American Thoracic Society Workshop

Proceedings of the First Jack Pepys Occupational Asthma Symposium

Introduction

Because Canada has played a leading role in the field, we thought this country would be an appropriate venue for the workshop. We took advantage of the ATS meeting held in Toronto to schedule the event. Together we chose to name the workshop after Jack Pepys as a tribute to the memory of this outstanding clinician and researcher, a man justifiably known as the "father of occupational asthma."

There were two purposes for this meeting. First, for the specialists in the field, and there were about 50 of us here, it presented an opportunity to discuss the major issues and gave us the contact we needed to prepare recommendations for international studies. Second, for the general audience interested in occupational asthma (OA), it provided a state-of-the-art into the state of scientific knowledge about the condition as well as its controversies and challenges.

We were honored to have the support of several prestigious organizations for this meeting: the American Thoracic Society, the workers' compensation agencies in Québec, the Commission de la santé et sécurité du travail, and in Ontario, the Workplace Safety and Insurance Board, as well as the Research Institute of the WCB in Quebec, the Institut de recherche en santé en sécurité du travail.

We are indebted to the other international members of the scientific committee, Tony Newman Taylor, David Bernstein, and Cristina Mapp for their insightful criticism and input into the scientific program.

The working definition that was used during the symposium is the one achieved by consensus in the most recent edition of Asthma in the Workplace; that is: "Occupational asthma is a disease characterized by variable airflow limitation and/or airway hyperresponsiveness due to causes and conditions attributable to a particular occupational environment and not to stimuli encountered outside the workplace. Two types of occupational asthma are distinguished by whether they appear after a latency period: 1) Immunological, characterized by a latency period, encompassing a) that caused by high and low-molecular-weight agents for which an immunologic (IgE) mechanism has been proven, and b) that caused by agents (e.g., western red cedar) for which a specific immune mechanism has not been identified. 2) Nonimmunological i.e., irritant induced asthma or reactive airways dysfunction syndrome (RADS) which may occur after single or multiple exposures to non-specific irritants at high concentrations" (1).

A Historical Perspective of Occupational Asthma with a Special Account on the Contribution by Professor Jack Pepys

The evolution of OA as a specific clinical entity was only possible after a unique convergence of advances in immunology and pulmonary pathophysiology at the mid-20th century mark. Therefore, this appears to be the most appropriate vantage point for comparing the earliest stepping stones with contemporary progress that now facilitate the diagnosis and prevention of OA.

HISTORICAL PERSPECTIVE OF OCCUPATIONAL ASTHMA

Asthma was a well-recognized clinical entity in the Graeco-Roman era. Hippocrates particularly noted its presence in various occupations. Aretaeus, the Cappadocian, described the symptoms and signs of asthma in greater detail and emphasized the striking association with exercise (2). Apart from recognizing the benefit of natural remissions, Galen outlined the relevance of the role of the environment and advised "taking care of cleanliness of the surrounding air which enters the body." Maimonides, the famous Jewish scholar-physician of the Middle Ages, carried this observation on the role of environment one step further. In his "Treatise on Asthma," he noted "clean fresh air free of any contamination is advisable for all people" and "town air is stagnant, turbid and 'thick' compared with that found in the open country" (2).

It was not until the Italian renaissance that a direct connection between the occupational environment and pulmonary diseases was first observed by physicians in the famous Italian medical schools of that era (2). Magnus described respiratory symptoms among threshers of grain in 1555. Both Paracelsus and Agricola recognized the harmful effects of metallic dusts in the sixteenth century. But it remained for Bernardino Ramazzini to clearly describe occupational diseases for the first time in bakers, handlers of old clothes, and workers with flax, hemp, and silk (2). The illnesses that he recognized in sifters and measurers of grain probably included asthma, mill fever, and hypersensitivity pneumonitis. Moreover, he noted that working in ghettos where underventilated, crowded conditions prevailed was a special risk factor in workers repairing old mattresses and/or carding used wool.

The next step arose with the Industrial Revolution in the UK. Charles Thackrah published in 1832 a fine book on the effects of arts, trades, and professional and civic status and habits of living on health and longevity in which he mentioned the occurrence of probable asthma and/or respiratory symptoms in coffee roasters, malters, hairdressers, and pharmacists (2). The classic complex of Monday morning symptoms that occurs in flax and textile workers was reported by Mareska and Heyman in 1845, and Proust introduced the term "byssinosis" in 1877. In the same years, Dr. Charles Blackley inhaled a grass pollen extract and, in this, paved the way to the use of inhalation challenges in humans, a topic which will represent a major contribution of professor Jack Pepys in the field of OA one century later.

The confluence of accelerated progress in immunology and pulmonary pathophysiology in the 20th Century played a key role in the evolution of OA as a clinical entity. On the one hand, namely in the field of allergy, landmark contributions about the role of allergy were made by Freeman (3) and Cooke (4). Squire modified Blackley's scratch test into a prick/puncture test (2). In addition, without Karl Landsteiner's basic research on the specificity of hapten-protein conjugates, none of the recent investigations about the role of chemical hypersensitivity in the workplace would have been possible (5). The histopathologic nature of asthma was first described by Huber/Koessler in the early 1930s. Ishizaka and coworkers discovered IgE, and Wide and colleagues adapted it as a pragmatic serologic test for specific hypersensitivity (5, 6, 7). These diagnostic techniques ultimately proved to be essential for evaluating many types of OA induced by proteins. On the other hand, namely in the field of lung physiology, John Hutchinson's invention of the spirometer in 1841 as a means of measuring vital capacity paved the way for a series of elegant experiments by Baldwin/Cournand and Richards dealing with normal and abnormal pulmonary physiology, which later won two of them the Nobel Prize. These investigators were succeeded by a brilliant young generation of pulmonary physiologists (Riley, Forster, Tiffeneau, and Dubois), who discovered clinically practical ways of measuring gas transfer, airway resistance, and elastic recoil of the lungs. These findings made possible the assessment of airway caliber and responsiveness through the use of bronchial challenges from the 1840s onwards, when almost simultaneously and in rapid succession a spate of bronchoprovocation studies by American and European investigators were reported. The concept of nonspecific bronchial hyperresponsiveness was also elucidated by several of these early pioneers.

The post-World War II technological era created several key, iatrogenic problems vis-a-vis bronchial asthma in the workplace. Polyurethanes and resins, the basic commodities of the plastic industry, required highly reactive chemicals such as polyisocyanates and the acid anhydrides (2). The advent of enzymes in the detergent industry resulted in a significant incidence of OA among heavily exposed workers (2). This experience served as a prototype for recognizing the potential hazards of protein sensitizers and how to prevent their ill effects by controlling exposure in the workplace. Many workers developed asthma after exposure to wood dust in Canada and the United States (2). Finally, a new phenomenon of nonimmunologic asthma or the reactive airways dysfunction syndrome was recognized as occurring after the first exposure to a variety of fumes, gases, and many irritant chemicals (8).

What will the current century bring? As with naturally occurring asthma, there will be more emphasis on mechanisms (2). Applications of animal models—wild type, knockout, and transgenic—will be pursued more vigorously. The roles of cytokines, chemokines, and the Th1/Th2 paradigm will be explored. Genetic susceptibility will most certainly be in the forefront. Finally, research about the why and hows of RADS will be expanded.

CONTRIBUTION OF PROFESSOR JACK PEPYS

Having reviewed the pertinent continuum of discoveries in OA, attention will now be focused on the seminal contributions of Professor Jack Pepys and how they influenced the emergence of OA as a bona fide occupational disease in the last half century.

His first major work was a combined immunologic clinical investigation about the role of *Aspergillus* species in a spectrum of pulmonary diseases ranging from asthma to hypersensitivity pneumonitis (9). In particular, his findings contributed greatly to establishing diagnostic criteria for allergic bronchopulmonary aspergillosis, a condition first identified in 1952 by Hinson, Moon, and Plummer. His laboratory was the first to emphasize the importance of precipitins to various peptide and polysaccharide antigens of *Aspergillus fumigatus*. He also extended these studies to *Candida albicans* (9).

His next project, which was almost contemporary to the pioneer work of Barbee and coworkers in establishing the cause of farmer's lung, was a comprehensive series of investigations of extrinsic allergic alveolitis caused by a variety of thermoactinomycetes, vegetable dusts, and protein antigens. By a combination of inhalation and serologic tests, it was established that *Micromonospora faeni* was the agent in moldy hay causing farmer's lung (9). The principles elaborated in this study provided a sound basis for investigation of other organic dusts and proteins subsequently assessed in his and other laboratories.

Jack was an avid teacher. Teaching has its own rewards, but Jack received one that was totally unexpected. An occupational physician by the name of Dr. Michael Flindt had attended one of Jack's lectures in 1966. Two years later, when Flindt first suspected that detergent enzymes were human sensitizers, he consulted Jack for assistance and collaboration. Jack prepared the first enzyme skin prick test reagents that elicited positive results in symptomatic enzyme workers(10). One month later, Fred Hargreave and Jack demonstrated positive inhalation tests in three of these workers. These findings were soon confirmed in other clinics in the UK and the United States (11). There followed a rapid succession of clinical studies dealing with OA induced by a variety of chemicals including isocyanates, drugs, colophony, and acid anhydrides (2). As the modern father of OA, Jack Pepys was highly respected by students and peers alike. A significant proportion of future progress in OA during the next millennium will be based on Jack's unique contributions to OA.

A researcher/teacher can experience no greater fulfillment of a life's work than to be honored in this way, by a named symposium dedicated to Jack Pepys as the modern father of OA. As Jack Pepys' collegial peer who respected his work and advice, I want to thank him on behalf of all of us, especially as we anticipate that much future progress of OA in the next millennium will be based on Jack's unique contributions to OA.

How Often Does It Occur?

In recent years, an important development in the field of OA is related to a broader and more satisfactory estimate of the frequency of this condition. The role of epidemiology and methodologic issues of this discipline, with detailed discussion of study designs as well as of outcome measurements (questionnaires, immunologic assessment, functional evaluation) and assessment of risk factors (exposure and host markers), in the specific field of OA have been thoroughly reviewed in a recent contribution (12). Two points are worth being outlined: (*1*) looser definitions and means are used to ascertain OA for epidemiologic studies than for medical or medicolegal purposes; and (*2*) selection bias due to the "healthy" worker effect is a more important concern in OA than in other occupational lung diseases.

The features considered essential to establishing a clinical diagnosis of OA may differ among clinicians and jurisdictions. In epidemiologic studies the definition of OA usually varies according to the circumstances and purposes of the study (12).

EPIDEMIOLOGICAL CONSIDERATIONS

The definition of asthma can vary with different methods of ascertainment of cases. In cohort and case-control studies, specific methods, such as nonspecific bronchial challenge test, functional monitoring at work, and, occasionally, specific inhalation challenge in the laboratory to support the evidence, are useful. Questionnaires are most appropriate in the first phase of a prevalence study (13). They can be supplemented with skin-prick testing, measures of serum specific IgE levels, and nonspecific bronchial challenge tests (14).

How Often Does OA Occur?

Incidence. Estimates of incidence have been made using registers based on mandatory or voluntary physician reporting, self-reporting by workers, medicolegal statistics, and other national disease or disability registers. A meta-analysis of most of these studies was recently published by Blanc and Toren (15). The Sentinel Event Notification System for Occupational Risks (SENSOR) was introduced in the 1980s in several states in the USA (16), and since 1993, in four states for work-related asthma. In the UK, a sentinel system (SWORD) was introduced in 1989; it was based on voluntary reporting by selected physicians across the country (17). Similar systems were introduced in Canada, in particular in Quebec and British Columbia, and estimates of incidence have also been derived from national registers in Sweden and Finland, as reviewed (18).

Estimates of incidence vary considerably between countries, ranging from 3–18 per million per year in the United States (16) to 187 per million per year in Finland (18), with 20–40 per million in the UK (6) and about 50 per million in Canadian sentinel projects as reported by Meredith and Nordman (19). In Quebec, medicolegal statistics indicate an annual incidence of 25 per million (19). These differences are likely due in part to the varying purposes for which the information was collected and the different methods used; they may also be a reflection of the differences in local industrial activities. However, within-country differences are an important source of information for time trends (12). Several studies suggested an increase in the incidence over the 1980s (18, 20). Cases of work-related asthma may include new-onset asthma caused by workplace exposure to sensitizers or irritants and work-aggravated asthma; in the United States, the incidence of OA was estimated at 80.9% among cases of work-related asthma (16).

