Occupational Medicine

Occupational asthma

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Introduction

Occupational asthma may be defined as asthma induced by exposure to an inhaled agent (or agents) in the workplace. Its presentation is sometimes dramatic. Occupational exposure to platinum salts, for example, has been known to induce asthma in over 50% of an exposed workforce. For those affected, the consequences are often devastating, while the economic effects for an industry may be no less profound. Although occupational asthma was barely recognized 30 years ago, its study in recent years has led to much insight into the aetiology and the mechanisms of asthma in general. A number of comprehensive reviews are available.^{1–3}

It is important to distinguish the induction of asthma from the mere provocation of symptoms in those who are already asthmatic. Any asthmatic worker whose occupation involves moderate exertion might wheeze at work but exercise alone will never induce asthma in the way that chemicals and other occupational agents sometimes do. The concept of airway hyperresponsiveness is useful in understanding this distinction. It refers to the exaggerated responses of the airways to stimuli such as exercise or cold air which are a universal feature of active asthma. If an asthmatic state (airway hyperresponsiveness) has been induced, whether occupationally or not, exposure to these non-specific stimuli gives rise to bronchoconstriction and the symptoms of wheeze, breathlessness and cough. In the case of occupational asthma, there is an additional specific sensitivity to the causative agent in the same way that some, but not all, asthmatics wheeze when exposed to the house dust mite. The quantification of airway responsiveness can be useful in assessing asthmatic activity and in following changes associated with occupational exposures.

The overall prevalence of occupational asthma is not known with any certainty. Some 3–6% of the adult population in Britain have symptoms of asthma, and of these approximately a third deny

being affected in childhood. The prevalence of asthma beginning in adult (working) life is therefore likely to be 1–2% in any workforce but most of these cases will arise coincidentally rather than through a direct effect of occupation. In Japan, it has been estimated that up to 15% of adult onset asthma might have an occupational aetiology, though, for Britain, the figure is considered to be of the order of 2–5%.

More accurate information about the epidemiology of occupational asthma in Britain will shortly become available as data from two ongoing investigations are analysed. Under the SWORD (Surveillance of Work-related and Occupational Respiratory Disease) project respiratory and occupational physicians report each month on all new cases of presumed occupational lung disease. In 1989, the first year in which the scheme was operational, asthma proved to be by far the single most commonly reported occupational lung disease. The overall national incidence was of the order of 20 per million employed per year but with very much higher incidences in certain occupations. The second reporting scheme is centred on the West Midlands region and suggests that the local incidence of occupational asthma is appreciably higher.

Agents causing occupational asthma

Individual agents capable of causing occupational asthma can be found in a wide variety of occupational settings and range in type from small molecules such as formaldehyde (HCHO) to complex animal proteins. Over 200 agents are recognized and new cases are identified almost monthly. Some are potent and have caused asthma in almost epidemic proportions when exposures were not controlled. Others have caused asthma in only one or two workers. A complete list of these agents is beyond the scope of this article but some of the more important agents are listed in Table I where they are classified into five major categories: animal, vegetable, microbial, pharmaceutical and chemical. However, occupational exposures are

Table I Some agents causing occupational asthma

1. Animal	arachnids (storage mites) laboratory animals* seafood (crabs, prawns)
2. Vegetable	beans (castor*, coffee, soy) colophony fumes* flour/grain* papain woods*
3. Microbial	<i>Bacillus subtilis</i> enzymes* mixed (humidifiers, oil mists)
4. Pharmaceutical	cimetidine* cephalosporins* ippecacuanha* methyl dopa pancreatic extracts penicillins* psyllium*
5. Chemical	acid anhydrides* aluminium smelting azodicarbonamide* diisocyanates* formaldehyde nickel persulphates (hairdressers) platinum salts* reactive dyes vanadium

*Prescribed agents for which state compensation can be obtained in Britain.

frequently multiple and in some cases it is clear that occupational asthma is present without a single aetiological agent being identifiable. For example, asthma occurs in the aluminium smelting industry where workers are exposed to aluminium salts, fluorides, sulphur dioxide, carbon monoxide and several other gases and chemicals.⁴ The agent or combination of agents responsible has not yet been identified.

