-related symptom was more than five times greater in the highest (category 4) than in the lowest (category 1) of four exposure categories. Exposure–response gradients were observed for new work-related chest, eye/nose and skin symptoms and for the immediate skin prick test response to rat urinary protein. The increase in risk for those employed in jobs in exposure category 3 (OR 5.5) was twice as great as the increased risk to atopics (OR 2.7) of developing new work-related chest symptoms. For all new work-related symptoms (and for skin prick test responses to RUP) the increased risk from working in the higher exposure categories (3 and 4) was twice or more the increase in risk to atopics. The study identified airborne rat urinary protein concentration as the major determinant of disease and, by implication, its reduction as the most effective means to reduce disease incidence.

Similar findings were reported in a companion prospective cohort study of flour mill and bakery workers exposed to flour and to fungal α-amylase and a historical cohort study of acid anhydride workers employed in four factories in the UK (Cullinan et al., 2001). Among the flour-exposed workers the incidence of work-related chest symptoms in those with a positive skin prick test reaction to flour dust or α-amylase was 1/100 person yr. Those in the high exposure group (category 3) were 7.7 times more likely to develop chest symptoms than those in the low exposure group (category 1); atopics were no more likely than non-atopics to develop chest symptoms. Of interest, the level of exposure to flour in the high exposure group was, on average, 4.4 mg/m³, suggesting the induction of work-related chest symp-

toms at concentrations less than the contemporary exposure limit of 10 mg/m³.

In one factory in our study of acid anhydride workers, which used trimellitic anhydride (TMA) in the manufacture of cushioned flooring, the risk of developing an immediate skin prick test response to TMA and new work-related chest symptoms showed a clear exposure–response relationship, increasing with increased maximum full shift exposure to TMA (Barker et al., 1998). This relationship was not modified by atopy or smoking. Of particular relevance, 11 of the 12 cases of new work-related chest symptoms (and six of the eight with an immediate skin test response to TMA) had worked in conditions where the maximum full shift exposure was less than the current occupational exposure standard in the UK of 40 μg/m³.

Although more confident inferences can be drawn from the results of cohort studies of occupational asthma, as compared to cross-sectional studies, they are more expensive and more difficult to undertake, requiring that a high proportion of those within the cohort are kept in view over several years. These problems can, however, be reduced by case–referent analysis of longitudinally acquired data.

This was the approach taken in a study of occupational asthma caused by isocyanates in a factory manufacturing polyurethane products (Meredith et al., 2000). One factory with 27 cases, which had developed over several years, had past records of measurements available, allowing estimation of exposure by job category. Referents without disease were matched with cases on work area, start and duration of employment. Those exposed to an 8 h time-weighted average exposure to isocyanates in excess of 1.25 p.p.b. (the median concentration experienced by the referents) were some 3.2 times more likely to be a case.

Another approach has been to use a cross-sectional survey of period prevalence to identify a ‘cohort’ of persons employed during the previous 2 yr, when measurements of exposure were available. A prospective analysis was made in the knowledge that a high proportion had remained in employment and on the assumption that case ascertainment was close to complete. This was the approach taken in a cross-sectional survey of enzyme detergent workers, in whom there was evidence of an exposure–response relationship, but only measured area samples for protease concentrations in the 2 yr before the survey in 1998 (Cullinan et al., 2000). The geometric mean concentration of airborne protease was 4.25 ng/m³, with 5% above the industry guidelines of 15 ng/m³. The highest value was 57 ng/m³ [below the American Conference of Governmental Industrial Hygienist (ACGIH) threshold limit value (TLV) of 60 ng/m³]. Measurements in 1998 indicated that the airborne concentration of amylase was consistently half that of
protease. Of 74 who started work in or after 1997, two had work-related chest symptoms and five work-related nasal symptoms. Five had a positive skin test reaction to protease and five to amylase.

OUTCOME OF OCCUPATIONAL ASTHMA

The outcome of occupational asthma has been reported in several surveys. Most have concentrated on the persistence of respiratory symptoms and abnormal lung function. These studies need to be interpreted with caution, as several were based on hospital patients: those with severe disease are more likely to be referred and those with continuing symptoms more likely to be kept in view. In four studies, of snow crab process workers (Malo et al., 1988) and of tetrachlorophthalic anhydride (TCPA) (Venables et al., 1987) and azodicarbonamide workers (Slovak, 1981) and 12 cases from one factory within a hospital-based study of isocyanate workers (Lozewicz et al., 1987), the cases of asthma were identified not through hospital referral, but from survey of a factory population. Follow-up was complete in all four. Each study reported evidence of continuing asthma (respiratory symptoms, reduced FEV$_1$ or increased airway responsiveness) in more than 50% of cases. In the snow crab process and TCPA workers, a progressive decline in specific IgE following avoidance of exposure, confirmed that exposure to the cause had been avoided during the period of follow-up.

