State of the Art

Occupational Asthma

Cristina E. Mapp, Piera Boschetto, Piero Maestrelli, and Leonardo M. Fabbri

Section of Hygiene and Occupational Medicine, Department of Clinical and Experimental Medicine, University of Ferrara; Department of Environmental Medicine and Public Health, University of Padua; and Section of Respiratory Diseases, Department of Oncology and Hematology, University of Modena, Italy

Substantial epidemiologic and clinical evidence indicates that agents inhaled at work can induce asthma. In industrialized countries, occupational factors have been implicated in 9 to 15% of all cases of adult asthma. Work-related asthma includes (*1*) immunologic occupational asthma (OA), characterized by a latency period before the onset of symptoms; (*2*) nonimmunologic OA, which occurs after single or multiple exposures to high concentrations of irritant materials; (*3*) work-aggravated asthma, which is preexisting or concurrent asthma exacerbated by workplace exposures; and (*4*) variant syndromes. Assessment of the work environment has improved, making it possible to measure concentrations of several high- and low-molecular-weight agents in the workplace. The identification of host factors, polymorphisms, and candidate genes associated with OA is in progress and may improve our understanding of mechanisms involved in OA. A reliable diagnosis of OA should be confirmed by objective testing early after its onset. Removal of the worker from exposure to the causal agent and treatment with inhaled glucocorticoids lead to a better outcome. Finally, strategies for preventing OA should be implemented and their cost-effectiveness examined.

Keywords: asthma; management; risk; susceptibility; workplace

CONTENTS

(*Received in original form November 19, 2003; accepted in final form April 25, 2005*)

Supported by the Ministry of University and Scientific Research, Associazionne per la Ricerea e la Cura dell'Asma (ARCA), and by the Consorzio Ferrara Ricerche.

Correspondence and requests for reprints should be addressed to Cristina E. Mapp, M.D., Section of Hygiene and Occupational Medicine, Department of Clinical and Experimental Medicine, University of Ferrara, Via Fossato di Mortara 64/b, 44100 Ferrara, Italy. E-mail: mapp@unipd.it

Am J Respir Crit Care Med Vol 172. pp 280–305, 2005
Originally Published in Press as DOI: 10.1164/rccm.200311-1575SO April 28, 2005
Internet address: www.atsjournals.org

OCCUPATIONAL ASTHMA: DEFINITION AND CAUSAL AGENTS

Occupational asthma (OA) has become one of the most common forms of occupational lung disease in many industrialized countries (1, 2), having been implicated in 9 to 15% of adult asthma (3, 4). OA is important to recognize clinically, because it has serious medical and socioeconomic consequences (5, 6). Like asthma that develops in childhood, OA is probably the result of multiple genetic, environmental, and behavioral influences (7). Because in most cases OA can be accurately identified and exposures to the causal agent can be measured, and because OA does not differ in its clinical and pathologic features from nonoccupational asthma, it is likely that studies of OA have the potential to provide us with useful information about the effects of genetic, environmental, and behavioral interactions in adult-onset asthma (8).

A better understanding of the natural history of adult asthma will allow us to assess the effects of early diagnosis, environmental control, and therapy on the outcome of this disease. Of the criteria necessary to determine the natural history of any disease (9), the first, a precise definition of the disease, is met if the definition of OA is limited to those conditions in which asthma is caused by occupation (10); this definition allows subjects with the disease to be identified. The second criterion is the availability of longitudinal studies of the disease. OA can be studied throughout its course from onset to remission or persistence (11). An advantage of these studies is that if OA is diagnosed early, it can be cured in substantially higher proportion than adult-onset nonoccupational asthma. In addition, the ability to perform prospective studies of workers before exposure for the presence or absence of risk factors and to monitor the workers after onset of exposure for development of disease may help to determine the relevance of various predictors and their interaction with exposure. The third criterion is the evaluation of the effect of therapy on the course and outcome of the disease. In this regard, OA is unique, because it is possible to investigate not only the effects of treatment, but also the effects of ending exposure to the causal agent (12, 13).

What Is Occupational Asthma?

For a disease that was first described many centuries ago, attempts to define OA have met with surprising difficulty until more recently. Although the broader category of work-related asthma encompasses both OA and asthma aggravated by work or the work environment, what emerged in all the proposed definitions was the causal relationship between workplace exposure and asthma and/or the specificity of the causal agent to the workplace. In guidelines published by the American Thoracic Society, OA is defined as asthma caused by work exposure (14). Similarly, authors of a critical review of the definitions and types of OA (15) stated that the definition of OA should be limited to those conditions in which asthma is caused by occupation.

Briefly, OA 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 (10, 16). Two types of OA are distinguished by whether they appear after a latency period. (*1*) Immunologic: OA appears after a latency period of exposure necessary for the worker to acquire immunologically mediated sensitization to the causal agent. This type encompasses OA that is induced by an IgE mechanism (most high- and some low-molecular-weight agents), and OA in which an IgE mechanism has not been demonstrated consistently (low-molecular-weight agents, such as diisocyanates, western red cedar, and acrylates). (*2*) Nonimmunologic: OA is characterized by the absence of a latency period. It occurs after accidental exposure to high concentrations of a workplace irritant. This clinical entity has been defined as irritant-induced asthma (17, 18). The most definitive form of irritant-induced asthma is "reactive airway dysfunction syndrome" (RADS) occurring after a single exposure to high levels of an irritating vapor, fume, or smoke (19). In addition, work-related asthma encompasses variant syndromes, including eosinophilic bronchitis and asthma-like disorders caused by exposure to organic dusts.