Non-occupational exposures to domesticated animals are extremely common and are sometimes associated with exacerbations of asthma. Yet their potency does not appear high, and occupational asthma in their handlers is unusual. Small mammals are more frequently implicated, particularly rodents whose urine may contain large amounts of highly allergenic protein. Asthma among exposed laboratory workers has been reported with a prevalence of the order of 10%. To some extent this is likely to reflect higher exposure levels in the confined environment of a laboratory animal house as well as different asthmagenic potencies. Insects such as locusts, and mites such as the grain storage mite (*Glyphogagus destructor*) can also induce occupational asthma. The latter contaminates farm produce and can render farm workers,

grain handlers, dock workers, road hauliers, bakers and others at risk.

Asthma among bakers is more commonly due to flour itself or enzyme additives than any contaminating storage mites. In some studies, up to 20% of bakers have been reported to be affected. Asthma due to flour or dust from soybean illustrates the potential overlap between occupational and other environmental causes of asthma. Soybean dust is a recognized cause of occupational asthma and its release into the atmosphere of Barcelona (which followed its unloading from ships in the harbour) resulted in a number of epidemic outbreaks of asthma in that city in the early 1980s. A total of 687 people were affected in 26 outbreaks and 1155 emergency hospital admissions were recorded.⁵

Wood and wood products may cause asthma. Western Red Cedar (*Thuja plicata*) is the most frequently implicated because it is rapidly growing and widely used, but several other species (principally hardwoods) pose significant risks. In the case of Western Red Cedar, plicatic acid in the sap appears to be the agent directly responsible. Colophony (rosin) obtained from pine tree resin is widely used in the electronics industry as a soldering flux. Fumes from the soldering process contain colophony pyrolysis products and are asthmagenic. Asthma was found in 21% of workers in a high exposure group in one electronics factory.

Enzymes obtained from *Bacillus subtilis* have been used extensively by manufacturers of 'biological' detergents. These enzymes are potent sensitizing agents and in the early days of their use, prevalences of up to 50% of occupational asthma and rhinitis were observed. Hygiene improvements in the manufacturing process, coupled with an encapsulation process which increased the particle size beyond the respirable range have greatly reduced the risk to current workers. Little evidence has emerged of asthma attributable to these agents in consumers, though the use of pancreatic enzymes for the treatment of cystic fibrosis has resulted in asthma in some families.

Occupational asthma due to other therapeutic agents is not confined to those directly involved with manufacture. Asthma induced by occupational exposure to antibiotics and laxatives has occurred among nurses. Aerosolized antibiotics are increasingly being used therapeutically, and administration by this means may carry some risk of sensitization to patients and to staff if nebulisers are not used with extraction devices. Occupational asthma caused by a therapeutic agent carries an additional risk. Systemic hypersensitivity may occur and this provides the potential for multi-organ reactions should a worker be treated therapeutically with an agent to which he has been sensitized occupationally.

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A wide variety of low molecular weight chemicals are capable of causing clinical effects in the airways, which are identical to those caused by common aeroallergens. These agents tend to be reactive rather than inert but share no other common structural or chemical property. The commonest reported cause of occupational asthma in Britain is exposure to isocyanates such as toluene diisocyanate (TDI). These are employed in the production of polyurethanes which are widely used in the manufacture of plastics, surface coatings and foams. Asthma prevalences of up to 10% have been reported among exposed workers. Once sensitized, workers may develop symptoms following exposure to extremely low levels (0.001 ppm). TDI is notorious for causing asthma in environments which appear well removed from its manufacture or transport. Any process involving heating or burning polyurethane may liberate isocyanate. TDI has also been reported as a contaminant of an office environment because the air conditioning intake was too close to the exhaust vent of a neighbouring building where polyurethane was being made.