The largest survey of outcome was the attempt to obtain information in 1994 on all 1940 cases of occupational asthma reported to SWORD in 1989–92. Although questionnaires were returned for 1769 (91%), the data required were available for only 1317 (68%). It seems likely, nonetheless, that the findings were reasonably representative. Of patients reported by occupational physicians, 45% had recovered, as compared with only 14% reported by chest physicians (even after excluding medico-legal cases), presumably because of differing severity of the cases seen. Among cases reported by chest physicians who were able to provide information on subsequent employment, 48% of patients had remained with the same employer, 16% were with another employer, 6% had retired and 30% were unemployed or medically retired (Ross and Mcdonald, 1998). None of these studies, however, included objective evidence of normal airway function, FEV$_1$, airway responsiveness before onset of the relevant exposure or a comparison with an appropriate referent population.

Nonetheless, these findings imply that occupational asthma can persist for several years, in many cases indefinitely, after avoidance of exposure to the initiating agent, particularly low molecular weight chemical sensitizers. Except in the SWORD survey, the outcome in cases caused by several of the other more frequent causes of asthma, such as laboratory animals, flour and enzymes, has not been specifically reported. In addition to the SWORD survey, the wider social and financial consequences of occupational asthma have been investigated in studies of patients referred to hospital physicians. In one study, 59% had lost or changed their job and 74% reported loss of income (Weir et al., 1987). In the other, one-third were unemployed at the time of interview, 57% reported difficulty in finding alternative employment and 49% had lost income (Venables et al., 1989).

PREVENTION OF OCCUPATIONAL ASTHMA

The considerable risk, in cases of asthma induced by agents inhaled at work, of progression to chronic asthma with consequent social and financial disadvantages should, at a minimum, act as a stimulus to the investigation and evaluation of effective means of intervention to reduce the incidence of the disease. In fact, the data reported to SWORD, although liable to variation in ascertainment and reporting, suggest that in 10 yr of surveillance little reduction has occurred in the incidence of the disease in the UK by cause or occupation. Although host factors such as atopy, smoking and HLA phenotype can influence the risk of sensitization and asthma to several of its causes, the evidence from several studies now indicates that the level of exposure to the cause is the most important determinant: the studies I have reviewed indicate that the risk of developing asthma increases with increasing levels of exposure among those exposed at work to laboratory animals, flour, enzymes, acid anhydrides and isocyanates. The results of these studies imply that for these agents at least, and probably for causes of occupational asthma in general, a reduction in disease incidence can be best achieved by reducing airborne concentrations of the responsible agents. Although exposure–response relationships can be modified by host factors, these are far from sufficiently strong or discriminating to form the basis of pre-employment screening. Analysis of the relationship of atopy and asthma in one study of laboratory animal workers, among whom atopics were five times as likely as non-atopics to develop asthma, indicated that a policy of excluding atopics would mean the exclusion of seven atopics to prevent one case (Venables et al., 1988). Cigarette smoking has a similar false positive rate and is an equally poor predictor of disease risk. There is also evidence that for HLA phenotype, at least in relation to sensitization to acid anhydrides and platinum salts, the strength of association varies with intensity of exposure, being greater at lower levels of exposure (Newman Taylor et al., 1999). In addition to these scientific objections, there are ethical concerns about a programme to reduce disease incidence by screening out potential employees on the basis of an identi-
Asthma and work

571

fiable host factor: it implies a shift of responsibility for the cause of occupational disease from the employer, for ensuring safe working conditions, to the individual susceptibility of the employee. The clear demonstration of exposure–response relationships for an allergic disease, occupational asthma, considered to be a consequence of individual susceptibility, has shifted the focus for prevention back to effective control of exposure to the allergen and chemical in the workplace.

The ideal means of prevention is elimination of the hazard. There are a few examples: the use of gum acacia in the printing industry (Fowler, 1952) and of lycopodium spores, used until recently to dust rubber condoms (Cullinan et al., 1993).

Direct evidence that disease can be prevented, or its incidence reduced, by reducing exposure comes primarily from the history of the outbreaks of asthma caused by soya beans in Barcelona in the 1990s and of enzymes in the detergent industry since the late 1960s.

During the 1990s for some 8 yr the number of asthma cases admitted each day into hospitals in Barcelona increased several fold, intermittently and irregularly on ‘asthma epidemic days’. The cause of ‘asthma epidemic days’ was eventually identified as allergenic dust released during the unloading of soya beans in the harbour which, on days when the meteorological conditions were appropriate, generated high concentrations of soya bean dust in the city (Anto et al., 1989). Installation of filters in the silos led to a marked reduction in the concentration of airborne soya bean allergen in the city and no further ‘asthma epidemic days’. Since this intervention, the concentration of airborne soya bean allergens has not been significantly greater on soya bean unloading days than on other days and the frequency of admission to intensive care units in Barcelona on soya bean unloading days has fallen 25-fold (Anto et al., 1993).

In the late 1960s the proteolytic enzyme Alcalase was added as a powder to laundry detergents to increase their cleaning properties. Flindt (1969) reported cases of asthma with immediate skin test responses to the proteolytic enzyme Alcalase in workers from a detergent factory in the UK. Belin et al. (1970) also reported allergic reactions to Alcalase in a small number of Swedish consumers. Studies of detergent manufacturing workforces in the UK, USA and Australia all demonstrated a high prevalence of respiratory symptoms associated with immediate skin test responses to Alcalase. Newhouse et al. (1970), for instance, reported allergic symptoms in 47% of a factory workforce surveyed in the UK. These observations stimulated the exclusion of atopic workers and a search for methods to reduce the concentration of airborne enzyme dust in the workplace. This was achieved by improved engineering controls and the development of encapsulation by granulation of the enzymes used in detergent manufacture.