There is general agreement that the key element in defining OA is evidence of a direct causal relationship between workplace exposure and the development of asthma; nevertheless, several issues and controversies persist.

One controversy involves the definition of OA. The definitions of OA have varied according to the focus of the authors, such as epidemiologic studies (20), workplace surveillance programs (16, 21, 22), clinical diagnosis (23), and medicolegal assessment (24). The clinical diagnosis of OA requires the highest level of evidence, because it has significant implications for both worker health and socioeconomic status.

Few authors have suggested the inclusion of work-aggravated asthma in the definition of OA (14, 25, 26), because this entity is common (27, 28) and may cause disability and socioeconomic consequences that are potentially preventable (29, 30). Work-aggravated asthma is defined as preexisting or concurrent asthma that is exacerbated by workplace exposure (15). Exertion and exposure to cold, dry air, dust, fumes, and sprays are common in the workplace and may aggravate asthma (27, 28), especially in those with moderate to severe disease and in those not receiving optimal treatment. When work-aggravated asthma occurs on a regular basis rather than from a single incident, it can be assessed by measuring peak expiratory flow rates (PEFRs) and by symptom/medication diaries. Work-aggravated asthma should be distinguished from OA, because the outcome, medical management, and preventive measures differ substantially. Reducing workplace exposure to respiratory irritants; limiting exposure to relevant environmental allergens and nonoccupational irritants such as tobacco smoke; and optimizing antiasthma therapy, educating the patient about how to use the drugs, and emphasizing the importance of compliance often allow workers with this type of asthma to continue working in the same job. These options could probably be managed at lower costs than the cost of completely removing a subject with OA from the workplace. However, these measures are not sufficient to prevent the relapse of true OA. Some individuals with work-aggravated asthma, as a consequence of new exposures to specific agents in the workplace, may develop true OA. Thus, OA can occur in workers with or without prior asthma. A label for this situation has often provoked controversy, because the individual has OA as well as nonoccupational asthma.

In the nonoccupational setting, the hypothesis that allergens are a direct cause of asthma is largely based on indirect evidence (31, 32). However, in the occupational setting, some studies, even if concerning few causal agents of OA, have shown that the environment can cause asthma *de novo* (33–35).

An area of uncertainty is the diagnosis of RADS, which requires that several criteria be met (16, 19), the most important being the strong temporal association between inhalation exposure and the rapid onset of asthmatic symptoms. It follows that a diagnosis of RADS should never be made in subjects with preexisting asthma. There is debate about how to define the worsening of preexisting asthma caused by inhalation of high levels of irritants (36). For some authors, strict application of criteria required to make a diagnosis of RADS causes difficulties in achieving an appropriate diagnosis and the recognition of an occupational accident when the patient has a history of cured allergic asthma or smoking-related chronic obstructive pulmonary disease (37). Another debate concerns whether RADS is a subset of irritant-induced asthma (38). We believe that RADS should be considered a subset of irritant-induced asthma, a broader term that characterizes workers who develop asthma after both single and multiple irritant exposures (39, 40). Vandenplas and Malo (15) suggested that, although widely used, the term "RADS" should be replaced in future nomenclature by "acute irritant-induced asthma" or "sudden-onset irritant-induced asthma" to avoid confusion with delayed or progressive forms of asthma associated with irritant exposures at work.

Another issue concerns whether asthma develops from multiple exposures, as suggested by two studies (18, 41), rather than from a single exposure to high levels of irritants. However, in the studies suggesting the requirement of multiple exposures, it is possible that the changes were progressive, because changes in asthma after each exposure were not measured. Data obtained in these studies confirmed that initiation of asthma required a single high-level exposure. Therefore, asthma resulting from multiple high-level exposures to irritants can be considered irritant-induced OA, provided that the onset of persistent asthmatic symptoms is temporally related to one documented, severe accidental inhalation exposure.

There is still controversy about whether intermittent high-level exposure and chronic low-level exposure to irritants can cause OA (39, 42). Both seem possible. It was shown that repeated peak exposure to irritant gases, for example, in the pulp industry, increased the risk for both adult-onset asthma and wheezing (43), and also that asthma symptoms developed in three patients after repetitive exposure to irritants that took place over a period of several days to months (44).

