Occupational asthma

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Summary: Occupational asthma is important both as a potentially curable and preventable cause of asthma and as a model of adult onset asthma. It is induced by sensitization to a specific agent inhaled at work; for many of its causes, including inhaled proteins and the low molecular weight chemicals acid anhydrides and reactive dyes, it is probably IgE dependent. The risk of developing specific IgE and associated asthma is markedly increased in cigarette smokers, probably as a consequence of non-specific damage to the respiratory mucosa. Asthma caused by several agents, which include some of its most frequent causes, isocyanates, colophony and plicatic acid (Western Red Cedar) persists in some 50% of cases for years, and possibly indefinitely, after avoidance of exposure. The development of chronic symptomatic asthma seems particularly to occur in those with longer duration of symptomatic exposure.

Asthma, occupational asthma and airway hyper-responsiveness

Asthma is usually defined as airway narrowing which is reversible over short periods of time, either spontaneously or as a result of treatment. This definition, valuable for clinical purposes, focusing on the characteristic variability in airway calibre which distinguishes asthma from the less reversible airflow limitation in chronic bronchitis and emphysema, does not include airway hyper-responsiveness. The increased bronchoconstrictor response to non-specific provocative stimuli is a cardinal characteristic of asthma which reflects important pathophysiological changes in the asthmatic airways. Airway responsiveness describes the ease with which acute transient airway narrowing can be provoked by a variety of non-specific stimuli. These include physical stimuli such as exercise and hyperventilation of cold and ambient air, inhalation of chemicals such as sulphur dioxide and of pharmacologically active agents such as histamine and methacholine. Patients with asthma require smaller doses of these stimuli to provoke airway narrowing. The degree of airway responsiveness is conveniently expressed as the dose of the stimulus which provokes a specified reduction in lung function, commonly the concentration or dose of the stimulus which provokes a 20% fall in the forced expiratory volume in one second (FEV₁), the PC₂₀ or PD₂₀. These stimuli are

described as non-specific because they provoke airway narrowing in all asthmatics. In contrast, specific stimuli, both protein allergens and low molecular weight haptens provoke airway narrowing only in individuals sensitized to them. Inhalation of specific stimuli provokes changes in airway calibre and increased non-specific airway responsiveness. Two groups of agents which provoke an acute asthmatic response can therefore be distinguished: non-specific stimuli which provoke airway narrowing in individuals whose airways are hyper-responsive, but which do not themselves increase airway responsiveness; and specific stimuli which both provoke airway narrowing and increase non-specific airway responsiveness. These specific stimuli are 'inducers' of asthma, able to 'switch on' airway hyper-responsiveness, distinguishable from non-specific 'inciters' which can provoke airway narrowing in those with pre-existing airway hyper-responsiveness.

Occupational asthma is asthma induced by sensitization to an agent inhaled at work. The specific agent 'switches on' asthma and airway hyper-responsiveness. Occupational asthma is a special example of airway hyper-responsiveness induced by identifiable environmental agents. It is important because it is potentially preventable because, with avoidance of exposure to its specific cause, it can be curable, and because it can be studied as a model of asthma caused by specific environmental agents in adult life.

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Causes of occupational asthma

Occupational asthma can be caused by both complex molecules of biological origin, which include not only proteins but also resin acids and antibiotics, and by synthetic low molecular weight chemicals. Exposure to materials of biological origin occurs in a wide variety of occupations. These include agriculture, handling and processing of agricultural products, food manufacture, the use of laboratory animals, forestry, carpentry and the commercial exploitation of microbes as sources of food, of antibiotics and proteolytic enzymes. In the majority of these situations the cause of asthma is inhaled as a dust, but exposure may also be to a fume of which the most important example is pinewood resin, colophony, used as soft solder flux in the electronics industry, which fumes at the temperature of soldering.

Synthetic chemicals which cause occupational asthma are more limited in number, but exposure to them occurs in a wide variety of occupational situations. Important examples of such chemicals are isocyanates, acid anhydrides and polyamines, reactive dyes and complex platinum salts. Isocyanates are bi- and tri-functional molecules used commercially to polymerize polyhydroxyl and polyglycol compounds to produce polyurethanes. The polyurethane reaction is exothermic with sufficient heat generated to vaporize isocyanates, particularly those with high vapour pressures such as toluene (TDI) and hexamethylene (HDI). Evaporation of diphenylmethane (MDI) and naphthalene (NDI) occurs when heat is applied during their use. In addition isocyanates may be generated in high concentration as aerosols during processes such as spray painting. Acid anhydrides such as phthalic and trimellitic anhydride and polyamines such as triethylene tetramine are used as curing agents in the production of epoxy and alkyd resins. Reactive dyes are used increasingly in the textile industry to bind a colouring agent (chromophore) covalently to textiles. Complex platinum salts are essential intermediates in platinum refining.