Mechanisms of occupational asthma

The mechanisms leading to asthma, whether occupational or non-occupational, are poorly understood. A type I (IgE-mediated) hypersensitivity is likely to be involved in childhood asthma but this is less obviously the case among adult asthmatics in whom the association between allergies and asthma is not so close. Airway hyperresponsiveness, and possibly asthma, can sometimes be induced by accidental exposure to smoke from domestic fires, or exposure to ozone and viral upper respiratory infections, adding support to the view that other mechanisms can sometimes be involved.⁶

In some circumstances, for example among laboratory animal handlers, detergent workers exposed to enzymes, and platinum workers, occupational asthma is associated with positive skin prick tests and elevated specific IgE levels typical of a type I hypersensitivity reaction. However, for the majority of inducers of occupational asthma, specific IgE antibodies have been identified in only a minority of affected workers or not at all. In the case of low molecular weight chemical agents, their molecular size is too small to allow the chemical to act as an allergen unless coupled as a hapten with body proteins. Thus problems in identifying a specific antibody do not necessarily imply their absence but may simply reflect the difficulties in preparing a relevant hapten or in handling a highly reactive chemical.

The frequent failure to identify immunological mechanisms has led to suggestions that 'pharma-

cological' reactions might sometimes be important. A non-occupational example of such a mechanism might be seen with aspirin-induced bronchoconstriction which occurs in up to 10% of asthmatic patients, probably because of alterations in prostaglandin or leukotriene levels.⁷ Similarly, TDI can in theory facilitate bronchoconstriction by inhibiting beta-adrenergic responses, and organophosphorus pesticides can cause cholinergic-mediated bronchoconstriction by inhibiting cholinesterase. However, neither of these mechanisms seems likely to be important in the induction of occupational asthma in general.

Occasionally asthma arises after a single accidental exposure to high levels of irritating fumes, aerosols or gases (e.g. chlorine or sulphur dioxide). This is not typical of occupational asthma and the term 'reactive airways dysfunction syndrome' has been coined.⁸ Symptoms begin at the time of exposure and typical asthma persists thereafter. Asthma is frequently not exacerbated by re-exposure to low levels of the same chemical. An acute inflammatory insult to the airways appears to be causative, the rapidity of the onset of symptoms making it unlikely that any hypersensitivity mechanism could be involved.

In the majority of cases, whether or not specific antibodies can be identified, occupational asthma bears all the hallmarks of an acquired hypersensitivity reaction. Only a small proportion (usually fewer than 10%) of exposed workers are affected. There is a latent period of weeks to years before symptoms develop but once developed, symptoms are provoked by exposures which were previously tolerated and which continue to be tolerated by other workers. There is therefore no convincing evidence to suggest that occupational asthma usually arises through a unique or uncommon mechanism not relevant to asthma in general. Indeed, improving understanding of the mechanisms leading to occupational asthma is likely to lead to a greater understanding of asthma in the population at large.

Predisposing factors

Asthma has arisen with very high prevalences (over 50%) in some working populations suggesting that under appropriate conditions everyone may be susceptible. The level of exposure is of major importance but, as asthma typically arises in only a minority of those exposed, there are likely to be host factors, such as pre-existing asthma, cigarette smoking and atopy, which render some workers more susceptible than others.

A number of studies have shown an increased prevalence among workers who have experienced asthmatic symptoms previously, often in child-

hood. However, as the majority of cases of occupational asthma arise in subjects without any previous asthmatic symptoms, this risk factor exerts only a minor effect overall. Current asthma ought to be at least as relevant but this has been less easy to identify. Such an effect might be masked by a number of biases such as the tendency of employers to discriminate against asthmatic job applicants and of asthmatic workers to avoid known industrial inducers. Whether low (i.e. asymptomatic) levels of airway hyperresponsiveness can predict or predispose to the subsequent development of occupational asthma is as yet unknown. It does, however, appear that airway responsiveness is not closely associated with atopy in adults.⁹ This implies that if it does predispose to the development of occupational asthma it exerts this influence independently of atopy.