Prezant and coworkers (45) described a condition called "World Trade Center cough" in many firefighters exposed to inorganic dusts, products of pyrolysis, and other respirable materials at the site of the World Trade Center after the terrorist attacks on September 11, 2001. Airway hyperresponsiveness was present in about one-quarter of the firefighters who had high levels of exposure, whether or not they had World Trade Center cough. Other abnormalities included airway obstruction and a bronchodilator response, without evidence of parenchymal changes on chest radiography. These observations are consistent with irritant-induced asthma due to high levels of dust inhalation (46, 47) and suggest that, at variance with previous studies (48, 49), a severe inhalation injury requiring hospitalization is not needed for the development of irritant-induced asthma. A longitudinal study showed that airway hyperresponsiveness shortly after the collapse of the twin towers predicted reactive airway dysfunction at 6 months in highly exposed firefighters (50). It has been reported that the high alkalinity of the World Trade Center dust produced the airway hyperresponsiveness, persistent cough, and increased risk of asthma (51).

The main characteristics of the various forms of work-related asthma are shown in Table 1 (52).

TABLE 1. CHARACTERISTICS OF MAIN FORMS OF WORK-RELATED ASTHMA

Characteristic	Immunologic OA (Sensitizer-induced)	Irritant-induced OA	Aggravation of Preexisting or Coincident Asthma
Clinical and occupational history			
Asthmatic symptoms	Yes	Yes	Yes
Onset	During working life	Within 24 h of exposure to high levels of a respiratory irritant‡	Before or during working life
Relation to work	Symptoms worsen during the working day, and may improve away from work	Reexposure to the same exposure conditions as occurred in the acute incident is not recommended; persistence of symptoms for at least 12 wk	Symptoms worsen while at work
Other characteristics	Exposure to a known sensitizer	No previous diagnosis of asthma or other chronic lung diseases	Presence in the workplace of triggers of asthma, such as dusts, fumes, cold air, smoke, or exercise
Investigation			
Confirm asthma and work relationship			
Lung tests	Objective evidence of asthma*	Objective evidence of asthma*	Objective evidence of asthma*
Serial PEFR plus symptoms and medication diaries	Worse during periods of regular work than when off work	No changes unless the irritant is also a sensitizer	Worse during periods of regular work than when off work
Methacholine challenge	Airway hyperresponsiveness usually present; often worse at the end of a work week than at the end of a holiday period	Airway hyperresponsiveness usually present	Airway hyperresponsiveness usually present; no difference between work periods and when off work
Specific challenge	Positive response to the causal agent	Not feasible	—
Immunologic tests	Positive response to the sensitizer	—	—
Induced sputum test	Eosinophilia, ECP increase during periods of work exposure	Not investigated	Baseline eosinophilia, no further increase after exposure to a sensitizer at work
Assess exposure	Review MSDS† and patient's history to confirm exposure to a respiratory sensitizer in the workplace	Review patient's history to confirm temporal relationship between exposure to large quantities of a respiratory irritant and onset of asthma, usually requiring "medical attention"§	Review patient's history to confirm temporal relationship between exposure to dust, fumes, smoke, or exercise and respiratory symptoms

Definition of abbreviations: ECP = eosinophil cationic protein; MSDS = material safety data sheet; OA = occupational asthma; PEFR = peak expiratory flow rate.

Adapted from Reference 52 by permission of the publisher, © 2003 CMA Media Inc.

* Airflow limitation with significant reversibility to bronchodilator (at least 12% increase in FEV_1); airway hyperresponsiveness to methacholine or histamine challenge.

† Additional agents are reported each year and may not be listed in the MSDS.

‡ There is still debate on the limit of 24 hours.

§ "Medical attention," especially hospitalization, is not a necessary criterion.

The most common type of OA, accounting for more than 90% of cases, is immunologic OA, induced by an IgE mechanism or other immune responses, such as cell-mediated immunity to specific workplace agents. The less common type of OA, irritant-induced asthma, accounts for about 7% of cases (52). Whereas immunologic OA can be induced only by sensitizers, irritant-induced asthma can be induced by exposure to either sensitizers or irritants (53). It should be underlined that sensitizers cause irritant-induced asthma only if the exposure is in the irritant range. These distinctions are complicated because respiratory irritants have been shown to exacerbate allergic airway inflammation and preexisting IgE response to allergens in the human respiratory tract (54).

This picture is further complicated by the description in clinical practice of other conditions that mimic asthma, for example, asthmalike disorders and eosinophilic bronchitis, and it is still debated whether these conditions should be considered OA.

Variants

Asthmalike disorders. Asthmalike disorders have been especially related to exposure to vegetable dusts such as grain, cotton, and other textile fibers and to dust from animal confinement buildings. A population-based study performed on 1,906 subjects has shown that occupational exposure to organic dust is associated with an increased risk of asthma, particularly in atopic subjects (55). How can these disorders be differentiated from OA? One way is that, in asthmalike disorders, asthma symptoms may be associated with systemic symptoms, which are usually not present in OA. There is no latency and symptoms can occur in naive subjects on first exposure; these are not typical features of OA. Third, asthma symptoms in asthmalike disorders may be associated with transient increases in nonspecific airway responsiveness, increases that are usually important and persistent in OA. Finally, in asthmalike disorders, asthma symptoms may be associated with neutrophilic airway inflammation (56), which has been shown for some but not all causal agents of OA. Asthmalike disorders have been associated with exposure to endotoxin, and this observation makes their mechanism more intriguing (*see* PATHOPHYSIOLOGY).