Few valid prospective studies in workers at risk of developing OA have been performed, partly because of the difficulty of maintaining a high participation rate. In a three-and-a-half-years prospective study, Cullinan and coworkers looked at the inci-

dence of work-related symptoms in a cohort of 342 laboratory-animal workers in the UK (21). They found that 37 subjects (11%) seen every 6 months for 3.5 years developed skin reactivity to rat urine and symptoms (eye/nose, chest, or skin), an incidence of 4.1/100 person-years, whereas 36 employees developed work-related chest symptoms, an incidence of 3.5/100 person-years (21).

In Canada, in a prospective study investigating the incidence of OA among 769 apprentices in animal health technology, pastry-making, and dental hygiene, a questionnaire and skin-prick tests with work-related allergens were administered on entry and at follow-up visits at the end of each year of the three- to four-year programs; responsiveness to inhaled methacholine was also assessed at baseline and at follow-up in apprentices who developed a new skin sensitization to laboratory animal–derived allergens. The incidence of specific skin sensitization to animal-derived antigens in the animal health program was 8.9/100 person-year (22). The incidence of skin sensitization to latex was 2.5/100 person-year in the dental hygiene program (23).Twenty-eight apprentices (7.5%) in the animal health technology program satisfied the study definition for incident OA, the incidence of OA being 2.7/100 person-year (24).

Prevalence. A very large number of workforce-based surveys have been conducted, some after new cases of OA were identified by physician referral or sentinel programs, others to examine risks associated with particular asthmagen exposures. The methods of investigation were generally symptom questionnaires and job-history questionnaires; in some studies, however, a full clinical investigation was undertaken in suspected cases of OA. We feel that the prevalence rates are more valid if all suspected cases, whether on the grounds of questionnaires, lung function tests, or immunologic investigation, undergo objective testing that can document lung function changes in a serial way in relation to workplace exposure or exposure to the causal agent in the laboratory. This is what we have done in our studies, which show prevalence rates of approximately 5% or less in the case of high-molecular-weight agents (except for snow-crab–producing workers) and greater than 5% for low-molecular-weight agents (12). In a number of studies in which exposure was estimated through measurements of dust and/or aeroallergen levels and job history, some relationship was demonstrated between exposure and prevalence of work-related asthma symptoms (12).

Recently, a number of community-based studies performed in several countries have shown a consistent relationship between occupational exposure and wheezing. Despite some limitations of this type of study, significant relationships were found between wheezing complaints and occupational exposure to dust alone or dust with fumes and/or gases in most of these studies, as summarized in the article by Becklake and coworkers (12). Among studies performed following the protocol for the European Community Health Survey, there were large differences in the frequency of wheezing attributable to occupational exposures (from 3 to 20%) despite the fact that the same methodology was used. A recent study performed in six Canadian cities proposes a figure of work-attributable risk as high as 36% for what is referred to as possible or probable OA (25). Recently, Blanc and Toren reviewed and assessed citations from 1966 to 1999 to extract or derive risk estimates of asthma attributable to workplace factors; they came to the conclusion that "occupational factors are associated with about 1 in 10 cases of adult asthma, including new onset disease and reactivation of preexisting asthma" (15).

The frequency of adult-onset asthma with an occupational component can be estimated from data in medical records by determining the proportion of subjects with asthma seen in a general or specialized practice for whom OA can be suspected. This approach has recently been favored by Tarlo and coworkers (26). These authors found that out of 731 adult subjects with asthma seen in a secondary and tertiary asthma clinic, 435 had adult-onset asthma; of these, 310 were employed at the time of the visit. Fifty-one of the 310 subjects (16%) reported that their asthma was worse at work. The particular interest of this study lies in the fact that the authors tried to estimate the likelihood of OA in these 51 subjects by reviewing their charts for objective evidence to support a work relationship, though the investigational tools were clearly incomplete for many subjects. Sixteen subjects—5% of the 310 adult-onset subjects with asthma who were employed at the time of the visit—had probable OA.

Frequency of Irritant-induced Asthma

The frequency of irritant-induced asthma has rarely been assessed. The SWORD (17) and SENSOR (16) sentinel projects estimated that 15% and 11%, respectively, of OA cases were of the irritant-induced type. Also, approximately 15% of all cases of OA in an occupational clinic in Ontario were subjects with irritant-induced asthma (27).

The number of cases of OA accepted by the WCB in Québec has remained relatively stable in recent years, accounting for approximately 50 to 70 new cases each year. In Finland, the number of accepted cases doubled from 1981 to 1991, at which time there were almost 400 accepted claims (28).

It would also be relevant to document the frequency of OA in developing countries where no surveys have been performed. The impact of prevention programs and screening measures on incidence figures needs to be assessed.

Important Causes of Occupational Asthma

Although the types of agents vary in different parts of the world (western red cedar is still a significant cause on the West coast of North America), isocyanates and flour seem to be the most common causes worldwide. In recent years, latex has become an important recent cause of OA. Although new chemicals are regularly introduced, overall there has not been any trend in changes of the proportion of cases due to high- versus low-molecular-weight agents.

Although textbooks, review articles, and web sites (*see* www.cssst.qc.ca) do present extensive tables of all documented causes of OA, the information should also be made available in a form that is classified by occupation at risk. Such combined information has been prepared by Henriette Dhivert-Donnadieu and coworkers in Montpellier on the asthmanet.com web site.

Conclusions

Findings regarding the significance of occupation as a cause of asthma vary according to the source of information and the methods used for case ascertainment. As it stands, there is a need for longitudinal studies in newly exposed workers to determine the incidence of OA in high-risk occupations. There is also a need to assess the frequency of OA in developing countries.

In field studies, questionnaires should be combined with skin testing and/or assessment of bronchial responsiveness. The information on frequency, causal agents, and jobs at risk should be provided on web sites, some currently existing. Finally, irritant-induced asthma is a significant problem but not yet to the extent of OA due to "sensitization."

Occupational Asthma with Latency (Sensitizer-induced Occupational Asthma)

Factors Predisposing to Sensitization, Development, and Persistence of Symptoms

INTRODUCTION

In common with asthma developing in childhood, OA is probably the outcome of an interaction between multiple genetic, environmental, and behavioral influences. Investigation of the determinants of OA has several advantages over similar investigations of asthma in childhood. Cases of asthma can be accurately identified, as can their denominator population, together with the relevant (often measured) exposures experienced; the second and third of these can prove particularly difficult in studies of non-OA.

Several studies of OA have investigated exposure–response relationships in relation to a specific cause of asthma, the effect of behavioral influences (particularly cigarette smoking), potential genetic susceptibility, and, in a few cases, genetic–environmental interactions.

Environmental factors can be either high-molecular-weight agents, usually allergens such as proteins from laboratory animals, flour, or plants, or low-molecular-weight-agents, usually chemicals, such as diisocyanates, biocides, or drugs. The mechanism for sensitization to high- and some low-molecular-weight agents is IgE-mediated. Although some studies suggest that environmental factors could be a direct cause of asthma, more likely they are an indirect cause, leading to asthma in a two-phase process. The first step involving a phase of induction (immunologic memory development favoring allergic sensitization) is regulated by interactions between Th1 and Th2 cytokines. The second effector phase involves the expression of Th2 inflammation in target tissues of sensitized individuals (29).

Although considerable insight has been gained into the immune mechanisms involved in the pathogenesis of OA, much remains to be learned. This section will discuss first what is known about the mechanisms that lead to the development of sensitization to allergens and/or chemicals, and then the mechanisms that lead to the expression and persistence of OA. We then briefly discuss animal models for studying OA and end by suggesting directions for future studies. This section considers only OA that develops after a latency period, not the uncommon type of OA that develops without a latency period, for example following spills, or high concentrations of irritants or chemicals.

CAUSES OF SENSITIZATION

In the nonoccupational setting, allergens do not appear to be a direct cause of asthma. To date, no published studies in a random general population sample have related allergen exposure in infancy to the risk of asthma after the age of 6 years (30). A recent study found that less than half the cases of asthma were attributable to atopy, defined as skin prick test positivity to allergens, and that the association between the prevalence of asthma and the prevalence of atopy was weak and inconsistent (31). So if allergen exposure causes asthma directly, through the development of allergic sensitization, we can conclude that only about one half of asthma cases are directly caused by allergen exposure. Moreover, because the hypothesis that allergen exposure is a direct cause of asthma is largely based on indirect evidence, the existence of a direct causal mechanism between allergic sensitization and asthma remains an assumption (32).

Adult asthma includes persistent childhood asthma, early-onset asthma that is reactivated in adulthood, and new-onset disease. Occupational factors are associated with about 1 in 10 cases of adult asthma (15), including both reactivation and new-onset disease (22, 33–37). Occupational studies have provided some evidence for a direct causal role of allergen and/or chemical exposure in the development of asthma. However, as in the case in the general population, specific allergen exposure may determine the specificity of sensitization in susceptible individuals (30).

It is well established that genetic determinants play a role in the susceptibility to the development of asthma (33). It is likely that asthma is a polygenic disease in which many genetic variants may determine the genetic–environmental interactions that determine susceptibility to asthma.

The search for the genes involved in OA is just beginning. To date, no genes that cause OA have been definitely identified. Evidence for human leukocyte antigen (HLA) associations is available only for a few sensitizing agents (34–37), and has not been confirmed for any of them (38, 39). Evidence for a significant association can imply a causal relationship, but can occur by chance (because of multiple comparisons, often made without prior hypothesis) by confounding from population admixture, or from linkage disequilibrium. Confidence in a significant association between a particular HLA polymorphism and sensitization or asthma comes from its strength and repeatability in two or more study populations.

However, two pools of genes that might be involved in causing OA have been suggested. First, it has been shown that HLA class II molecules encoded by the major histocompatibility (MHC) complex genes on chromosome 6p are required for the presentation of an antigen to a T cell receptor to initiate the chain of events that leads to an antibody response. Preliminary data obtained in occupational studies suggest that MHC class II proteins may be important factors for the specificity of the response to occupational sensitizers such as acid anhydrides, diisocyanates, and platinum salts.

Several studies have now reported significant associations between HLA haplotype and sensitization or asthma. Young and colleagues reported an association between HLADR3 and specific IgE to TMA, with an odds ratio of 16 in comparison to factory referents with a similar duration and intensity of exposure (35). Interestingly, this relationship was not observed in cases with specific IgE to phthalic anhydride (PA).

In a study of South African platinum refinery workers, Newman Taylor and colleagues found in cases with a skin test response to ammonium hexachloroplatinate (ACP) an excess of 'HLA DR3 and deficit of HLA DR6, as compared with referents matched on ethnic origin, intensity, and duration of exposure (40). The odds of a case being HLA DR3–positive or HLA DR6–negative were greater in the "low" than in the "high" exposure groups.

A second pool of candidate genes that could be involved in causing OA is that containing the members of the glutathione-S-transferase (GST) superfamily. This superfamily of genes is critical for protecting cells from the formation of reactive oxygen species (ROS). ROS, which can be generated by several types of

airway cell, including macrophages, eosinophils, and neutrophils, form in response to oxidative stress (41). Oxidative stress, a key component of airway inflammation, is a main feature of asthma. Evidence supporting the possibility that GST superfamily genes lead to asthma is that individuals differ in their ability to deal with an oxidative burden, and such differences are in part genetically determined. We recently found that, in OA induced by diisocyanates, the frequency of GSTP1 Val/Val genotype was significantly lower in individuals with asthma. Similarly, the frequency of this genotype was significantly lower in subjects with moderate/severe airway hyperresponsiveness to methacholine suggesting that homozygosity for the GSTP1*Val allele confers protection against the development of toluene diisocyanate asthma and nonspecific airway hyperresponsiveness. The protective effect increases in proportion to the duration of exposure to the sensitizing agent (42). GSTP1 may play a role in modulating and maintaining airway inflammation and airway hyperresponsiveness in both allergen- and chemical-induced asthma.