Juniper et al. (1977) undertook a 7 yr follow-up of the factory workforce which had employed the original cases of enzyme-induced asthma reported by Flindt (1969). The study population included all those employed when enzymes were introduced in 1968 and all new employees during the subsequent 7 yr period. Total dust levels had exceeded 1200 g/m³ in 1969 and 1970 but subsequently fell, rarely exceeding 400 g/m³ after 1972. The number of cases transferred out of the factory because of development of respiratory symptoms fell from 50 between 1968 and 1971 to one in each year in 1972–74. In parallel, the proportion of non-atopic workers who developed an immediate skin test reaction to Alcalase fell with decreasing intensity of exposure and later era of starting employment in the factory. Forty-one per cent of those employed in 1968/69 developed a skin test response to Alcalase, 29% of those entering employment between 1969 and 1971 and 11% of those employed between 1971 and 1973. This study remains one of very few in occupational asthma to have documented a fall in the incidence of sensitization and asthma in parallel with a fall in the measured airborne concentration of its cause. The experience of the UK detergent industry is shown in Fig. 4.

The maintenance of control, however, requires continuing vigilance. A modern detergent factory in Northern Europe, which had exclusively used granulated protease, cellulase and bacterial amylase since starting production in the early 1990s, experienced an outbreak of allergy and asthma caused by these enzymes equal in magnitude to those in the detergent industry in the late 1960s. More than 50 cases of enzyme-induced asthma occurred in a workforce of <350, attributable to failure of control of exposure and the lack of effective personnel surveillance (Cullinan et al., 2000).

The benefits of combining effective control of exposure with workforce surveillance is seen in the history of isocyanate-induced asthma in Ontario, Canada. Isocyanates had been responsible for some 50% of cases of occupational asthma in Ontario and were targeted for control. A planned programme of exposure control in the workplace coupled with regular medical surveillance of the exposed workforce led initially to the identification of more cases but subsequently to a reduced incidence of cases identified at an earlier, less severe and more remediable stage of disease (Tarlo et al., 2002).

**OCCUPATIONAL ASTHMA: PAST AND FUTURE**

Studies of occupational asthma during the past 30 yr have put the disease into perspective and provided a scientific basis for interventions to reduce its incidence.
The importance of an accurate diagnosis of occupational asthma and the identification of its cause in the individual case has long been recognized: the disease provides one of the few circumstances in which asthma of onset in adult life resolves, or improves, with avoidance of exposure to its cause. Asthma of occupational cause probably accounts for between 10 and 15% of new or relapsed cases of asthma in adult life in Western Europe and the USA. The data from SWORD over a decade of reporting and other similar reporting schemes have identified asthma as the single most frequently reported category of occupational lung disease, caused by the same agents within similar occupations. The estimated incidence of the disease has not changed in the past decade and has, in Finland, shown an increase. The studies of outcome of the disease, although in many, but not all, cases are likely to have included more severe cases, indicate persistent asthma with disproportionate financial and social consequences, as compared with asthma not of occupational cause. The frequency of the disease and its persistence in many cases indicate a clear need for interventions to reduce its incidence. Studies of the determinants of occupational asthma due to several of its causes have consistently identified exposure–response relationships: although modified by host and behavioural factors, the level of exposure is the most important determinant of the disease. The question for the next decade is therefore how best to reduce the incidence of occupational asthma through a reduction in the intensity of exposure to its causes.

Adam Smith suggested we would learn more from studying the causes of the wealth than the poverty of nations, but the lessons of success from the soya bean asthma epidemic in Barcelona and the enzyme detergent industry in Western Europe and the USA, although instructive, may mislead. In both instances the prescription was clear and technologically feasible; in both instances government agencies were able to enforce compliance with change. Indeed, Alcalase, or subtilisins, remains the only protein allergen ascribed a TLV by the ACGIH. While regulation and enforcement may be practical levers for change in large industries, they are probably less effective in small businesses employing <500 people, where much innovation now originates and where many of those currently developing occupational asthma are employed. A new strategy needs to be developed based on economic incentives to employers and knowledge both by employers and employees of health risks and effective means of safety. In parallel, the major focus of research in this field needs to turn from understanding the causes of occupational asthma, which in the main are now sufficiently well understood, to the means of reducing its occurrence, with studies evaluating the effectiveness of different interventions. The Health & Safety Executive has stated the aim of reducing the frequency of occupational asthma by 30% in the next decade. The challenge lies equally with industry, government agencies and the scientific community to design the interventions, both engineering and economic, to effect this and to test their effectiveness in appropriately designed evaluative studies.

Fig. 4. Decline in the number of cases of asthma in the enzyme detergent industry in parallel with a progressive fall in enzyme concentration (1968–92). After SDI.
REFERENCES