Eosinophilic bronchitis. Eosinophilic bronchitis has been described as a cause of chronic cough characterized by sputum eosinophilia in the absence of demonstrable variable airflow limitation or nonspecific airway hyperresponsiveness (57). Exposure to acrylates, natural rubber latex, mushroom spores, and an epoxy resin hardener in the workplace can result in increased sputum eosinophilia in the absence of airflow limitation and increased nonspecific airway responsiveness (58–60). Because increases in sputum eosinophils are remarkable and reproducible, the condition should be considered occupationally induced.

Although this condition clearly does not meet the definition

TABLE 2. ESTIMATED PREVALENCE OF WORK-RELATED ASTHMA FROM CROSS-SECTIONAL STUDIES

Type of Work*	No. Subjects	Prevalence (%)	Reference
Snow crab processors	303	15.6	87
Spiramycin	51	7.8	88
Guar gum	151	3.0	89
Psyllium and senna products	125	3.2	90
Eastern white cedar	31	10.0	91
Isocyanates, painters	730	7.1†	92
Clam/shrimp	56	4.0/2.0	93
Poultry workers	134	11.0‡	94
Poultry workers	15	14.3	95
Snow crab processors	107	9.0	96
Rat allergens	113	4.4	97
Natural rubber latex	196	7.1	98
Domestic cleaning	593	25.0	99
Florists	128	14.1	100
Supermarket bakery workers	66	9.0	101

* Type of work is organized chronologically, according to the year of publication.
† All subjects were nonsmokers.
‡ In subjects with high exposure.

of asthma, it is not known whether it can progress to typical OA (60). In children, it has been proposed that eosinophilic bronchitis may be a precursor of asthma (61), whereas in adults, one study suggests that eosinophilic bronchitis is unlikely to progress to typical OA, because it has been shown that eosinophilic bronchitis and nonoccupational asthma have different clinical, physiological, and pathologic features (62). However, Park and coworkers (63), by performing a prospective follow-up study on patients with eosinophilic bronchitis, found that repeated episodes of eosinophilic bronchitis are associated with the development of chronic airflow obstruction, including asthma.

Whether the immunopathologies of eosinophilic bronchitis and asthma are similar is uncertain. One study suggests that eosinophilic airway inflammation and increased basement membrane thickening are regulated independently of airway hyperresponsiveness because airway hyperresponsiveness is absent in eosinophilic bronchitis (64). In another study, results obtained in both sputum samples and bronchial biopsies have shown that both sputum concentration and expression of interleukin (IL)-13 were higher in patients with mild asthma than in patients with eosinophilic bronchitis (65).

Causal Agents

Agents that cause OA with latency encompass more than 300 natural and synthetic chemicals (Tables 2 and 3). They are listed in textbooks (17, 66), review articles (67–70), and websites (e.g., www.asmanet.com, www.asthme.csst.qc.ca) (71, 72). These agents are categorized into high-molecular-weight and low-molecular-weight agents. High-molecular-weight agents are proteins of animal or vegetable origin acting through an IgE-mediated mechanism. Low-molecular-weight agents include organic and inorganic compounds that, with a few exceptions, are not associated with an IgE mechanism (Table 4). Common identified agents of OA with latency are diisocyanates, flour, allergens from laboratory animals and insects, enzymes, colophony fluxes, solders, wood dusts, natural rubber latex, acrylates, and glutaraldehyde. After sensitization, workers with OA may develop an asthmatic attack on low exposures to the sensitizer. The extent of airway responsiveness may diminish away from exposure but usually increases with reexposure to the sensitizer.

Chlorine, sulfur dioxide, combustion products, and ammonia are the most common agents that can induce irritant-induced asthma.

A few comments are necessary after consulting the long list of causal agents of OA. First, several case reports of OA due to unusual allergens have been published, but from a practical point of view, many of them are allergens one would never see in one's lifetime. Second, in addition to emerging low-molecular-weight sensitizers, such as acrylates, there are still new causes of OA due to high-molecular-weight agents. Third, some workers, for example, spray painters, health professionals, bakers, food processors, farmers, hairdressers, and plywood mill workers (73), are exposed to more than one sensitizer, raising the possibility that sensitization may occur through the interaction of different agents. Furthermore, some jobs, such as that of radiographer, expose workers to both sensitizers and irritants (74). Fourth, information about the causal agents of OA should be made available to workers in the occupations at risk. Such information has been prepared by Henriette Dhivert-Donnadieu and coworkers (71) in Montpellier, France, and is available at the site www.asmanet.com. Finally, OA can be caused by agents that are not found on existing lists and databases.

EPIDEMIOLOGY AND RISK FACTORS

Prevalence and Incidence of OA

Epidemiology is the study of the distribution, determinants, and outcome of a disease (75). In the 1980s, some studies of industrialized countries reported an increase in the incidence of OA (76, 77). Blanc and Toren (3) reviewed most of the epidemiologic studies on OA published from 1996 to 1999, and gave a median overall estimate of the attributable risk (i.e., the fraction of cases in a population that arise because of occupational exposures) of OA of 9% (range, 5–25%). More recently, after a review of the published literature regarding the magnitude of the attributable risk of asthma due to occupation, a median value of 15% (range, 4–58%) among all asthma cases was proposed as a reasonable estimate by Balmes and coworkers (4). In the general population, the occupations that contribute to asthma are in particular industries such as construction, metal work, rubber work, plastic work, printing, and industrial cleaning (78, 79).