Atopy, which is the propensity to develop high levels of IgE antibodies to common aero-allergens, is present in up to 20% of the population. As atopy poses an increased risk of occupational asthma in some occupations (e.g. detergent workers exposed to enzymes), tests for atopy have been widely used to screen potential employees. However, atopy is not necessarily a good predictor of the ability to mount specific IgE responses. Allergy to bee sting venom is no more common among atopic than non-atopic bee keepers, and for many occupational agents (e.g. TDI and epoxy resins) atopy does not appear to confer any increased risk for the development of occupational asthma. Even when there is an association (e.g. with laboratory animal asthma), the predictive value of screening tests for atopy is poor.¹⁰

Cigarette smoking has a variety of effects on the immune system.¹¹ It increases circulating total IgE levels but does not increase the symptoms of allergy or the frequency of positive skin prick tests to common allergens. In contrast, it has a suppressive effect on IgG-mediated reactions, extrinsic allergic alveolitis being less common among smokers than non-smokers. Smoking has been shown to increase the risk of developing specific antibodies to platinum salts in exposed workers by a factor of five and to increase their risk of developing occupational asthma. Smoking has been found to increase the risk of asthma in other occupational settings also, for example workers exposed to epoxy resin curing agents such as tetrachlorophthalic anhydride. On the other hand, smoking appears to protect sawmill workers exposed to plicatic acid against Cedar asthma. Among 185 cases of occupational asthma, 70% were in lifelong non-smokers and only 5% were in current smokers. Such diverse effects of smoking on the risk of developing occupational asthma might offer some clues to the mechanisms involved.

Diagnosis

The recognition that asthma in an affected worker is related to the occupation is often not easy. At an early stage in the illness, symptoms may comprise little more than an intermittent cough, occasional breathlessness or wheezing. A smoker may regard these symptoms as normal and antibiotics may be prescribed for repeated 'chest infections'. Once an occupational link is suspected, the history may be confounded by the expectation of compensation or the fear of unemployment.

Occupational asthma usually begins within 1–2 years of initial exposure to the inducing agent, and not uncommonly within a few months. Rarely, the sensitizing period is only a matter of days or weeks or symptoms may begin with an accidental heavy exposure. Once sensitized, symptoms may start within seconds of entering the workplace if immediate asthmatic reactions are provoked, but may be delayed for several hours or may begin after work if late reactions only are occurring. Under the latter circumstances, recognition of the occupational aetiology might be delayed.

In the early stages, airway responsiveness and asthmatic symptoms tend to increase following exposure, and decrease when this ceases temporarily. Thus there may be an improvement in symptoms at weekends and especially on holidays, when away from work. As the severity of the asthma increases, these features may become less apparent and airflow obstruction may become less readily reversible, making the occupational aetiology and the distinction from smoking related fixed airflow obstruction difficult.

Rhinitis, conjunctivitis or skin rashes may also be present or may affect other workers. The knowledge that fellow workers are affected strengthens any suspicion of occupational asthma as does the presence of a known asthma inducer in the working environment. Even in the apparent absence of both, the possibility of an occupational cause should always be considered when asthma arises or appreciably worsens in adult life.

If there is known exposure to a recognized asthma-inducing agent in the workplace, the history alone might suffice for a diagnosis of occupational asthma to be made once asthma itself is established, particularly if the agent is of high potency and other members of the workforce are affected. Objective evidence for the presence of asthma should be sought from tests of lung function or by quantifying airway responsiveness. If the subject has been away from work for some time, the asthma may have substantially improved or disappeared and all tests might be normal.