The relative role of genetic factors and environmental factors (i.e., exposure to a sensitizing agent) at the onset of sensitization has been examined in IgE-mediated sensitization (43, 44). Atopy, much more than the degree of exposure, was the principal determinant in the development of symptoms. Atopy is an important risk factor for sensitization to high-molecular-weight agents. Studies that assessed the natural history of OA from the time of exposure to high-molecular-weight allergens in the workplace began have demonstrated that in this type I immune response, the risk of specific sensitization to these allergens is related to atopy and nonspecific airway responsiveness, that immunologic sensitization may occur after a short latency period, that the concentration level of aeroallergens is not the only determinant for the development of sensitization, and that some allergens are more potent than others (e.g., laboratory animals more than flour or latex) (22). Low-molecular-weight agents are also well-recognized causes of OA. In the case of immunologic asthma, some agents (e.g., anhydrides) induce asthma via a type I IgE-mediated mechanism, whereas for others (e.g., diisocyanates, plicatic acid) the mechanism is less defined. Atopy is not a risk factor for asthma induced by either red cedar (45) or diisocyanates (46), but a link to the HLA system has been demonstrated for these agents, suggesting the role of genetic factors for the expression of the disease (36, 37).

Tobacco smoking increases the risk of sensitization and asthma, particularly to its low-molecular-weight chemical causes, such as complex platinum salts (47) and the acid anhydride (48) tetrachlorophthalic anhydride (TCPA), chemicals which cause asthma that is associated with specific IgE production. In contrast, smoking does not increase the risk of asthma caused by agents such as isocyanates and colophony, where specific IgE does not unusually accompany the development of asthma.

In one study of platinum refinery workers, smoking was shown to interact with exposure, increasing the risk of sensitization in those in both high- ($> 2 \ \mu g/m^3$) and low ($< 2 \ \mu g/m^3$)-exposure categories (49). Exposure has not been reported in other studies in a manner which would allow analysis of a possible interaction.

It is likely that low-molecular-weight agents act as haptens, combining with human proteins in the respiratory tract to become complete immunogens. Evidence for a structural basis for human respiratory sensitization due to chemicals, usually of low-molecular weight, is that certain structural fragments are related to respiratory sensitizing chemicals, and that certain physical properties of chemicals, such as molecular weight and water solubility, are associated with chemicals that cause respiratory sensitization (50). The isocyanate fragment, anhydrides, and some substituted aromatic fragments are electrophilic functionalities which can react with nucleophilic moieties, such as amino groups of proteins. Sensitizers had greater hydrophilicity and lower log P (octanol/water partition coefficient) than did nonsensitizers. Because airways contain hydrophilic secretions, molecules with hydrophobic regions may less readily reach reactive sites on respiratory cells.

The findings that structural fragments are associated with activity are based on only forty active chemicals that met the criteria for inclusion in the structure-activity model of chemicals. However, the model yielded a sensitivity of 0.95, and a specificity of 0.95 (51).

Sensitization to low-molecular-weight agents requires a shorter interval than sensitization to high-molecular-weight agents (52). Among those with OA, approximately 40% of subjects exposed to western red cedar and diisocyanates developed symptoms within the first year after exposure started, whereas only 18% of subjects exposed to high-molecular-weight agents developed asthma during this period.

IMMUNOLOGIC ASTHMA

Once a person is sensitized to an allergen or chemical, he or she may develop asthma. To be recognized by T cells, an antigen must be processed into small peptide fragments and presented on the surface of an antigen-presenting cell (APC) in association with MHC class II proteins. The major APC among several appears to be the dendritic cell. Indeed, the number of dendritic cells is greater in the bronchial mucosa of subjects with asthma than in that of normal individuals (53). Upon exposure to a sensitizing antigen, dendritic cells capture and internalize the antigen, and then migrate to the draining lymph node, where the processed peptides are displayed on the cell surface in association with MHC class II proteins. Naive T cells recognize the antigen–MHC complex through a T cell receptor that is specific for a particular antigenic peptide. The naive T cell is activated by costimulatory signals provided through the interaction of the receptor CD28 and the molecule B7 on the APC. The resulting Th0 cell population, which requires the production of interleukin (IL)-2 and the expression of the IL-2 receptor CD25, may differentiate into Th1 or Th2 effector cells under the influence of the cytokines IL-12 and IL-4, respectively. Th2 effector cells contribute to allergen-induced airway inflammation by generating IL-4, IL-5, IL-9, and IL-13. The immune response is limited by the programmed T cell death (apoptosis), but some T cells develop into memory T cells, which are responsible for the inflammatory response upon subsequent exposure to the sensitizing antigen.

The inflammatory process is modulated or prolonged by mediators released in the IgE response. In the IgE response, antigen binds to surface-bound IgE and stimulates mast cell release of histamine, leukotrienes, prostaglandin D$_2$, thromboxane B$_2$, platelet-activating factor (PAF), and several cytokines, including tumor necrosis factor-α (TNF-α), granulocyte-macrophage colony-stimulating factor (GM-CSF), and IL-1, -4, -5, -6, -8, and -13, as well as chemokines including RANTES, eotaxin, and MCP-1 and -3.

Although OA studies generally treated sensitization and asthma as equivalent outcomes, the progression from a normal state to the development of OA after exposure to allergens or chemicals may not be concurrent with the development of sensitization (54). Although in most cases, OA induced by high-molecular-weight agents is accompanied by the production of allergen-specific IgE antibodies, for OA induced by low-molecular-weight agents, only in some cases are specific antibodies detectable (55–57). The absence of antibodies in some patients with OA has led some investigators to suggest nonimmunologic mechanisms for the development of asthma. However, the evidence for an immunologic basis of asthma induced by two low-molecular-weight agents, such as diisocyanates and western red

cedar, is quite strong. One line of evidence is that the pathology of low-molecular-weight asthma, based on BAL, bronchial biopsy, and induced sputum is similar to that of atopic asthma: subepithelial fibrosis and increased numbers of T-lymphocytes and eosinophils that exhibit signs of activation (58–60). A second line of evidence is provided from inhalation challenge and genetic studies. Evidence for T cell-mediated immunity has also been provided for asthma induced by cobalt and nickel (61, 62), and for OA induced by high-molecular-weight agents (63). This asthma may be driven and maintained by the persistence of a specialized subset of chronically activated T-memory cells sensitized against an array of allergenic, viral, or occupational agents (64). T cells lead the inflammatory process, and key effector cells, such as eosinophils, mast cells, epithelial cells, and neutrophils, through the release of several inflammatory mediators, cause the characteristic pathologic phenotype of asthma, i.e., smooth muscle contraction, mucus hypersecretion, plasma exudation, edema, and epithelial damage.

In long-term follow-up studies, OA has been shown to be permanent, both in individuals removed and not removed from exposure (65). When an individual is no longer exposed to the sensitizing agent, asthma improves but is generally not cured. When patients who are no longer exposed to occupational agents are treated with glucocorticoids, the asthma is further improved, though again not cured (66). These findings suggest that structural changes ("remodeling") in the airways are important for the persistence of OA (67). However, the factors that initiate remodeling and contribute to its progression and how these changes alter airway function are poorly understood. Thus, the association between asthma severity and airway remodeling remains controversial (68). Recent findings are beginning to shed some light on this association. One recent study showed that ongoing inflammation and subepithelial fibrosis are linked to the persistence of exacerbations and nonspecific airway hyperresponsiveness (69). Chronic airway inflammation may contribute to remodeling by promoting turnover of extracellular matrix, producing profibrogenic factors, and damaging the epithelium (70). In support of these possibilities, in chronic asthma, epithelium manifests increased fragility and a phenotype characterized by a continuous source of proinflammatory products as well as growth factors that drive airway wall remodeling (71). The effector cells that secrete these products and thus maintain airway inflammation and contribute to airway remodeling may be airway smooth muscle cells, which can secrete several cytokines, chemoattractants (72), growth factors, and matrix metalloproteinases (73). In addition, bronchial vessels may play a role in airway remodeling by increasing the airway wall thickness through the processes of angiogenesis, dilatation, or permeability (74). Further, sensory neuropeptides may play a role in inflammation as well as in repair (75). Finally, key cells such as eosinophils and macrophages are important factors in the development of fibrosis (76, 77). Eosinophils produce ECP, MBP, metalloproteinases (MMP-3, -9), and reactive oxygen species (ROS), and macrophages secrete growth-promoting factors for fibroblasts,

cytokines, and growth factors, such as fibroblast growth factor (b-FGF), transforming growth factor-β (TGF$_\beta$), and insulin growth factor (IGF), which can be important in fibrosis. Thus, epithelial cells, smooth muscle cells, bronchial vessels, neuropeptides, eosinophils, and macrophages may all contribute to airway remodeling and thus maintain airway inflammation in workers with asthma who are no longer exposed to allergens or chemicals in the occupational environment.

ANIMAL MODELS

Animal models of OA due to both high- and low-molecular-weight agents might provide answers to many questions about OA, including the mechanisms involved in OA, the role of genetic and environmental factors in the development of sensitization and OA, the natural history of OA including the role of airway remodeling, the link between airway physiology and airway pathology, and the possibility to cure OA. Various species have been used as models of human asthma, including guinea pigs, mice, rats, cats, and dogs. Each possesses advantages and disadvantages (78, 79) In general, animal models represent models of sensitization and anaphylactic bronchoconstriction rather than asthma, and a limited number of chemicals has been used to understand the mechanisms, especially those involved in OA, induced by low-molecular-weight chemicals. No single model may work for all chemicals. However, if animal models are interpreted with caution, they may provide information useful to increase our understanding of mechanisms involved in the development of sensitization and OA, and to establish protective exposure guidelines, but none reflects the chronic and variable nature of the disease. The majority have focused on acute inflammatory changes, but a few have also examined the effect of more prolonged allergen exposure (80, 81). To date, the ideal model of asthma including OA does not exist.

SUMMARY

We know that OA with latency can be caused by high- and low-molecular-weight agents. High-molecular-weight agents and some low-molecular-weight agents cause OA through an IgE-dependent mechanism. There is also evidence that cell-mediated responses are involved in OA. Specifically, activated lymphocytes (T cells) and eosinophils infiltrate bronchial biopsies, as shown in studies of patients with OA. The key players in orchestrating airway inflammation, the hallmark of asthma, are T cells. In addition, several inflammatory mediators (cytokines, chemokines, leukotrienes, histamine) have been identified in the inflammatory process present in the asthmatic airways. However, the role of ongoing inflammation in the persistence of the disease and of the various structural airway changes observed in patients are not yet clear. Studies to date are limited by the use of sensitization to allergens rather than actual asthma as the endpoint. Sensitization to allergens or chemicals is a complex phenomenon, and cannot be used as an equivalent outcome to asthma.

Immunochemical Measurement of Occupational Aeroallergenic Bioaerosols
Determination of Permissable Exposure Limits?

Site air sampling and immunochemical analysis are a prerequisite to understanding the magnitude and extent of airborne dispersion of workplace aeroallergens and planning abatement measures. Measurements are also a valuable and underused approach for inclusion in clinical documentation of OA. Once a problem is recognized, occupational aeroallergen monitoring can

improve the effectiveness of preventive health measures, thereby reducing health care costs while maintaining or increasing the quality of life in the work environment.

REVIEW AND COMMENTS ON QUANTITATION OF AIRBORNE PROTEINACEOUS OCCUPATIONAL AGENTS

Detailed information on air sampling and equipment, focusing on high-molecular-weight allergens, has been recently published (82) and will be shortly reviewed hereafter.

Air Sampling and Equipment

Depending on the concentration of an airborne allergen, the volume of air that will allow sufficient concentrations of allergen to be collected for accurate analysis may vary from 0.5 to 1,000 m^3. Because flow rates generally are fixed on most sampling devices, the run times are varied to accommodate the required collection volume. Longer sampling periods have the disadvantage of lessened ability to correlate temporal changes in concentration with specific activities that generate exposure.

Proper filter selection is essential, including low airflow resistance and efficient retention of respirable particles. The filter should permit high yields of allergen recovery and allow extraction in small volumes (1 ml or less) so that concentration of the extract is not needed. Special bilaminate polytetrafluoroethylene (PTFE or Teflon) filters offer these features.