Epidemiologic study designs include the cross-sectional study, the population-based study, the randomized control trial, the prospective cohort, the retrospective cohort, the case-referent study, and the case series. These designs vary regarding advantages, limitations, and information obtained. A community-based study with special reference to single and multiple exposures showed that application of job exposure matrices can be a useful tool with which to estimate asthma risk attributable to specific occupational exposures (i.e., exposures to high-molecular-weight agents) in the general population (80). The authors underlined the importance of interpreting specific exposure risks in connection with all concomitant exposures present in the work environment.

Most epidemiologic studies of OA have been cross-sectional. This type of study suffers from survivor bias (i.e., it underestimates the prevalence because of the workers with OA who left work), whereas prospective cohort studies, even if more expensive, are less affected by selection or survivor biases.

Both prospective and retrospective studies (81) have been successful in determining the exposure–response relationship. Some case-referent studies have been undertaken in workers exposed to causal agents of OA, such as acid anhydride (82), rat allergens (32), and flour (83). These studies are useful in identifying and quantifying risk factors. In addition, as reviewed by Newman Taylor (84), they show a clear exposure–response relationship, enabling the development of strategies to prevent sensitization and disease. Evidence of this relationship has also been obtained in a case-referent study on workers exposed to isocyanates (85). Available information indicates that the expo-

TABLE 3. ESTIMATED INCIDENCE OF WORK-RELATED ASTHMA AND ESTIMATES OF PROPORTION OF ASTHMA ATTRIBUTED TO OCCUPATION

Study Design*	Period	Subjects	Incidence	Risk (%)	Reference
Prospective cohort					
Health maintenance organization members		79,204	71/100,000 person-yr		25
Animal health	8–44 mo	395	96/1,075 person-yr		102
Pastry making		186	8/192 person-yr		
Dental hygiene		109	7/282 person-yr		
Apprentice welders	15 mo	194‡	6 (3%)¶¶		103
Surveillance, compensation, sentinel†					
British Columbia	1991	124§	9.2/100,000 person-yr		104
Sweden (SRROD)	1990–1992	1,010§	8.0		105
UK (SWORD)	1990–1992	1,954§	3.7		1
Quebec (PROPULSE)	1992–1993	287§	6.3		106
Michigan (SENSOR)	1988–1994	725§	2.9		107
Michigan (SENSOR)	1988–1995	933§	2.7		108
UK (OPRA)	1996–1999	43,764‖		38.3	109
Finland (FROD)	1990–1995	2,281§	17.5		110
New Zealand (NODS)	1996–1999	54§		39	111
UK (SWORD)	1999	4,393¶		26	112
Finland	1986–1998	49,575**	165 men, 247 women		113
California (SENSOR)	1993–1996	945§	2.5		114
South Africa (SORDSA)	1997–1999	324§	1.75		115
France (ONAP)	1996–1999	2,178§	2.4		116
Midlands (SHIELD)	1990–1997	1,097**	4.3		117
Australia (SABRE)	1997–2001	448††	3.09		118
Population-based					
Italy		1,635‡‡		26	119
Spain		2,646‡‡		5, bronchial reactivity; 6.7, bronchial reactivity + symptoms	120
ECRHS		15,637‡‡		5–10 among young adults	121
Norway		2,819§§		14.4 due to dust or fume exposure	122
ECRHS		15,039‡‡ + 2,528‖‖		10, wheeze at work; 4, work-related disability	123

Definition of abbreviations: ECRHS = European Community Respiratory Health Survey Study Group; FROD = Finnish Register of Occupational Diseases; NODS = Notifiable Occupational Disease System; ONAP = Observatoire National des Asthmes Professionnels; OPRA = Occupational Physicians' Reporting Activity Surveillance Scheme; PROPULSE = Physician-based Surveillance System of Occupational Respiratory Disease; SABRE = Surveillance of Australian Workplace Based Respiratory Events; SENSOR = Sentinel Event Notification System for Occupational Risks; SHIELD = Voluntary Surveillance Scheme for OA in the West Midlands (UK); SORDSA = Surveillance of Work-related and Occupational Respiratory Diseases; SRROD = Swedish Register of Reported Occupational Disease; SWORD = Surveillance of Work-related and Occupational Respiratory Disease.

* Studies are reported chronologically, according to the year of publication.

† The estimated incidence of occupational asthma obtained with surveillance, compensation, and sentinel studies is reported as number of cases per 100,000 person-years (with the exception of References 109, 111, and 112).

‡ Tested by methacholine challenge.

§ Cases of work-related asthma.

‖ Cases of work-related diseases.

¶ Cases of occupational respiratory diseases.

** Cases of asthma.

†† Patients with occupational respiratory diseases.

‡‡ Randomly selected.