Serial measurements of ventilatory function may be useful both to confirm active asthma and to

demonstrate work-related decrements (or improvements when away from work). This is most conveniently achieved by the subject using a Wright Mini-Peak Flow meter. Figure 1 illustrates such measurements for a foundry worker who was exposed to isocyanates and formaldehyde from resins in sand moulds when they were vaporized by molten steel. His symptoms were suggestive of occupational asthma and a substantial improvement in ventilatory function could be seen during a short period away from work. However, the physician should be aware of a number of potential pitfalls when interpreting unsupervised measurements such as these. Aside from the possibility of poor compliance, failure to make measurements at identical times on work and non-work days has led to spurious results when the subject wakened later on non-work days, thus missing the early morning dip in peak flow rate.¹²

Skin prick tests or radioallergosorbent tests for specific IgE antibodies may be useful, particularly when an organic agent is the suspected cause of occupational asthma. Skin prick tests to flour and wheat have a reported sensitivity of 96% for bakers' asthma. However, the specificity of these tests is generally lower (of the order of 50% for detergent enzymes), the antibodies merely reflecting exposure to the relevant antigen or the presence of another allergic disease (rhinitis, eczema) rather than asthma. For the majority of low molecular weight chemicals there are no specific immunological tests for the reasons discussed above though skin tests have been useful in diagnosing allergy to platinum salts and acid anhydrides.

Further information might be sought from

Figure 1 Reduction in circadian rhythm and improvement in peak expiratory flow (PEF) on rest days in a steel foundry worker.

measurements of ventilatory function during either a supervised exposure in the workplace or a laboratory based series of inhalation challenge tests with the suspected agent. Such tests are time consuming and not without risk. They demand supervision by an experienced investigator and should only be performed in centres where the appropriate expertise exists. They are not routinely required to diagnose occupational asthma or to justify a claim for compensation. Nonetheless, they are useful in evaluating potential new causes of occupational asthma and in clarifying difficult cases.

Three patterns of response are recognized;¹³ an isolated immediate reaction beginning within minutes of exposure and subsiding over 1–2 hours, an isolated late asthmatic reaction beginning after 2 to 8 hours (occasionally later), and a dual reaction, an immediate followed by a late reaction. The challenge agent and dose together with the degrees of airway responsiveness and specific hypersensitivity are all likely to be important in determining the nature of the response. Figure 2 illustrates a late asthmatic reaction following inhalation of the antibiotic ceftazidime in a sensitized worker. When the same dose was administered a few days later at a time when airway responsiveness (and, probably, specific antibody levels) had been increased by the first challenge, a dual reaction occurred.

Late asthmatic reactions following inhalation challenge tests are associated with temporary increases in airway responsiveness. These may be reflected in increased asthmatic symptoms and more marked circadian rhythms in ventilatory function. They may persist for several days follow-

Figure 2 Two inhalation challenges with ceftazidime 3.2 mg (—) were performed about a week apart. On the first occasion there was an isolated late asthmatic reaction whilst a dual reaction was seen following the second challenge. The results of control challenges with saline are also shown (---).

ing a single challenge exposure. Circadian rhythms in asthma may, of course, confound the identification of late asthmatic reactions and it may be useful to quantify the magnitude of such changes on control days prior to any challenge. This may be done using a summary measurement such as the mean change in ventilatory function over a given period (e.g. 2–12 or 2–24 hours from the time at which a challenge dose might be given). Changes following a challenge which are significantly in excess of normal circadian rhythms can thus be recognized.