Area sampling is the most appropriate means to indicate the presence or absence of offending allergens and to confirm the identity of the allergen. Automated samplers with programmable filter-changing devices simplify collection of sequential samples, and are well suited for unattended long-term collections to monitor the success of control measures.

Personal breathing zone sampling is used to define particular job tasks that are associated with heavy and likely dangerous exposure. Such equipment also allows evaluation of remedial measures that have been taken.

Immunoassay Reference Standards

The choice of a working standard depends upon the situation. A single protein allergen, such as papain, may be used in purified form and can be expressed in mass units, but more often the exposure involves complex dusts with mixtures of many allergenic molecules. In this case, it is necessary to prepare a reference extract of the source material that is generated at work. Results of the assay can be expressed in terms of the protein content of the reference extract or in terms of an arbitrary unit. Usually this will be an overestimate of allergen mass, although usually not more than double the mass. Stability of the standard is optimized when stored undiluted at –20°C in 50% glycerine.

It is also useful to visualize the relevant allergens extracted from complex source material by immunoblotting.

Antibodies

Several kinds of antibodies are suitable for immunoassay. When they are available and a single component is of interest, two monoclonal antibodies of high avidity directed to different epitopes on an allergenic molecule are the most suitable. One antibody serves as a capture antibody; the other, after labeling, serves as detecting antibody. In monoclonal systems, unfractionated mouse ascites fluid serves well for capture antibody, but the detection antibody should be purified. One advantage of the monoclonal system is that the antibody is available in unlimited amounts as long as the clone is maintained. A high-titer polyclonal animal or human IgG containing antiserum can also be adapted to a two-site assay or can be used for inhibition assays.

For the two-site assay, the whole hyperimmune animal serum can serve as the capture antibody, and the affinity-purified form of the antibody serves as the detection.

For some applications, it is best to employ human IgE antibody. It may be the only antiserum available, and has the advantage of assuring that the substance causing the disease is being measured when the identity of the allergenic molecules is uncertain or the dust contains a complex mixture of allergens. If a human IgE system is adopted for the study, it is desirable to obtain a large pool, at least 250 ml from each of five to ten donors, to assure sufficient antibody to complete the entire project. The antibody remains stable for several years stored at –70°C.

Assay Design

For most applications, the two-site assay is the simplest to perform and the most sensitive. It has the additional advantage over inhibition assays of being accurate over a several-log range of protein concentrations. The serum or ascites fluid containing the polyclonal or monoclonal capture antibody is diluted in 20 to 200 mM carbonate buffer at pH 9.2, and a fixed volume is added to wells of a microtiter plate, which is then incubated overnight at room temperature in a humid chamber and the wells washed. The appropriate antibody dilution must be determined for each new assay system to be certain that the capture antibody is in excess. Albumin and other nonspecific proteins in the serum or ascites fluid usually suffice to block all unoccupied protein-binding sites on the plate, but this point needs to be confirmed experimentally for each system. Then the air sample extract, an internal standard, and dilutions of the reference standard antigen preparation are added. After a second overnight incubation and washing, the detection antibody is added. After the third incubation, the wells are washed and counted. The incubations are performed in a humid chamber at room temperature.

In addition, it is possible to use an animal polyclonal antiserum for capture and a human IgE antibody containing serum for detection. The amount of IgE antibody bound to the plate in this sandwich assay is measured with anti-IgE. Inhibition assays are used when there is only a single antibody available.

TOWARD THE DEVELOPMENT OF "PERMISSIBLE EXPOSURE LIMITS"

A final objective of the measurement of airborne occupational allergens is establishment of criteria allowing recommendations for permissible exposure limits (PEL) (83). This goal is in contrast to the determination of threshold limit values (TLV) (84). Aeroallergen exposure is more complicated than exposure to toxic material. A TLV can be determined because the toxicity of a substance is quite uniform among those who are exposed. The concentration of aeroallergen that provokes asthma in sensitized workers, however, varies over at least two orders of magnitude, and two very different aeroallergen concentrations must be considered: first, the concentration that initially sensitizes, and second, the concentration that provokes symptoms in workers already sensitized. The minimum concentration for sensitization seems to be at least one order and probably two orders of magnitude greater than the minimum concentration required to elicit symptoms. From a practical standpoint, PEL for eliminating sensitization is easier to set and monitor than a PEL for elimination of symptoms. Another less stringent approach to aeroallergen exposure assessment might be termed "tocsin hygiene," where concern is given to a liberal range of bioaerosol concentrations. For example, it is possible to estimate roughly the minimum aeroallergen concentrations required to sensitize (100–1,000 ng/m^3) and provoke symptoms (10 ng/m^3 or less), for

egg proteins, laboratory animal allergens, and natural rubber latex.

Certainly, in situations where a purified allergen is aerosolized, such as enzymes, these concentration ranges will no doubt be too liberal by as much as an order of magnitude. There is general agreement that the TLV for subtilisins (60 ng/m^3) was set because of analytical limitation and not clinical observation. These analytical limits no longer apply, and considerable thought and study should be given to the exposure–response relationships involved with OA associated with these bioaerosols.

In the same way as stringent standards have been proposed and applied for exposure to inorganic dusts such as silica and asbestos, it is of outmost importance to evolve toward a situation in which international standards will be adhered to. Although it remains to be determined whether peak exposures or mean exposures are more relevant in inducing sensitization and development of OA, studies in bakers have shown that sensitization is unlikely to occur below concentrations of 0.5 mg/m^3 of dust during a workshift (85). Similar standards have to be established for other high-molecular-weight agents as presented and discussed (86).

In conclusion, in recent years, assessment of the working environment has improved due to improvement in methodology and the use of personal sampling. The use of immunologic techniques has enabled the measurement of high-molecular-weight allergens in the workplace. These technical achievements should pave the way to the establishment of PEL at which sensitization is unlikely to occur.

Exposure to Chemical Agents

INTRODUCTION

This section is an overview on assessment of exposure to low-molecular-weight asthma agents by chemical assays, which is proposed in greater details in a recent chapter (87). Herein, we plan to outline and propose discussion of some key features.

EVALUATION STRATEGY AS RELATED TO OA

Exposure limits referred to as Threshold Limit Values, either of the time-weighted average (TWA) or short-term exposure (STEL) types, are often suspected of being inadequate or irrelevant in the prevention of OA where individual susceptibility could play an important role in the sensitizing process. The existence of a sensitizing threshold for which "Permissible Exposure Limits" could be developed (*see* section by M. C. Swanson) has not yet been scientifically proven, but the risk of developing OA has been shown to be related to the degree of exposure, even though studies continue to clarify the contribution of the duration and pattern of exposure, individual susceptibility, and routes of absorption (88). There are at least three justifications for quantifying worker exposure: first, to verify that a worker is really exposed to a specific agent in the workplace; second, for surveillance and prevention purposes; and third, to aid in the diagnosis through laboratory challenges. Whereas the role of immunologic method is important for the quantitation of high-molecular-weight proteinaceous agents (*see* section by M. C. Swanson), low-molecular-weight agents are evaluated through chemical assays.

MONITORING METHODS

In relation to OA, the main route of exposure to sensitizing chemicals is by inhalation, which emphasizes the importance of methods of determination of the concentration of chemicals in the air.

Sampling Techniques and Analytical Methods

In ambient air, a chemical pollutant can be present as a gas, vapor, or aerosol (mist or dust). Sampling of gases and vapors by active sampling on a solid adsorbent or passive sampling by diffusion is routinely done and well documented. Aerosols, mists, or dusts are often sampled on filters (or membranes) placed in a plastic cassette, bubblers, or impingers containing liquid being used less and less. The choice of the filter is set according to the requirements of the analytical methods. The cassette containing the filter is connected to a pump.

Various analytical methods are used to quantify the sample. This includes gas chromatography, HPLC, atomic absorption spectrophotometry in the case of metallic atoms, spectrometry, infrared spectrophotometry, ion chromatography, mass-spectrometry, etc. It is beyond the scope of this presentation to discuss the indications, limitations, and advantages of each of this processes.

Evaluation of Exposure to Specific Sensitizing Agents

Isocyanates. Most sampling methods have been developed for impinger sampling and subsequently modified for sampling on adsorbent tubes or filters. A combination of analytic methods, including visible spectrometry, UV spectrometry, and HPLC, allow for detection with the sensitivity required for low-concentration (from 1 to 75 μg/m^3) or short-duration exposures. There are two types of commercial direct-reading instruments that incorporate either an impregnated paper tape or a gas cell. Biological monitoring of isocyanate is possible using albumin adducts and their corresponding diamines in plasma and urine. Research is continuing to further improve the limit of detection, assess representative samples of mists containing isocyanate monomers and oligomers, and to provide levels of polyisocyanate prepolymers. The applicability of direct-reading instruments to different diisocyanates can still be improved as well as their response to simple interferences such as humidity.

Acid anhydrides. Methods for sampling and analysis of anhydrides have been described (89). Anydrides are sampled on a cellulose membrane filter, hydrolysed to the corresponding diacid, extracted with an aqueous ammonia solution, and anlayzed by HPLC with a UV detector. A gas chromatography method recommended by NIOSH for trimellitic anhydride should be adaptable to organic anhydrides that can be volatilized without decomposition.

Formaldehyde and other aldehydes. The analytic methods for quantifying formaldehyde are well developed on a wide range of air concentrations. Methods for other aldehydes, including glutaraldehyde, which is a sensitizer in health professionals, have not reached the same level of development. Direct-reading instruments for the work environment are available and easy to use, but are plagued with many types of interferences with other chemicals (phenols, alcohols, ketones). A proper strategy will have to be developed for the analysis of complex mixtures before their sensitization properties are examined.

Amines. The analytic techniques use gas or liquid chromatography for the analysis of airborne volatile amines sometimes collected in impingers, but as often as possible in sorbent tubes

or on treated filters. In general, the low limits of detection required by the application to OA (amines are often present in workplaces where isocyanates are used, and some workers can be sensitized to amines as others are to isocyanates) are attainable only with methods in which the amine group is derivatized. However, in the case of secondary and tertiary amines that frequently cause OA, straight application of gas chromatography or HPLC with specific detectors is possible, but such methods have not yet been validated.

Colophony and fluxes. This natural complex pine resin commonly used in the electronic industry is largely composed of acidic resins of which abietic acid is the main constituent. Colophony can be used in two different applications, depending on whether it is heated below (as in paint and varnish application) or above its decomposition temperature of about 200°C (as in soldering or welding). Methods of assessing abietic acid concentrations in the air when colophony is used have been published (90).

Metals. For metals that have been reported as causing sensitization, particularly in welders (Pt, Co, Mn, Ni, and Cr), industrial hygiene samples are collected on filters and analyzed by atomic emission spectroscopy or inductively coupled plasma atomic emission spectroscopy.

Other substances. In industrial hygiene, the sampling and analytical methods for most substances are well developed and could be used for OA studies. Some compounds would require extensive efforts in analytic method development. This includes the various types of acrylates that frequently cause OA.

CONCLUSIONS

This review of chemical monitoring of agents that induce OA emphasizes the progress being made in developing highly sensitive detection methods for certain compounds such as diisocyanates, formaldehyde, and anhydrides. Special efforts should be done for quantifying chemicals which have recently been described as causing OA, such as glutaraldehyde and acrylates. Moreover, in the same way as in the case of high-molecular-weight agents for which determination of PEL is aimed, a similar strategy should be adopted for low-molecular-weight agents. Finally, at the instance a new chemical is introduced in the market, its potential for sensitization should be explored using structure-activity models (91).

RADS—A Special Entity?
The Role of Irritant Exposures in Asthma

The issue of irritant-induced asthma has engendered a fair amount of controversy since the specific syndrome descriptor, Reactive Airways Dysfunction Syndrome (RADS), was first introduced by Brooks and coworkers in 1985 (8). The purpose of this review is to place irritant-induced asthma in its epidemiologic context. By doing so, the goal is to better understand the determinants of irritant-induced asthma, thus gaining insights into its mechanisms, natural history, and potential public health importance.