§§ Community cohort.

‖‖ Respiratory symptom oversample.

¶¶ Over an average period of 15 months, the incidence of probable occupational asthma was about 3% (6 of 194 students entering an apprenticeship program in the welding profession).

sure–response relationships are more evident in those workers who develop immunologic sensitization and work-related symptoms soon after the onset of exposure (33, 86).

Table 2 reports an update of the estimated prevalence of work-related asthma obtained from 15 cross-sectional studies (87–101). The estimated incidence of work-related asthma and estimates of the attributable risk for work-related asthma are shown in Table 3 (1, 25, 102–123). It should be emphasized that, in epidemiologic studies, the definition of OA varies according to the study population, the study design, and the aim of the study (20). Estimates of incidence have been made using national registers, medicolegal statistics, registers based on voluntary or mandatory physician reporting, and self-reporting by employees (1, 33, 116, 124–127). In addition, estimates are reported in a variety of units, and some of the data cannot be converted into percentages, making the studies difficult to compare.

Information on the population-attributable risk of work-related asthma and work-related wheezing has been obtained from population-based studies (77, 78, 119–123, 128). Data from the Third National Health and Nutrition Survey, 1988–1994, in the United States indicated a prevalence of work-related asthma of 3.70% (95% confidence interval [95% CI], 2.88–4.52) and a prevalence of work-related wheezing of 11.46% (95% CI, 9.87–13.05). The population-attributable risk for work-related asthma was 36.5% and for work-related wheezing was 28.5%, suggesting that OA should be a priority on the public health agenda (128). In a population-based incident case-control study (1997–2000) of 521 cases and 932 control subjects in south Finland, Jaakkola and coworkers (129) showed that, in men, the strongest risk factors for asthma were metal work (odds ratio [OR], 4.52; 95% CI, 2.35–8.70) and forestry work (OR, 6.00; 95% CI, 0.96–37.5), whereas for women, asthma risk was highest for waitresses (OR,

TABLE 4. SOME OF THE MOST COMMON WORKPLACE SENSITIZERS TO WHICH WORKERS IN VARIOUS JOBS MAY BE EXPOSED

Sensitizer*	Occupation
Diisocyanates	Painters, automotive workers, manufacture of rigid or flexible polyurethane foam and glues, insulation installers
Dusts from woods, phenol formaldehyde resins, diisocyanates in glues	Woodworkers, carpenters, forest workers
Natural rubber latex in gloves, glutaraldehyde, formaldehyde, penicillin and other aerosolized or powdered medications, methyl methacrylate	Health care workers
Anhydrides	Users of plastics
Epoxy compounds in spray paints	Automotive workers
Animal, plant, insect, and fungal allergens	Farmers and gardeners
Enzymes or cleaning agents	Cleaners and laboratory workers
Food or animal protein allergens (e.g., egg proteins, wheat, fungal amylase)	Food processors and animal workers
Flour dust	Flour mills, bakeries
Persulfate	Hairdressers
Solder flux containing pine products	Electronic workers
Metal dusts, fumes (e.g., cobalt, chromium, nickel, platinum salts)	Welders, other metal workers, platinum-refining workers

* More than 300 sensitizers have been reported to induce occupational asthma. Lists are available in textbooks (17, 66), review articles (67–70), and websites (e.g., www.asmanet.com; www.asthme.csst.qc.ca) (71, 72).

3.03; 95% CI, 1.10–8.31), cleaners (OR, 1.42; 95% CI, 0.81–2.48), and dental workers (OR, 4.74; 95% CI, 0.48–46.5).

Large discrepancies in the prevalence of work-related asthma have been reported. One reason might be that many prevalence studies have relied on symptom and job history questionnaires. When objective testing was included in the studies (20), prevalence rates of about 5% for high-molecular-weight agents and greater than 5% for low-molecular-weight agents were found. Other confounders included the definition of OA adopted in the study, the type of agent, the work practice, and the fact that the studies were performed in different countries.

Surveillance systems enable us to estimate the incidence of work-related asthma, to describe the characteristics of affected workers, and to implement and facilitate public health interventions. These programs have been undertaken in many countries including Europe, the United States, South Africa, Australia, and New Zealand (Table 3). Incidence estimates obtained with surveillance programs are usually lower than those obtained from population studies. Gautrin and coworkers (75) gave an explanation for this observed difference. Population-based studies are likely to include all individuals ever exposed in at-risk workplaces, rather than those currently exposed, with the consequences of a higher incidence of OA and a reduction in survivor effects.

To develop a health surveillance strategy, investigators in the United Kingdom used data from 351 laboratory animal workers participating in an ongoing cohort study to develop diagnostic and prognostic models that detect and predict occupational allergic diseases (130). The study showed that, in these workers, both the risk of future sensitization and the severity of allergy can be predicted accurately with diagnostic and prognostic prediction models based on questionnaire items. An interesting observation of this study was that workers with an increased risk of future sensitization also showed severe allergic symptoms at follow-up over a 2- to 3-year period.