Importance of occupational asthma

The contribution of occupational causes to the prevalence of asthma in the community is not known. Different estimates have suggested that occupational causes account for between 1% and 15% of asthma in the population, but the basis of none of these can be regarded as secure. The majority of epidemiological studies reported to date have estimated disease prevalence in working populations exposed to a particular agent, that is the

proportion of those currently employed who have occupational asthma. Since many who develop asthma will leave an occupation which exposes them to the cause of their symptoms, estimates of disease prevalence can seriously under-estimate the real frequency of the disease. Nonetheless, the majority of information currently available on the frequency of occupational asthma has been derived from such studies.

Several studies of disease prevalence among laboratory animal workers have reported with remarkable consistency that between one quarter and one third of those exposed have laboratory animal allergy, and between 5 and 10% have asthma.¹ The number of persons whose work brings them into direct contact with laboratory animals has been estimated at 32,000, suggesting laboratory animal allergy to be an important problem.²

Attack rates are a more secure estimate than prevalence rates of the frequency of occupational asthma. The cost and inherent difficulties in undertaking this type of study, in particular maintenance of contact with leavers has meant that relatively few such studies have been reported. A follow-up study of a workforce manufacturing TDI found that 4.3% of those exposed to TDI vapour developed asthma which in the majority occurred within the first year of employment.³ It has been estimated that the use of polyurethanes in the United States will reach 2.2 million tonnes by the end of this decade and that between 50,000 and 100,000 workers are exposed in the United States in their work to isocyanates. The number of people exposed in their work to complex platinum salts is few, but the risk of disease, at least in the past, has been high. In one study of platinum refinery workers, 35 (40%) of 86 new entrants to employment in 1973 and 1974 left within 18 months of starting work because of the development of asthma caused by sensitization to the complex platinum salt ammonium hexachloroplatinate.⁴

Disease mechanisms

Asthma caused both by complex biological molecules and low molecular weight chemicals fulfils the criteria for an acquired hypersensitivity response. Only a proportion, usually only a minority of those exposed to the specific agent, develop asthma. The risk of developing asthma amongst those working with laboratory animals and those exposed to isocyanates is of the order of 5–10%. Asthma develops only after a disease-free interval from initial exposure (the sensitizing interval). This is usually several weeks or months and the majority of cases

of asthma caused by allergy to laboratory animals and by isocyanate sensitization occur within the first 1–2 years of exposure. Finally, in those who develop occupational asthma, an asthmatic response is provoked by exposure to atmospheric concentrations of the specific agent which were previously tolerable and which do not cause asthma in others similarly exposed. In those with asthma caused by TDI, an asthmatic response may be provoked by atmospheric concentrations of 0.001 ppm, about one five hundredth of the concentration irritant to mucosal surfaces (0.5 ppm).

Investigation of disease mechanism in occupational asthma has therefore concentrated on identification of specific immunological responses and in particular evidence of specific IgE antibody to the responsible agent. The presence of specific IgE to a protein or hapten-protein conjugate can be demonstrated in serum by the radioallergosorbent test (RAST) and other similar immunoassays or, more usually, inferred from its capacity to elicit an immediate 'weal and flare' response in the skin. Specific IgE antibody has been identified to the great majority of proteins which cause occupational asthma, but to few of the other complex biological molecules or low molecular weight chemicals. Proteins of animal, vegetable and microbial origin to which IgE antigen has been found in the sera of patients of occupational asthma include the secretions and excreta of laboratory animals, both small mammals and locusts,⁶ wheat and rye flour,⁷ grain storage mites⁸ and proteolytic enzymes derived from *Bacillus subtilis*.⁹ Specific IgE antibody has also been identified in the serum in those whose asthma has been caused by acid anhydrides¹⁰ and by reactive dyes.¹¹

However, for several of the non-protein molecules which cause asthma, including plicatic acid from red cedar, colophony from pinewood and isocyanates, either no evidence of an immunological response has been found, or if found, no consistent relationship demonstrated between the immunological response and asthma. This may reflect the difficulties of working with highly reactive chemicals in *in vitro* systems or the failure to prepare the relevant *in vivo* hapten for the *in vitro* test. Reactants of the isocyanate water reaction for instance may be formed in the water-saturated respiratory tree and these rather than the parent isocyanate may be the relevant immunogen binding to tissue proteins. Similarly colophony is a mixture of resin acids and, at the temperatures of soldering, their thermal degradation products result. Whether any of these can act as a hapten has not as yet been elucidated.