The initial debate over irritant-induced asthma was focused on its acceptance or rejection as a discrete syndrome which occurs sporadically if not predictably. The subsequent case report literature has more than put that matter to rest. These reports have been well summarized by the excellent review of Alberts and DoPico (92), which included 28 published reports through 1994 involving 113 individuals with irritant-induced asthma consistent with the original syndrome criteria of RADS. Those RADS-defining criteria were a brief, high-intensity irritant inhalation exposure followed by acute-onset, persistent respiratory symptoms and ongoing airway hyperresponsiveness. Moreover, there has been a wider recognition that irritant-induced respiratory illness has ample historical precedent, dating back to bronchitis among 19th-century bleaching workers and asthma and bronchitis among survivors of WWI irritant gas attacks (93).

Subsequent to the case experience summarized by Alberts and DoPico (92), a number of additional case reports have appeared as reviewed (94). Taken as a group, the RADS case experience is dominated by several large outbreak series that have contributed more than one-third of the reported cases (metam sodium, zinc chloride, and 2-diethylaminoethanol). Of the remaining cases, the most common single agents have included chlorine gas or hypochlorite bleach misadventures releasing chlorine, acids, other discrete irritants (for example, bromine or ammonia), and isocyanates (the latter chemical group being both an irritant and a sensitizer).

Unfortunately, these case reports have added little to our understanding of the role of irritants in potentially causing asthma, beyond establishing the accuracy of the original observation of RADS. The obvious limitations of this literature include the referral biases inherent in specialty-based or medical-legal referral cases (a common feature of many but not all of these reports), a potential "publication bias" tending to favor novel exposures or unusual exposure scenarios, and, most importantly, the absence in most of the reports (with a few exceptions) of any estimate of the exposed population from which the cases emerge. Without knowing this "denominator" value, the incidence of the syndrome cannot be estimated, nor can predictors of adverse outcome be quantified.

One attempt at incidence estimation was based on poison control center cases after chemical inhalation exposure. In a 6-month prospective series of 323 interviewed subjects, 6% had symptoms lasting 14 days or longer (95). Although half the group reported exposure to chemicals independently classified as moderate to severe irritants, the irritant potential of the chemicals was not a predictor of persistent symptoms. In a second study also based on poison control cases, a subgroup of symptomatic subjects were recruited for methacholine challenge (96). Of these, 8 of 10 had airway hyperresponsiveness at 2 weeks; 7 of these 8 were still hyperresponsive at 3 months, even though 4 of the 8 had ceased to be symptomatic.

Taken together, these two studies suggest that persistent irritant-induced respiratory symptoms are uncommon after inhalations over a wide spectrum of irritant intensity and severity, but when such symptoms are present they correlate with airway hyperresponsiveness. Three separate cohort investigations (acetic acid, n = 33 subjects; metam sodium, n = 197; and nitrogen tetroxide, n = 234) have estimated new-onset asthma incidence after acute irritant inhalation to range from 3 to 20% (97–99). Another incidence estimate, based on surveillance data in the UK, found that of 589 irritant exposure cases, 26% were symptomatic at 1 month, whereas only 8% were still symptomatic at 3 months (17). Combining all of the cases together (n = 1387)

yields a follow-up incidence of 7.2% (95% confidence interval [CI], 6.8–7.6%).

Another indirect measure of the incidence of irritant-induced asthma is its frequency relative to "classic" OA in referral-clinic based series and in surveillance data. Classic OA refers to new-onset OA associated with exposure followed by an immunologic response to a high- or low-molecular-weight sensitizer. Although one important investigation of an occupational lung clinic found that cases meeting criteria for RADS had a 1:5 ratio to classic asthma (27), two more recent clinical series (100, 101) have observed ratios closer to 1:1. In contrast, limited data published from the US "SENSOR" surveillance program of work-related asthma still suggests that irritant-induced asthma is less common than classic OA, but these data may reflect the biases inherent in workers' compensation insurance data (16).

Comparisons between irritant-induced asthma and classic sensitizer-induced OA may also be useful for the mechanistic insights their differences and similarities may provide. The primary differences between sensitizer- and irritant-induced OA are threefold. Sensitizer-induced asthma requires a latency period, is immunologic, manifesting an anamnestic response by definition, and is marked by specific airway responsiveness upon appropriate challenge with the causative agent. Irritant-induced asthma as defined by RADS criteria is of immediate onset, does not involve specific sensitization, and is characterized by *nonspecific* airway hyperresponsiveness. Although these differences may be straightforward, the similarities between irritant- and sensitizer-induced asthma are also worth noting: in both, inflammatory cellular responses are a component of their pathophysiology, and antiinflammatory treatment, therefore, is commonly employed in their treatment regimens. As importantly, both can be disabling, even without further exposure (94).

Although it is now generally accepted that the phenomenon of irritant-induced asthma does occur, there is no steadfast delineation of its terminology or diagnostic criteria. RADS, in its originally proposed clinical criteria, intentionally excluded exacerbations of preexisting lung disease. It also focused attention on high-intensity, single exposures rather than repeated, intermediate, or lower lever inhalations (8). The broader concept of "irritant-induced asthma" includes scenarios of repeated exposure, although this less narrow definition in and of itself does not advance our understanding of the syndrome or syndromes involved. Overlap in causal agents, particularly asthma after high-level exposure to isocyanates, adds to the nosologic confusion (92, 102). In addition, the range of possible chronic sequelae after irritant respiratory tract exposures, including bronchiolitis obliterans, bronchiectasis, vocal cord dysfunction, cough without airway hyperreactivity, and isolated nasal deficits, including the entity of Reactive Upper Airway Disorder (RUDS) (103, 104), only further serves to complicate the picture.

Nonetheless, there are several potential models of human irritant-induced asthma that could provide important information. Smoke inhalation is one of the most overlooked of these. Studies of wildland and urban firefighters, of smoke inhalation victims, and controlled human smoke exposure studies have all demonstrated exposure-related changes in airway responsiveness relevant to mechanisms of irritant-induced asthma (94). Chlorine exposure has also provided a rich vein for research, in part because periodic high-intensity exposures, or "gassings," are endemic to industries where compressed chlorine gas is used (93) and because chlorine, too, can be studied in controlled human exposures. Potroom asthma in the primary aluminum smelting industry may prove to be one of the most important models for irritant-induced asthma (105), although this, like the isocyanate model, may be complicated by overlapping sensitization cases. Candidate industries for the study of lower level, chronic irritant effects include ammonia use in fertilizer, vanadium in metal refining, and oxides of nitrogen from explosives used in mining, one of the earliest irritants systematically studied in terms of airflow obstruction.

Future research in the study of irritant-induced asthma must address a critical need for prospective studies with adequate baseline data. Both intermittent, high-level exposures and lower-intensity, chronic exposures are of interest. The potential roles of atopy and cigarette smoking status should also be studied prospectively. Without such studies, we cannot hope to delineate risk factors for the irritant-induced asthma and thus adequately plan prevention strategies. Linking epidemiologic methods with detailed biologic studies in systematically selected subsets of patients should also be a research priority, if we are to better understand the mechanisms of this disease. This has already begun to happen in innovative and important studies of bronchoalveolar lavage after exposure to chlorine (99, 106), sulfur mustard (107), and methyl isocyanate (108). Finally, more attention should be paid in our research agenda to the aggravation of preexisting lung disease if we are to fully meet the challenges of irritant-induced asthma (109).

Diagnosis and Management of Occupational Asthma

DIAGNOSIS OF OCCUPATIONAL ASTHMA

There is some suggestion that OA remains largely unsuspected by health care providers. A recent survey of asthmatic members of a health maintenance organization in the United States found that only 15% of medical records documented asking about work-related symptoms by general practitioners (109). Furthermore, allergists and chest physicians addressed work-related asthma symptoms in only 50% of the referred patients (109).

Improved detection implies that the possibility of OA should be considered by all physicians (general practitioners, chest physicians, allergists, and occupational health physicians) in all working-age individuals with asthma. An occupational history should be part of the initial evaluation of all adults with asthma. However, exposure to potential asthma inducers may remain unrecognized when exposure is indirect or intermittent. The absence of a known sensitizer does not exclude OA, because new causes of OA are reported each year due to rapidly evolving manufacturing processes. Physicians should systematically question patients with asthma about the temporal relationship between symptoms and work exposure by asking whether symptoms improve after several days away from work. Health surveillance programs should periodically assess whether respiratory symptoms develop in workers and whether such symptoms are temporally associated with exposure at work (110). Epidemiologic surveys suggest that questionnaires are sensitive but not specific for identifying OA (12). Physicians should, however, be mindful that questionnaires can be falsely negative, because workers may remain unaware of the association between work and asthma when the onset of OA symptoms is progressive, when there is poor perception of airway obstruction, or when exposure to the offending agent is indirect or intermittent. In addition, fear of job loss may lead workers to deny symptoms on a surveillance questionnaire.

The diagnosis of OA should be investigated before advising workers to leave their workplace, because prolonged avoidance of exposure may influence the reliability of diagnostic procedures (111). It may be easier to perform investigations for OA, such as serial peak expiratory flow monitoring or inhalation challenges, at work when the subject has not resigned his or her job. The diagnosis should be investigated as soon as possible to prevent deterioration of asthma.

Appropriate medical management and compensation decisions require an objective assessment of suspected OA as advised by recent guidelines (112) and consensus statements (113). The differential diagnosis of asthma in the workplace besides OA includes coincidental non-OA which is common and frequently has its initial onset in adult life (or recurrence after childhood asthma), which can complicate diagnosis of OA. Another possible diagnosis is the work-related aggravation of asthma in a nonspecific manner by exposure to dust, smoke, fumes, and low-level irritant chemicals, or by cold, dry air or exercise at work. In addition, symptoms that mimic asthma may be due to other conditions such as chronic bronchitis, hyperventilation, vocal cord dysfunction, or rhinitis. Therefore, although a history of asthma symptoms starting during a working period, especially with improvement on weekends or holidays off work, is suggestive of OA, evidence is needed (*1*) to verify that symptoms truly are on the basis of asthma, and (*2*) to document the relationship of asthma to the workplace exposure.

The diagnosis of asthma is objectively reached by spirometry pre- and postbronchodilator, and/or a histamine or methacholine challenge test, preferably performed toward the end of a typical work week and within 24 hours of the occurrence of symptoms. Results at this time which do not show evidence of asthma virtually exclude a diagnosis of OA.

Assessment of the work exposure from the patient's history can be supplemented by means of material safety data sheets (MSDS) from the workplace, and occupational hygienist work-site visit reports when available. However, agents present as less than 1% of the content of a material, and previously unrecognized respiratory sensitizers may not be identified by these means. Lists of reported sensitizers have been published (114) and are available on the internet (*see* www.csssst.qc.ca or www.asmanet.com), but additional agents are described each year and may not be listed in the MSDS.

The diagnosis of irritant-induced asthma or RADS currently remains circumstantial, based on the history, objective evidence of asthma, no previous known lung disease to explain the findings, and where possible, some supportive information to document a high-level exposure to a respiratory irritant within 24 hours before symptom-onset.

Objective investigations can, however, be used to assess other workplace relationships of asthma. A methacholine or histamine challenge that improves significantly while off work supports a diagnosis of OA unless explained by confounding factors. A provocation concentration causing a 20% fall in FEV_1 (PC_{20}) that increases more than threefold after a period of a few weeks off work, when measured within 8 weeks of the test at work, is significant (115), whereas a twofold increase is of possible significance. However, some sensitized individuals with asthma (perhaps those with longer duration of OA) can require more than a few weeks away from exposure before significant improvement occurs.

Symptom and medication diary recordings, including monitoring of serial peak expiratory flow rates (PEF), or spirometry (using inexpensive PEF meters or more expensive hand-held electronic devices which store serial peak flow and/or spirometry results), can add to other OA investigations (116), despite the frequent lack of good compliance with such studies. Comparison of PEF readings with serial FEV_1 recordings using a portable ventilometer showed better sensitivity (at 73%) and specificity (at 100%) for peak flow recordings, further validating this test as a useful component of investigations for OA (116).

However, nonoccupational factors can confound the interpretation of both PEF results and methacholine or histamine challenges (115). These include intercurrent respiratory viral infections within the preceding 6 weeks, or nonoccupational relevant allergen exposures to which the patient is sensitized. If the patient has left the implicated work exposure and cannot or will not return on a trial basis, workplace pulmonary function changes cannot be assessed.