Medicolegal data may be useful in estimating the incidence of work-related asthma, provided that the diagnosis is certain, even though the medicolegal handling of accepted cases of OA is unsatisfactory in many countries, developed and nondeveloped. Tarlo and coworkers (27) reported that only 5% of all cases of adult asthma (310 individuals) referred to a tertiary care hospital, and who were still employed at the time of doctor's visit, had probable OA.

Studies of the prevalence of irritant-induced asthma have been rare and often have relied on historical data or have modified certain diagnostic criteria, such as expanding the definition to include the onset of symptoms from 24 hours to several days after exposure. Although irritant-induced asthma is not as widespread as immunologic OA (131), the low prevalence (52) could be due to poor recognition of this condition as OA. Estimates of 15 and 11% of all work-related asthma cases were reported as irritant-induced asthma in two sentinel projects, the Surveillance of Work-related and Occupational Respiratory Disease (SWORD) in the United Kingdom (124) and the Sentinel Event Notification System for Occupational Risks in four states in the United States (21). Similarly, estimates of 15% of all work-related asthma cases in Ontario, Canada, were reported as irritant-induced asthma (39). In Finland, cases of irritant-induced asthma doubled between 1981 and 1991 (132). Cases also appeared to increase in the United States. Data obtained from surveillance systems of work-related asthma undertaken in some states of United States were used to identify cases of irritant-induced asthma associated with exposure to cleaning products at work (133). Among new-onset work-related asthma, 22% were consistent with irritant-induced asthma, and the most likely exposure was in medical settings, schools, and hotels. An increased risk of asthma from exposure to cleaning agents was confirmed in a study of the general population in France, where ORs increased from 1.55 (95% CI, 1.08–2.23) for "ever asthma" to 2.17 (95% CI, 1.41–3.34) for asthma onset after age 14 years, to 2.35 (95% CI, 1.38–4.00) for asthma onset after beginning current job, and to 2.51 (95% CI, 1.33–4.75) for asthma with airflow limitation (79).

There is insufficient evidence of new-onset work-related asthma due to chronic low-level exposures to irritants (75). Similarly, estimates of irritant-induced work-related asthma in developing countries are unavailable. Studies are needed to determine the airway effects of intermittent high-level and chronic low-level exposures, because a population-based study has shown a high relative risk of asthma in jobs with expected low to moderate exposure to irritants (121). Suitable industries for studying the effects of low chronic exposure to irritants include metal refining (vanadium), fertilizers (ammonia), and mining (oxides of nitrogen). A review of the effects of low-level exposure to respiratory irritants has been published (134).

A descriptive study examined not only the risk of work-related new-onset asthma but also the risk of work-aggravated asthma, by using cases reported to the National Institute for Occupational Safety and Health from four state Sentinel Event Notification System for Occupational Risks surveillance pro-

grams for 1993–1995 (135). Two hundred and ten work-aggravated asthma cases and 891 new-onset asthma cases were reported. The risk of work-aggravated asthma was highest in the public administration, and the risk of new-onset asthma was highest in both manufacturing and public administration. The authors concluded that work-aggravated asthma cases reported many of the same adverse consequences as new-onset asthma cases.

Role of Exposure and Risk Factors

In 1995, Chan-Yeung and Malo (136) stated that exposure is the most important determinant in the development of OA. In a review of studies on OA with latency, it was observed that the higher was the degree of exposure to an occupational agent, the higher was the prevalence of asthma (137). This concept was proposed again by Frew (13), who stated that, in general, the higher the level of exposure, the more likely the sensitized person is to develop asthma. Once a subject is sensitized, the main factor that influences the onset of symptoms is the degree of exposure (138, 139). However, there is still a lack of information regarding the risk of sensitization at low concentrations and the existence of a "no-effect level" (140). For isocyanate-induced asthma, one study has suggested that peak exposures could be more relevant than the cumulative dose of exposure (141); another stated that continuous exposure rather than intermittent acute exposure to high concentrations of isocyanates increased the risk of developing symptoms of asthma (92). Moreover, an experimental animal model of isocyanate-induced asthma has shown that sensitization can occur through subchronic inhalation of vapor-phase diisocyanate levels as low as 20 ppb (142). Other authors have suggested that in the development of sensitization to low levels of occupational sensitizers, genetic susceptibility markers seem to be important determinants (143), whereas the effect of atopy is independent of exposure level (33, 144).

Studies have shown that the intensity of exposure is an important determinant of sensitization and asthma caused by respiratory sensitizers. A review of exposure–response relationships for occupational inhaled allergens (145) suggests that there are enough data for assessment of exposure–response relationships for several occupational agents (146). Becklake and coworkers (20) reported a dose–response relationship for cedar, colophony, and flour. Other studies have shown a dose–response relationship between the levels of exposure to occupational sensitizers such as flour, fungal α-amylase, laboratory animal proteins, detergent enzymes, platinum salts, and acid anhydrides and the development of IgE-mediated sensitization and/or work-related symptoms (81, 86, 147–153).