The failure to find consistent evidence of a relationship between a specific immunological res-

ponse and asthma caused by these agents and in particular TDI has led to suggestions that asthma may be caused by a pharmacological rather than an immunological mechanism. TDI has been shown to inhibit the *in vitro* stimulation of lymphocyte adenylyl cyclase by isoprenaline in a dose-related fashion,¹² and could, hypothetically, cause asthma by beta-adrenoreceptor inhibition in those with pre-existing airway hyper-responsiveness. However, this hypothesis fails to explain the well documented latent interval between initial exposure to TDI and the development of asthma and the observation that in sensitized individuals, inhalation of TDI can induce airway hyper-responsiveness in those whose pretest airway responsiveness is normal.¹³ Furthermore, TDI fails to inhibit isoprenaline-induced tracheal smooth muscle relaxation.¹⁴ The mechanism of asthma caused by the agents remains unclear, although recent success in identifying specific immunological responses to acid anhydrides and reactive dyes provides hope that similar success will be obtained with these other agents.

Specific IgE and induced airway hyper-responsiveness

Understanding of how the allergen-IgE and hapten-IgE interaction is translated into acute airway narrowing and increased non-specific airway responsiveness has come from challenge studies in the skin and airways.

Intracutaneous challenge in individuals with specific IgE antibody with extracts of soluble allergens or human serum albumin conjugates of low molecular weight chemicals, such as acid anhydrides, provokes an immediate 'weal and flare' response. This develops within minutes and can persist for up to one to one and a half hours. It may be succeeded by a late 'oedematous' response which develops 4–8 hours after challenge and persists for 24–36 hours. Inhalation of extracts or soluble allergens or low molecular weight chemicals can in the same individuals provoke an immediate and subsequent late asthmatic response similar in time of onset and duration to the responses provoked in the skin. The late asthmatic response is associated with an increase in non-specific airway responsiveness. This provoked airway hyper-responsiveness was originally demonstrated after the late asthmatic response at 24 hours following challenge.¹⁵ More recently, in patients with asthma caused by a number of occupational sensitizing agents which include isocyanates, acid anhydrides and colophony, increased non-specific airway responsiveness to inhaled histamine was demonstrated at 3 hours after the inhalation test prior to the onset of

the late asthmatic reaction. The magnitude of the increase in non-specific airway responsiveness at 3 hours but not at 24 hours was significantly associated with the size of the maximum fall in FEV₁ during the late asthmatic response.¹³ These observations suggest that the tissue events underlying the induced increase in non-specific airway responsiveness are likely also to be responsible for the subsequent airway narrowing during the late asthmatic response.

Skin biopsies of the late skin response have shown these to be the response of a local inflammatory reaction with infiltration by neutrophils, eosinophils and lymphocytes. This late inflammatory response can be elicited by allergens and at passively sensitized sites by anti-IgE antibody and its F(ab)₂ fragment,¹⁶ demonstrating the response to be IgE dependent and independent of the formation and deposition of complement fixing immune complexes. There is now similar evidence that the late asthmatic response is also the expression of a provoked inflammatory reaction in the airways. The number of inflammatory cells, eosinophils in one study,¹⁷ eosinophils and neutrophils in another study,¹⁸ recovered by bronchoalveolar lavage during the late asthmatic response is increased as compared with numbers prior to challenge test inhalation and in individuals with lone immediate asthmatic responses. In addition, as with the late skin response, the late asthmatic response can be provoked by inhaled anti-IgE.¹⁹ Taken together, these observations suggest that the allergen-IgE interaction can lead to local recruitment and activation of inflammatory cells whose accumulation is associated with increased non-specific airway responsiveness and airway narrowing during the late asthmatic response.