Immunologic tests to demonstrate IgE antibodies to a high molecular workplace allergen when feasible can document immunologic sensitization to a workplace allergen with sensitivity and specificity up to 95% and 100% (117). However, they are limited by the frequent lack of commercially available or standardized skin test reagents for occupational agents. A positive skin test response supports a diagnosis of OA if associated with appropriate pulmonary function changes, but as a sole investigation is not diagnostic and can occur in up to 60% of asymptomatic workers (118).

In vitro assay of serum IgE antibodies can add to the diagnosis, especially for low-molecular-weight chemical sensitizers such as trimellitic anhydride, but there are relatively few laboratories where these tests are well standardized. Assessment of other possible immunologic mediators, such as chemokines in diisocyanate-induced asthma, may be useful in the future but currently are research investigative tools.

Specific occupational laboratory challenge tests with the suspected workplace sensitizer currently are performed in relatively few centers, and require specialized facilities (119). Although often considered to be the gold standard of diagnosis, potential false-positive and -negative responses are recognized. For example, there can be false-negative responses if the wrong agent is used, e.g., the wrong type of diisocyanate. After a long period away from exposure, sensitivity may be reduced or lost, although this is a rare occurrence (120), or there may be a need for multiple days of re-exposure to measure a response (121). Excessive levels of some agents can be irritant.

Exhaled nitric oxide and induced sputum analysis have recently been evaluated in diagnosis and impairment assessment of OA. Induced sputum eosinophils have been found to increase in OA with exposure to a relevant sensitizer at work or in the laboratory, whereas exhaled NO has not to date proven useful (122, 123).

Which diagnostic tests to use in an individual patient usually depends on feasibility, relating to the work status of the patient, the specific exposure agent(s), the assessment facilities, and requirements of the compensation system. There are limitations to all available tests (112, 113) and there is a continuing need to develop further simple, specific diagnostic tests for OA.

MANAGEMENT OF OCCUPATIONAL ASTHMA

Pharmacologic Treatment

Anti-asthma medications are used in the same way as for patients who have asthma that is unrelated to the workplace. However, pharmacologic treatment is not effective in preventing lung function deterioration in sensitizer-induced OA when the subjects remain exposed to the causal agent (124, 125). A study in subjects with OA due to various agents showed that adding inhaled steroids to removal from exposure resulted in a small but significant improvement in asthma symptoms, quality of life, bronchial responsiveness, and PEF (66). Interestingly, this study showed that the beneficial effects of inhaled steroids were more pro-

nounced if the treatment was started early after diagnosis. Patients with RADS/irritant-induced asthma are treated pharmacologically as for non-OA, but there are no controlled clinical trials as to the relative efficacy of specific medications.

Avoidance of Exposure

Longitudinal studies of workers with sensitizer-induced OA have shown that persistence of exposure to the causal agent leads to worsening of asthma (65). Complete avoidance of exposure is associated with improvement in asthma symptoms and functional parameters, although symptoms and NSBR persist in approximately 70% of affected workers. Early removal has been consistently found to be associated with a better outcome. However, removal from exposure is associated with the worst socioeconomic outcome, suggesting that some compensation systems and rehabilitation programs are currently not appropriate (124–127).

Reducing exposure to the offending agent through relocation to less exposed jobs, improvement in workplace hygiene, use of modified materials, and/or use of personal protective devices may be the only practical alternative to prolonged unemployment when the possibilities for alternative jobs are limited, or when a career depends on continuing a particular type of work.

The use of helmet respirators has been proposed (128, 129). Materials with a lower allergen content, such as low-protein latex gloves, can reduce the risk of developing an asthmatic reaction in subjects with OA, although highly sensitive subjects may still develop asthma after prolonged exposure (130). A few studies have investigated the long-term effects of reducing exposure to the causal agent in workers with sensitizer-induced OA. Analysis of available data shows that asthma remained stable or improved in 68% and worsened in 32% of workers who remained exposed to "lower" levels of the offending agent (131–135).

Complete avoidance of exposure remains the most effective treatment of sensitizer-induced OA, and should be strongly recommended to affected workers. Compensation systems and retraining programs should be improved to discourage workers from staying exposed to the agent causing OA. The long-term effects of reducing exposure to the causal agent should be further assessed.

In contrast, patients with RADS/irritant-induced OA without concurrent sensitization to the exposure agent can usually return to the same workplace if they have adequate pharmacologic control of their asthma and if there are appropriate occupational hygiene controls in place to prevent the likelihood of a repeat high-level respiratory irritant exposure.

Why and How to Compensate Workers Who Develop Occupational Asthma?

Although it was originally thought that OA was self limited, it is now clear that this is not the case. OA has serious socioeconomic consequences, as workers have to be taken off work to prevent further deterioration in their asthma. Satisfactory rehabilitation programs should be made available. Because the majority of workers have persistence of symptoms and abnormal pulmonary function, there is also a need for adequate impairment and disability assessment.

Several studies have looked at the outcome of workers with OA who have been removed from work. As shown in various studies summarized elsewhere (65), 49 to 100% have persistent symptoms between 1 and 11 years after work withdrawal. This is associated in most cases with increased nonspecific bronchial responsiveness. However, workers with OA do not seem at increased risk for developing IgE-mediated sensitization to common allergens (136).

In workers removed from exposure, Malo and coworkers have shown that there is a plateau of improvement in the spirometry (FEV_1 and FEV_1/FVC ratio) 1 year after cessation of exposure, whereas PC_{20} methacholine seems to plateau after 2 years (137). However, in a longer follow-up of workers, the same group of investigators more recently showed that the improvement toward normal bronchial responsiveness may take a longer interval (138). The factors predicting the outcome are baseline PC_{20} (the lower the PC_{20} at diagnosis, the less likely the chances that the PC_{20} would normalize), duration of exposure, and the interval since removal. Furthermore, subjects with OA to high-molecular-weight products seem to have a less favorable outcome.

Although there is clear evidence that cessation of exposure is associated with a decrease in specific IgE to high molecular agents such as crab, latex, and other agents, it is unlikely that workers removed from exposure will ever lose their specific sensitivity. Indeed, Lemière and coworkers evaluated specific bronchial responsiveness to occupational agents after a minimum of 2 years after removal from exposure in 15 workers (139). Fourteen still experienced an asthmatic reaction on exposure to the occupational agent.

The socioeconomic consequences of OA have been described in different countries and reviewed (140). In Quebec, it has been shown that about one third of subjects find a job with the same employer in which they are no longer exposed to the offending agent, whereas one third find a different job with another employer with or without needs for attending retraining programs. Only 8% of subjects remain unemployed after 2 years of follow-up (140). Ameille and colleagues reported a gloomier situation in the case of 209 French subjects with OA assessed on average 3 years after the diagnosis, with 25% unemployed and 32% still exposed in the same job (127). Gassert and coworkers reported on 55 U.S. subjects assessed on average 31 months after removal from exposure, the majority (69%) still being unemployed, presumably due to the severity of persisting asthma (141). Moscato and coworkers showed that subjects with OA who stayed at work needed more medication than those who ceased to be exposed (125). Quality of life of subjects with OA is slightly, though significantly, less satisfactory than subjects with common asthma of comparable severity (140). Finally, it has recently been shown that the risk for hospitalizations in 844 subjects accepted for compensation for OA in Ontario between years 1980 and 1993 was 1.4 (95% CI = 1.2–16) by comparison with subjects with musculoskeletal injuries. The risk was half the risk for admissions for common asthma, and was more marked in the first 5 years after the claim was accepted (142).

OA has features which are not shared by pneumoconiosis, such as asbestosis or silicosis. Asthma is a variable clinical and physiologic condition and it is amenable to therapy. There is no radiologic change (that is the essential diagnostic feature of pneumoconiosis), and increased nonspecific bronchial respon-

siveness may render subjects less able to work in an environment with continued exposure to irritants or cold air. In terms of lung function, assessment of lung volumes, CO transfer, and performance on exercise are needed to properly assess the impact of pneumoconiosis; all of these means are not relevant for the assessment of the impact of asthma (143).

The assessment for temporary disability should be performed immediately after making the diagnosis of OA. Workers with OA are 100% impaired for the job that caused the problem or for jobs with exposure to the same causative agent. We think that long-term assessment of impairment should be performed 2 years after removal from exposure, when improvement has been shown to plateau. Asthma should be optimally controlled at the time of impairment assessment. Guidelines on how to assess permanent impairment due to asthma have been proposed by the American Thoracic Society (143). Parameters to consider for rating of impairment are physiologic parameters, namely postbronchodilator FEV_1 and reversibility of FEV_1 or degree of nonspecific bronchial responsiveness and the minimum medication required to control the asthma. In addition, the less satisfactory quality of life of these subjects, although only marginally lower than for subjects with common asthma, might be considered in the assessment.

Although workers with irritant-induced asthma can generally go back to their usual environment as long as exposure to irritants can be avoided, the same recommendations for assessing impairment can be given. Permanent impairment should also be assessed 2 years after the inhalational accident, as there is still improvement up to this endpoint (144).

In conclusion, proper assessment of impairment using relevant disability rating and rehabilitation programs will ensure that workers with OA will cease exposure and have a reduced burden of this condition on their health and quality of life.

Prevention of Occupational Asthma

When discussing strategies for preventing OA, three steps are usually proposed; they are discussed in a previous publication (145). Primary prevention deals with all factors, environmental and personal, that can diminish the risk before "sensitization" occurs. Secondary prevention takes place at a preclinical stage, and tertiary prevention is intended to identify workers in an early phase of the disease.

PRIMARY PREVENTION

Risk identification is one of the most important aspects of primary prevention. Lists of agents and, equally important, occupations at risk should be made available, preferably on a web site as now proposed on www.asmanet.com. Dissemination of information on possible risks should be reinforced periodically. Relevant safety data sheets should be made available to workers at specific workplaces. Results of sentinel-declaration projects such as SENSOR and SWORD should be widely diffused. Medicolegal statistics should also be presented regularly to all interested audiences. Hazard surveillance, such as walk-through evaluations of the workplace, should be scheduled to improve controls in facilities. Simple but efficient measures can result from these visits: for example, the substitution of unpowdered for powdered natural latex gloves may substantially reduce the risk of workplace sensitization (130). The fact that psyllium can be administered as hard pills instead of in powder form has resulted in the almost complete elimination of cases of OA due to this in nurses working in chronic-care hospitals (J. L. Malo, personal observation). Awareness of likely "sensitizers" present in the workplace should be enhanced. Theoretically, every high-molecular-weight agent can cause immunologic sensitization and asthma. It is more difficult to predict whether a specific low-molecular-weight agent can lead to sensitization and asthma. However, it has been proposed that careful examination of the structure–activity relationship of chemical products can be worthwhile (51).

Although short-term exposure-level limits can be useful to set acceptable irritant effects of a product, these levels are of no help in establishing risk for sensitization. Efforts should be made to determine "permissible concentrations" of agents, that is, the level at which immunologic sensitization is unlikely to occur. Such efforts have already resulted in setting permissible levels for flour dusts at 0.5 mg/mg^3 (146). It is expected that a similar approach will succeed for other proteinic occupational antigens (86).

Wearing masks and respirators results in lowering exposure. However, both the compliance with and the effectiveness of these means remain questionable. Spray painters now commonly use full-face masks or helmet respirators, which offer better protection than dual-cartridge masks. However, spray painters have to lift the helmet to assess the quality of their work. Moreover, so-called "touch up" procedures can result in indirect exposure that can be as noxious as direct exposure in the spray booth.

Atopy is a predisposing factor in workers exposed to high-molecular-weight agents. However, atopy is generally a weak predictor. Also, in some instances, the fact of being atopic is a weaker predictor of sensitization and of developing OA than the fact of being sensitized to a more precise high-molecular-weight agent. For example, in a recent study, Gautrin and co-workers found that sensitization to pets was a significant predictor for developing OA to laboratory animals (RR = 4.11; 95% CI = 1.6–10.8), whereas atopy was not (RR = 2.09, 95% CI = 0.8–5.6) (24).