Airway responsiveness may also be quantified directly. A commonly used method¹⁴ involves the administration of doubling doses of the bronchoconstricting agent methacholine at 5 minute intervals. Forced expiratory volume in one second (FEV₁) is measured following each dose and further doses are given until there has been a 20% fall in FEV₁ or the maximum dose has been given. The provoking dose (PD20) of methacholine causing exactly a 20% fall in FEV₁ is calculated by interpolation from the dose–response plot. In a subject with stable asthma, repeated measurements within one half to twice the original value can usually be made. Figure 3 illustrates such stability of airway responsiveness (PD20) and the changes which occurred following two inhalation challenges with a detergent ingredient, SINOS. There was an increase in airway responsiveness (decrease in PD20) which took approximately 3 weeks to return to baseline. In fact the PD20 eventually improved above the pre-challenge baseline, probably because the subject's occupational exposures ceased at the time of the challenge tests. Measurements of airway responsiveness may be equally useful in following changes in asthmatic activity associated with exposures at work.

Figure 3 Stable levels of airway responsiveness (PD20 800–1600 µg) prior to two inhalation challenges with SINOS 32 mg. A marked increase in airway responsiveness (lowered PD20) was seen following the challenges. PD20 returned to baseline after about 3 weeks, and eventually improved beyond baseline levels.

Management and outcome

Once established, occupational asthma behaves as any other form of asthma apart from the association of symptoms with specific workplace exposures. There is likely to be an improvement in symptoms on commencing treatment with inhaled beta-agonists and inhaled or oral corticosteroids. However, initial management should be aimed at reducing exposure to the offending agent and, ideally, an affected worker will cease being exposed altogether. This is likely to require a change in job, often with a loss of earnings and a risk of unemployment and is rarely ideal from the patient's viewpoint. A change in the working practice which results in a substantial reduction in the level of exposure may sometimes be a suitable alternative. Such an approach should only be adopted where there are facilities for careful supervision and regular measurement of pulmonary function and airway responsiveness. Once a worker is sensitized, symptoms and airway hyperresponsiveness may be maintained by exposure to minute amounts of the agent and the above approach may not be successful.

On stopping exposure to the inducing agent, occupational asthma may improve or disappear altogether. However, in approximately 50% of workers, asthma will persist and may be severe and disabling. The most important factor in determining the outcome appears to be the length of time between the onset of symptoms and the cessation of exposure.¹⁵ The longer the period of symptomatic exposure, the greater the risk of permanent asthma. The early recognition of occupational asthma is thus vital if such an outcome is to be avoided.

A diagnosis of occupational asthma and identification of the responsible agent may be equally crucial to an industry particularly if more than a single worker is affected. The reductions in exposure levels necessary to eliminate the risks to other workers may require costly changes to a plant or changes in the manufacturing process, and economic viability may be imperilled.

Legislative aspects

Asthma arising as a consequence of an identifiable industrial accident has been compensatable in Britain for many years under the state administered Industrial Injuries Act. It was not, however, until 1982 that more conventional varieties of occupational asthma due to certain agents became compensatable and the list of prescribed compensatable agents was extended in 1986 (see Table I). Occupational asthma is presumed and compensation awarded if a worker who is occupationally exposed to one of the prescribed agents develops asthma

after a preliminary 'sensitizing' period.¹⁶ A further method by which compensation might be obtained is through a civil suit against an employer. Here, a judgement will rest entirely on the balance of probabilities in the individual case without reference to any prescribed list. Proof of negligence on the part of the employer will also be required and success is much more difficult. On the other hand, the level of compensation is likely to be much higher.

Conclusions

The study of occupational asthma has provided useful insights into the mechanisms of asthma and,

in turn, has raised numerous questions. Why does asthma frequently continue once exposure to the inducing agent has ceased? Is there any interaction between occupational exposures and other environmental agents, e.g. the antigenic house dust mite or mucosa-damaging viruses? What contribution are increasingly complex occupational exposures making to the apparently increasing prevalence and morbidity of asthma?

From a practical viewpoint, occupational asthma continues to be underdiagnosed. When asthma begins or substantially worsens in adult life, the question 'is it occupational?' is too important to be ignored.

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