Occupational asthma, specific IgE, atopy and cigarette smoking

The risk of developing asthma and specific IgE antibody to agents inhaled at work may be influenced by both atopy, the propensity to produce IgE antibody to allergens commonly encountered in the environment, and by cigarette smoking. Several studies of laboratory animal allergy have found that the risk of developing asthma (but not rhinitis, conjunctivitis or urticaria) is significantly greater in atopic than in non-atopic individuals.¹ Similarly, the risk of developing asthma in platinum refinery workers due to sensitization to ammonium hexachloroplatinate is greater in atopic than non-atopic individuals.⁴

Cigarette smoking can also exert an influence, often greater than atopy, on the risk of developing

IgE and occupational asthma. In one factory where tetrachlorophthalic anhydride (TCPA) was used as an epoxy resin curing agent, asthma developed in 7 persons, all of whom were current smokers, while only one was atopic.¹⁰ The prevalence of specific IgE antibody to TCPA in the 300 employees in this factory was 13% in smokers and less than 3% in ex- and non-smokers, an increased risk among smokers of between 5- and 6-fold.²⁰ In addition, smoking interacted with atopy to increase the prevalence of specific IgE antibody to TCPA which was found in 16% of smoking atopics, 12% of smoking non-atopics, 8% of ex- and non-smoking atopics, but in none of the 98 non-atopic ex- and non-smokers. Similarly, in a study of snow crab processing workers in Canada the risk of developing occupational asthma was found to be greater in smokers than in non-smokers.²¹ The basis of this enhancing effect of cigarette smoking on IgE antibody production and the development of asthma amongst those exposed to allergens and haptens in their work can only be speculative. In laboratory animals, inhaled cigarette smoke causes mucosal inflammation and increased airway permeability to a marker protein (horseradish peroxidase).²² Cigarette smoking also increases lung permeability in man²³ and could increase antigen access to immunoresponsive cells. The increased IgE responsiveness to environmental allergens which is the defining characteristic of atopy may also reflect abnormal mucosal permeability in these individuals. If both cigarette smoking and atopy increase mucosal permeability this could explain their interaction among the TCPA workers in stimulating specific IgE antibody production.

Outcome of occupational asthma

In a significant proportion of those who develop occupational asthma, respiratory symptoms and airway hyper-responsiveness persist for several years after avoidance of exposure to the initiating cause. Chan Yeung *et al.* have followed up 1 and 9 years from diagnosis 125 cases of occupational asthma caused by hypersensitivity to Western Red Cedar.²⁴ Fifty who remained in the same job continued to be exposed; all had continuing asthma and increased airway responsiveness to inhaled histamine. Seventy-five had changed their job and were no longer exposed to Western Red Cedar. One half of these were without asthmatic symptoms and their airway hyper-responsiveness was less than at diagnosis. In the other half, however, asthma continued and airway hyper-responsiveness persisted. The major factor which determined outcome was the duration of exposure after the development of

asthma: those with continuing symptoms and airway hyper-responsiveness had remained exposed for significantly longer following the onset of their asthma. Burge followed up 1 to 4 years from diagnosis 28 electronics workers with colophony-induced asthma.²⁵ Twenty had left the industry and 8 had been relocated. Airway responsiveness to inhaled histamine was unchanged in 7 of the 8 who had been relocated but also in 10 of the 20 who had left the industry.

The reasons why asthma and airway hyper-responsiveness persist are not known. One possible explanation is that those in whom asthma continues are those destined to develop asthma in adult life and that the occupational exposure was simply the trigger. However, the epidemiological characteristics of occupational asthma make this unlikely: asthma does not develop at a similar frequency throughout the period of employment but has a high incidence during the initial one to two years of exposure. Furthermore, persistence of asthma is not invariable: in one study of platinum refiners the number of cases of chronic asthma was small and no greater than among those who had left the factory without asthma. An alternative explanation is that asthma persists in those who inadvertently continue to be exposed to its cause. Few studies have

provided any direct or indirect evidence to test this hypothesis. One 5 year follow-up study of 6 cases of asthma caused by the acid anhydride TPCA examined specific IgE levels in serum.²⁶ Inhalation tests at diagnosis with TPCA in maximum concentrations of 0.96 mg/m³ (as compared with a contemporary suggested control limit of 12 mg/m³) inhaled for up to one half hour provoked transient rises in IgE, suggesting its concentration in serum to be a sensitive indirect indicator of exposure. Specific IgE to TPCA-HSA conjugate fell exponentially with a half life ($t_{1/2}$) of one year which did not differ significantly between the 6 cases during the period of follow-up, suggesting, at least in this situation, that continuing or intermittent exposure was not the cause of persistent symptoms and airway hyper-responsiveness.

Why chronic symptomatic asthma develops in about one half of those with occupationally-induced asthma following avoidance of exposure to several of its initiating causes is unknown. Understanding why might allow its prevention and shed considerable light on chronic asthma in general and 'intrinsic' asthma in particular, from which, other than for knowledge of the initiating cause, it does not differ in any important way.

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