Moreover, the fact that more than 50% of a young adult population is atopic means that it is now unacceptable to suggest excluding atopic subjects from certain workplaces. Finally, in a recent study of approximately 800 apprentices in animal health technology, pastry-making, and dental hygiene, we found that 27/85 (32%) incident cases of sensitization (22) and 8/30 (27%) incident cases of OA (24) were nonatopic subjects.

Taken together, these findings (more than 50% of atopic individuals in young individuals who start working, one third of subjects with OA who are nonatopic) make it unethical to exclude atopic subjects from high-risk workforces. Cigarette smokers may also be at greater risk of workplace sensitization to certain asthma-causing agents (viz. platinum salts). Although assigning jobs of varying risks on the basis of whether a person smokes is an inappropriate primary prevention strategy, the prohibition of cigarette smoking in the workplace itself is a cornerstone of primary prevention.

It is generally felt by clinicians who assess subjects with possible OA that a preexisting history of asthma is not a predictor for the development of OA, even to high-molecular-weight agents. However, it is possible that a lower baseline FEV_1 (RR = 1.06, 95% CI = 1.02–1.1) and a "measurable" PC_{20} (RR = 2.45, 95% CI = 1.0–5.8) may predict those who will develop OA (24).

Genetic markers still need to be explored and, for the time being, are more hypothetical than confirmed risk markers.

SECONDARY PREVENTION

The goal of secondary prevention is to identify preclinical changes in the disease.

The development of immunologic sensitization precedes the development of OA with a latency period. Skin-testing with high-molecular-weight agents is easy to do, has no side effects, and can identify people who have become immunologically sensitized. It is reasonable that they should then be followed more closely for development of bronchial hyperresponsiveness or asthma symptoms. In subjects who are sensitized, regular questionnaires or assessment of bronchial responsiveness can detect subjects at an early preclinical stage. However, we have recently found that only a small proportion of sensitized subjects will proceed to symptomatic status within a relatively short period of 3 to 4 years after getting sensitized (147). In a prospective study of 417 apprentices exposed to laboratory animals and seen before exposure and 8, 20, 32, and 44 months after starting exposure, 129 (32.7%) were found to have skin reactivity to a laboratory animal–derived allergen at at least one of the visits. The incidences of work-related cutaneous, nasal, and ocular symptoms were 21, 28, and 22%, respectively. The incidence of work-related dyspnea and wheezing was 5%. The positive predictive value of skin reactivity in relation to the concomitant or subsequent development of nasal and/or conjunctival symptoms was 40%, whereas it was only 7% and 9% in the case of work-related dyspnea and wheezing. These relatively low figures of positive predictive values may cast doubt on usefulness of skin testing in the secondary prevention of work-related rhinoconjunctivitis and asthma. For high-molecular-weight agents, rhinoconjunctivitis can be used as a predictor of the later development of OA as, contrary to the case with low-molecular-weight agents, rhinoconjunctivitis symptoms often precede the onset of OA (148).

It can also be advocated that all workers in high-risk workplaces be assessed initially for airway caliber and responsiveness to methacholine. A combination of increased bronchial hyperresponsiveness with a questionnaire suggesting OA has been found to correctly identify individuals with OA to a low-molecu-lar-weight agent, spiramycin, as confirmed by specific inhalation challenges (149). Again, however, the validity of this approach has not been assessed in epidemiologic surveys.

For OA without a latency period, that is, irritant-induced asthma, it is our impression that a respiratory questionnaire and bronchial responsiveness should be assessed before employment and after every visit to the first-aid unit with respiratory symptoms (150).

TERTIARY PREVENTION

Early detection of OA among employees in high-risk workplaces is justified on the grounds that the earlier the diagnosis is made and the affected worker is removed from the workplace, the more likely the patient is to be cured from persisting asthma. Referral to experts should be done quickly. It is unacceptable for subjects to wait a year or two before being assessed by medicolegal agencies. Such delays result in catastrophic social and psychological burdens. Once a referral is made, it is of the utmost importance to rely on a precise diagnosis of OA. Using results of skin testing and/or assessment of antibodies alone, or questionnaire, is not sufficient to diagnose OA. First, as discussed above, it is not because a person has immunologic sensitization that he/she has the disease. Questionnaires administered by experienced physicians have a high sensitivity but a low specificity for diagnosing OA. If OA is confirmed using the testing described above (*see* contribution by S. Tarlo and O. Vandenplas) and the exposure stopped, adding inhaled steroids can improve symptoms, quality of life, and lung function, but it will not cure the asthma.

Cost-effectiveness studies in the case of primary, secondary, and tertiary prevention programs are necessary. Very little data is available. Tarlo and coworkers recently showed a better prognosis in subjects with OA to isocyanates who underwent a prevention program in Ontario (151). Such results warrant confirmation.

In conclusion, all prevention strategies should be assessed according to favorable changes in outcomes such as reduced incidence of OA and/or, in cases where the disease cannot be reduced or eliminated, better medical and psychosocial prognosis of workers. Finally, all these strategies should also be examined in terms of their cost-effectiveness.

Recommendations of Working Groups

1. TOPIC: FREQUENCY OF OA, ENVIRONMENTAL DETERMINANTS AND HOST SUSCEPTIBILITY

Rapporteur: T. Newman-Taylor

Participants: J. M. Anto, M. Jaakkola, P. Cullinan, D. Banks, M. Becklake, H. Dhivert, C. Infante-Rivard, K. Venables, G. Perrault, M. J. Nieuwenhuijsen

1.1. Aspects of Determining the Frequency of OA

1.1.1 Aim. To estimate the public health burden of asthma in the workplace. Recommended means: broad community-based studies to develop tools to estimate the prevalence of various causes of asthma and the influence of work on asthma morbidity, as well as the influence of asthma on work.

1.1.2. Aim. To estimate geographical variation in the above relationships of asthma, and time trends in these. Recommended means: broad community-based studies.

1.1.3. Aim. To estimate the effectiveness of interventions at work. Recommended means: focus on high-risk occupations (industries + small workforces). Consider using available data (compensation registers) to identify these.

1.1.4. Aim. To estimate risk factors. Recommended means: incidence data comparing affected and nonaffected workers.

1.2. Determinants of OA

1.2.1. Exposure study aims.

1.2.1.1. To assess the importance of patterns of exposure (average versus peaks of exposure).

1.2.1.2. To correlate exposure variables with disease in the case of high-molecular-weight and low-molecular-weight agents.

1.2.1.3. To assess timing of exposures versus responses.

1.2.1.4. To exploit industrial interventions (e.g., laboratory animals exposure control measures) to assess possible beneficial effects.

1.2.1.5. To develop questionnaire-based assessments of exposure (e.g., European Community Respiratory Health Survey).

1.2.1.6. To standardize exposure assays.

1.2.2. Genetics study aims.

1.2.2.1. To ensure integration with exposure data. Estimate occupation-genetic-environmental interrelations.

1.2.2.2. To incorporate occupational information into linkage studies.

1.2.2.3. To study the association of candidate genes in exposed populations.

1.2.2.4. To estimate potential biases and power.

2. TOPIC: MECHANISMS OF OA

Rapporteur: D. Bernstein

Participants: C. Mapp, G. Moscato, R. C. Balkissoon, C. Lemière, P. Maestrelli, W. Brown

2.1 Aim. To explore the immunopathogenesis of disorders caused by low molecular weight agents (chemicals).

Recommended means: investigate immediate hypersensitivity, delayed or contact hypersensitivity, and nonimmunologic irritant and/or neurogenic pathways. Explore the possibility that immunologic and nonimmunologic mechanisms coexist in the same host.

2.2. Aim. To study the mechanisms of diisocyanate-induced asthma and the roles of immediate and cell-mediated mechanisms, pursuing the following hypotheses:

Hypothesis #1: Local immune and inflammatory airways responses occurring in workers with occupational asthma who have diisocyanate-antigen specific IgE differ from those of workers with diisocyanate asthma who fail to exhibit evidence of allergic sensitization.

Recommended means: a collaborative multicenter study is suggested in workers referred for evaluation of occupational asthma associated with HDI exposure. A case–control design would be employed in a group of workers with HDI asthma and elevated serum specific IgE to HDI-HSA and a second comparably sized group of workers with HDI-asthma in whom specific IgE is absent. In addition, a population of workers with occupational asthma caused by sensitization to a protein allergens should be included.

Characterization of cytokines, cell markers, and local antibody responses in lung secretions and bronchial tissues of two groups of workers with HDI asthma, including one group of HDI-HSA specific IgE producers and a second group of non-IgE producers.

Hypothesis # 2: Delayed or allergic contact hypersensitivity responses in the skin are relevant to the pathogenesis of occupational asthma. Demonstration of cellular proliferative responses to diisocyanate hydrolysis products (diamines) among workers with occupational asthma with and without cutaneous reactivity to isocyanates is suggested.

3. TOPIC: DIAGNOSIS, MANAGEMENT, MEDICOLEGAL ASPECTS, AND PREVENTION

Rapporteur: H. Nordman

Participants: O. Vandenplas, S. Tarlo, S. Burge, B. Nemery, P. Harber, J. Ameille, J. Côté, M. Labrecque, C. Leroyer, L. Perfetti, K. Ronsenman, L. Bernstein, A. Cartier, L. Holness, G. Liss, G. Wagner

Aims.

3.1. To investigate quality and effectiveness of Material Safety Data Sheet. Develop joint effort to improve Material Safety Data Sheet (e.g., list all specific sensitizers).

3.2. To enhance discussion on interesting case reports through e-mail or chat lines on a case repository web site.

3.3. To assess the value of a range of medical surveillance

programs. To include an evaluation of the causes of delays in diagnosis. Aspects of the evaluations should include:

The possible early-warning role of rhinoconjunctivitis symptoms preceding asthma

The role of skin testing with high-molecular-weight allergens

The role of bronchial responsiveness to methacholine as a screening tool

The effects of development and dissemination of guidelines

It is also relevant to develop data to determine "levels of probability" given data about exposure (e.g., sensitizers) and responses (e.g., sensitization, lung function changes, etc.).

3.4. To investigate long-term outcomes of irritant exposure among workers whose asthma is "aggravated" at work.

3.5. To study outcomes of various compensation systems and costs.

3.6. To examine cross-national descriptions of clinical and medicolegal practices.

3.7. To examine the effectiveness of immunotherapy in sensitized people who continue to work with exposure to a workplace allergen.

3.8. To evaluate the long- and short-term effectiveness of protection devices (masks).

TOPIC 4. IRRITANT-INDUCED ASTHMA

Rapporteur: M. Chan-Yeung

Participants: P. Blanc, S. Brooks, D. Gautrin, P. K. Henneberger

4.1. Questions Identified by the Working Group which Merit Further Research

4.1.1. Are the pathophysiologic mechanisms of irritant-induced asthma similar to those of allergen-induced asthma?

4.1.2. What is the pattern or severity of exposure in irritant-induced asthma?

4.1.3. What are the factors (other than work exposure) in irritant-induced asthma?

4.1.4. Does standard antiinflammatory treatment for allergen-induced asthma have the same impact on irritant-induced asthma?

4.1.5. Does early intervention with antiinflammatory drugs after a high-level irritant exposure prevent the development of irritant-induced asthma?

4.2. Recommended Means

4.2.1. A multicenter prospective cohort study of individuals in industries (chlorine: pulp mills, chemical plants, water purification plants; smoke: wildland firefighters; ammonia: fertilizer plant; suphuric acid: metal plating) with possible exposure to high levels or repeated exposure to lower levels of irritants would be able to answer questions 1, 2, and 3 addressing both high-level exposure and low-level or repeated exposure in irritant-induced asthma depending on the industries chosen for the study. Population baseline characteristics (questionnaire for demographic data, smoking history, occupational history, and job exposures; allergy skin test with common inhalants; lung function tests; measurement of nonallergic bronchial hyperresponsiveness; assessment of airway inflammation–induced sputum, exhaled nitric oxide). Exposure characteristics should be obtained through questionnaire on work history and job exposure, continuous monitoring of irritant exposure whenever possible; personal monitoring of exposure (whenever possible).

When a subject develops an acute event, defined as those with a history of high exposure and chest symptoms lasting for more than 24 hours, the following are to be performed: lung function testing, measurement of nonallergic bronchial hyperre-

sponsiveness, measurement of airway inflammation by induced sputum, or exhaled nitric oxide within 48 hours at 1, 2, and 6 months after the acute event. In some centers, repeated bronchial biopsies are suggested to study the pathology.

Follow-up studies of the cohort should be performed every 2 years using the same methods listed above. The follow-up measurement will allow identification of subjects who might have developed symptoms and lung function abnormalities (developed irritant-induced asthma from low-level or repeated exposure) and the level of exposure leading to the development of irritant-induced asthma.

A nested case–control study should be performed comparing the characteristics of those who develop irritant-induced asthma with appropriate control subjects.

4.2.2. Animal models of irritant-induced asthma will address questions 1 and 2 above. Using this model, one can study the pathophysiology of irritant-induced asthma, the type of inflammatory cells, mediators, cytokines, and chemokines responsible for the inflammatory response. The inflammatory response to different types of irritants, such as ammonia or sulphuric acid, can be assessed in a similar manner. In addition, the exposure characteristics, i.e., level, frequency, and duration of exposure leading to the development of irritant-induced asthma, can be determined.

4.2.3. Clinical Trials

4.2.3.1. To answer the question whether antiinflammatory treatment has the same effect on irritant-induced asthma as allergen-induced asthma, subjects with irritant-induced asthma should be recruited (defined as those with classical RADS) and matched with patients with allergen-induced asthma of similar severity. Both types of subjects should be treated with the same antiinflammatory drugs following the same protocol. Outcome assessment should include lung function, measurement of nonallergic bronchial hyperresponsiveness, and quality of life.

4.2.3.2. To answer the question whether early intervention with steroids will prevent the development irritant-induced asthma, subjects with a history of exposure to high levels of irritants and chest symptoms lasting for more then 24 hours should be recruited. Baseline lung function tests, measurement

of nonallergic bronchial hyperresponsiveness, and measurement of airway inflammation will be performed. They should be randomized into two groups, one treated with steroids and the other without steroids, and outcome assessment performed at 3 months.

This Official ATS Workshop Report was prepared by an ad hoc subcommittee of the Assembly on Environmental and Occupational Health. The subcommittee was co-chaired by Jean Luc Malo, Susan Tarlo, and Moira Chan Yeung. Members of the subcommittee are:

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Addendum: Lung Health and the Canadian Environment
A Review of Results of this Study to Date That Are Relevant to this Workshop

Dr. Margaret Becklake and Dr. Moira Chan-Yeung presented the enclosed work at the symposium. The editors who found this work relevant to the theme of the symposium include it for the interested reader.

Findings from a multicenter Canadian study entitled "Lung health and the Canadian environment" (152) that incorporate work-related features (25) are relevant to this workshop for several reasons. First, the findings are based on data gathered in community-based studies carried out in six sites across Canada (Vancouver, Winnipeg, Hamilton, Montreal, Halifax, and Prince Edward Island). Second, the Montreal data complement the cohort studies of Gautrin and coworkers (22, 24) also carried out in Montreal area trainees entering trades or professions at risk for occupational asthma. Third, the results address the issue of why definitions of study outcome (in this paper occupational asthma) need to vary according to the purpose for which the definition is to be used (12).

The study referred to in the title followed the two-stage protocol of the European Community Respiratory Health Survey (ECRHS), targeting adults aged 20 to 44 years of age. (153). In Stage I, a short questionnaire was answered by randomly selected population-based samples in all study sites. In a preliminary analysis of the results among 12,380 subjects (5,447 men and 6,933 women) from four of the six sites (Vancouver, Winnipeg, Hamilton, and Montreal), the rates of reported exposures at work were not trivial: for exposure to dusts at work, rates were 56.2 and 34.1% for men and women, respectively; and for exposure to gases, fumes, and chemicals at work, 44.6 and 24.0%, respectively (152). There were no differences between men and women in the prevalence of ever wheeze (26.9 versus 25.6%),

TABLE 1. THE ASSOCIATIONS OF SYMPTOMS AND WORK-RELATED JOB CHANGE WITH THE TWO CATEGORIES OF EXPOSURE IN 12,380 CANADIAN MEN AND WOMEN 20 TO 44 YEARS OF AGE, EXPRESSED AS ODDS RATIOS AND CONFIDENCE INTERVALS

	Dusts (20%)	Fumes, Vapours or Chemicals (8%)	Both (21%)
Wheeze in the last year	1.55 (1.3, 1.8)	1.08 (0.9, 1.4)	1.90 (1.6, 2.2)
Chronic bronchitis	1.57 (1.3, 1.6)	1.31 (1.1, 1.6)	1.97 (1.8, 2.2)
Health related job change	3.32 (2.4, 4.5)	4.22 (2.9, 6.2)	9.60 (7.3, 12.6)

though women were more likely than men to report an attack of asthma in the last year (7.5 versus 5.4%), to report breathlessness with wheezing (14.6 versus 11.6%), and to report being wakened by cough in the last year (36.8 versus 27.9%). Preliminary analyses of the associations of symptoms and health-related job change with exposures at work are shown in Table 1.

For the symptom of wheeze (used as a surrogate for clinical asthma), the estimated effects of both categories of exposure were more than additive (the ORs for both categories of exposure are higher than the sum of the separate categories), whereas for chronic bronchitis (defined by symptoms of chronic mucus hyper secretion), the estimated effects of both categories of exposure were closer to additive. In addition, the strong associations of health-related job change with both categories of exposure provides evidence of a "healthy" worker (survivor), an effect captured by a community-based study such as this one, but rarely by cross-sectional work force–based studies.

In Stage II of the ECRHS protocol, performed at the Montreal site, 498 subjects (238 men and 260 women), randomly selected from those participated in Stage I, took part in laboratory studies which included an extended health questionnaire, skin prick tests, and airway responsiveness to methacholine challenge (AR-MCH), considered to be increased if there was a 20% fall in FEV_1 before reaching a maximum cumulative dose of 2 mgm. An additional feature of the Canadian study was the completion of a comprehensive job/industry/exposure history. Preliminary analysis of the results in these men and women showed that the relationships of current wheeze were consistently stronger with *past* compared with *current* exposure both to high- and low-molecular-weight agents (HMW, LMW), to irritants, and to excess heat and excess cold at work, and after adjusting for sex, age, and smoking, all the ORs were statistically significant. By contrast, for increased AR-MCH, only the OR for exposure to excess cold was statistically significant. These data underline the strength of the "healthy" worker (survivor) effect in the Montreal participants (12). The multivariate analysis shown in Table 2 therefore focused on reported past (not cur-

rent) exposure. The associations of current wheeze and of increased AR-MCH with occupational exposure and with personal risk factors for asthma are shown as ORs (CI) for all subjects (n = 498) and then after exclusion of the 40 subjects with childhood-onset asthma from the analysis (n = 458).

From the above data, prevalence rates ratios were calculated for ever versus never exposed at work, standardized for sex, age, and height. These were then used to estimate population attributable risk % for two outcomes, wheeze and increased AR-MCH. These results are shown in Table 3 for all subjects (n = 498) and after exclusion of the 40 subjects with childhood-onset asthma (n = 458).

For current wheeze (adjusted for sex, age, and smoking) the estimates of Population Attributable Risk % for ever exposed to HMW/LMW agents at work (between 4.6 and 4.9%) were comparable to those for exposure to irritants at work (between 4.6 and 4.8%). When also adjusted for other pertinent risk factors but not for atopy, the changes were minor. By contrast, the estimates for Population Risk % for increased AR-MCH (adjusted for sex, age, and smoking) in Montreal adults was much higher for exposure HMW/LMW agents at work (from 30.8 to 33.8%) than for irritant exposures at work (from 6.8 to 7.2%). The negative association of AR-MCH with irritant exposure may be due to a high rate of health-related job changes and a strong health selection ("healthy" worker) effect. Finally, for both outcomes (ever wheeze and increased AR-MCH), the same risk factors operated whether the individual's asthma started in childhood (n = 498) or after age 16 (n = 458).

Several conclusions can be drawn from these findings. First, the "healthy" worker (survivor) effect is likely to result in underestimation of the role of work exposures in the genesis of occupational asthma unless past exposures are considered (12). Second, the fact that for increased AR-MCH, Population Attributable Risk is much higher for exposure to HMW agents than for irritant exposures may explain why, in individuals with exposures to agents such as grain and wood dust, the longer the duration

TABLE 2. THE ASSOCIATIONS BETWEEN CURRENT WHEEZE AND AR-MCH IN THE MONTREAL AREA MEN AND WOMEN WHO PARTICIPATED IN STAGE II OF THE STUDY

Determinants	Current Wheeze (n = 498)	Current Wheeze (n = 458)	AR-MCH (n = 498)	AR-MCH (n = 458)
Ever exposed to				
HMW/LMW	1.01 (0.6, 1.17)	1.02 (0.6, 1.7)	2.20 (1.1, 4.2)	2.05 (1.0, 4.2)
Irritants	2.12 (1.0, 4.3)	2.17 (1.0, 4.2)	0.35 (0.1, 1.3)	0.52 (0.1, 1.9)
Personal factors				
Asthma as a child	5.99 (2.6, 13.4)	n/a	8.72 (2.9, 26.7)	n/a
Pets in childhood	1.90 (1.1, 3.4)	2.4 (1.1, 3.9)	0.98 (0.5, 2.0)	1.17 (0.5, 2.6)
Has an older sib	0.44 (0.3, 0.7)	0.52 (0.3, 0.9)	0.54 (0.8, 1.0)	0.57 (0.3, 1.1)
Family hx asthma	2.26 (1.3, 3.8)	2.15 (1.2, 3.8)	2.09 (1.0, 4.2)	1.79 (1.1, 2.4)
Chest infection before age 2	2.94 (1.3, 6.5)	5.2 (2.9, 13.0)	0.21 (0.0, 1.0)	0.40 (0.1, 2.4)
Current smoker	3.60 (2.3, 5.8)	3.85 (2.4, 6.3)	2.24 (1.2, 4.2)	2.30 (1.2, 4.5)
Being a woman	1.74 (1.1, 2.8)	1.79 (1.1, 3.0)	1.69 (0.9, 3.3)	1.70 (0.9, 3.4)

Definition of abbreviations: AR-MCH = airway responsiveness to methacholine challenge; HMW = high-molecular-weight agents; LMW = low-molecular-weight agents.

TABLE 3. POPULATION ATTRIBUTABLE RISK % (CI) FOR WHEEZE AND FOR INCREASED AIRWAY RESPONSIVENESS AMONG CANADIAN ADULTS 20 TO 44 YEARS OF AGE

	Ever Wheeze (n = 498)	Ever Wheeze (n = 458)	AR-MCH (n = 498)	AR-MCH (n = 458)
Ever exposed*				
HMW/LMW	4.9% (n/a)	4.6% (n/a)	30.8% (13.3, 71.6)	33.8% (13.3,71.5)
Irritants	4.6% (0.9,21.5)	4.8% (n/a)	7.6% (2.6, 22.1)	6.8% (6.7, 6.9)
Ever exposed**				
HMW/LMW	2.4% (n/a)	3.1% (n/a)	29.6% (12.0, 72.5)	29.8% (10.7, 81.4)
Irritants	5.3% (1.4,19.9)	5.5% (1.4, 22.5)	−7.7% (n/a)	−5.0% (0.8, 31.9)

For definition of abbreviations, *see* Table 2.
n/a indicates that the CI were too wide to report.
* Adjusted for sex, and smoking.
** Also adjusted for other pertinent host factors but not atopy.

of their asthma symptoms before withdrawal from exposure, the less likely they are to regress. Third, the fact that the personal and other childhood determinants were as important in the genesis of both outcomes studied (ever wheeze and increased AR-MCH), whether or not these outcomes developed in childhood or after age 16 years, illustrates why different study definitions of asthma related to work are needed depending on the purpose of the study. For instance, if the objective is define a phenotype for genetic studies, or if the diagnosis is for workman's compensation purposes, then a rigorous definition is required (154). If, on the other hand, the objective is to estimate the public health burden of work-related asthma (and by how much it might be reduced if particular exposures were to be curtailed), then a broader definition covering all types of asthma, including preexisting asthma aggravated by work exposure, is appropriate (155).

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