The finding of a concentration of an occupational agent below which sensitization is uncommon is relevant for prevention. An important concept to keep in mind is that the concentration of an allergen that sensitizes is quite different from one that provokes symptoms in workers already sensitized (154). Thus, the minimum concentration that induces sensitization is at least one order, and probably two orders, of magnitude greater than the minimum concentration that elicits symptoms. So the permissible exposure limit (155) for eliminating sensitization is easier for industry to achieve than the permissible exposure limit for eliminating asthmatic symptoms. Furthermore, it is much more cost-effective to reduce exposure to prevent sensitization, and reduction of exposure should be done as early as possible. An animal model of rats sensitized to trimellitic anhydride showed that trimellitic anhydride challenge of sensitized rats caused concentration-related allergic airway inflammation, changes in breathing pattern, and an increase in nonspecific airway responsiveness, and that the lowest no-observed-effect level based on the most sensitive end point investigated was 0.2 mg/m^3, a value that is well below the concentration that causes irritation (156). The authors of this study concluded that the assessment of safe human exposure levels is feasible.

Even though aeroallergen exposure is more complex than exposure to toxic materials, new immunologic methodologies and the use of personal sampling have made possible the measurement of high-molecular-weight allergens in the workplace. Detailed information on this topic has been published (154, 157). In addition, data obtained by quantified environmental challenge with allergens may provide objective data for recommended permissible exposure limits and support of environmental assessment guidelines. For example, data obtained by performing quantified environmental challenge with powdered natural rubber latex gloves suggest that a concentration of 0.6 ng/m^3 (natural rubber latex aeroallergen) as a time-weighted average threshold, which is critical for allergic symptom onset or clinical features of natural rubber latex sensitivity, may be too conservative (158).

A strategy similar to that adopted for high-molecular-weight agents should be considered for low-molecular-weight agents (159). An overview of assessment of exposure to low-molecular-weight agents by chemical assays has been published (160). Despite some progress, it is still not known whether peak or mean exposures to low-molecular-weight agents are more important in causing sensitization and OA.

What is known is that, even if the level of exposure is a critical factor for the development of OA (161), given the same level of exposure, only a small proportion of workers will develop sensitization and/or OA, suggesting that host susceptibility may be a factor. This view is supported by the observation that, among workers exposed to rat urinary allergens, the sensitization rate increased with increasing aeroallergen exposure, but there was a difference between atopic and nonatopic subjects. Atopic subjects had a clearly elevated sensitization risk at low exposure levels, but the risk increased little with increasing exposure. For nonatopic subjects, a steadily increasing risk was observed with increasing exposure (149).

Various risk factors for OA have been established. Atopy (skin reactivity to common inhalants) is a predisposing factor in workers exposed to high-molecular-weight agents, but it is a weak predictor of sensitization and development of OA (162). Atopy is not a risk factor for asthma induced by low-molecular-weight agents such as western red cedar (163) or diisocyanates (164). An important observation was made by Gautrin and coworkers (34), who found that skin reactivity to pets (relative risk, 4.11; 95% CI, 1.6–10.8) was a significant predictor of laboratory workers who develop OA after exposure to laboratory animals, whereas atopy was not (relative risk, 2.09; 95% CI, 0.8–5.6). The same investigators conducted a study of about 800 apprentices in the fields of animal health technology, pastry making, and dental hygiene, and found that 32% of the incident cases of sensitization and 27% of the incident cases of OA were among nonatopic subjects (34, 102). A study conducted on a large cohort of bakers in Belgium showed that atopy and sensitization to bakers' allergens were independent of each other (144).

Other factors besides atopy, such as rhinoconjunctivitis symptoms and having a measurable PC_{20} (provocative concentration of histamine producing a 20% decrease in FEV_1), could be important in the development of respiratory symptoms and in the development and/or worsening of asthma. Of these potential factors, having a measurable PC_{20} was the most significant (165).

An important question concerns whether sensitization to common aeroallergens precedes or follows sensitization to occupational allergens. For exposure to high-molecular-weight work-related allergens, subjects with new occupational sensitization are at greater risk of developing sensitization to common aeroallergens than are subjects without sensitization (166). In addition,

new sensitization to common aeroallergens often occurs at about the same time as sensitization to work-related agents (166). However, after removal or diminution of exposure to both low- and high-molecular-weight agents causing OA, subjects are not at increased risk for developing IgE-mediated sensitization to common allergens, indicating that atopic status does not increase even years after the diagnosis of OA (167).

Cigarette smoking has been reported to be associated with the development of OA in workers exposed to platinum salts and anhydride compounds, which are chemicals that cause asthma through an IgE mechanism (168, 169). In workers exposed to platinum salts, cigarette smoking interacts with exposure to both high and low levels in inducing sensitization (170). Cigarette smoking also seems to affect the underlying mechanisms involved in OA, as the cellular composition of airway mucosa appears different in smokers with asthma and nonsmokers with potroom asthma (171). In addition, cigarette smoking increases the risk of sensitization to high-molecular-weight agents that cause OA through an IgE mechanism. In contrast, as reviewed by Mapp and Newman Taylor (172), cigarette smoking does not increase the risk of asthma caused by low-molecular-weight agents, such as diisocyanates and red cedar, for which a specific IgE is not usually considered the main mechanism of the development of the disease. Moreover, at the time of diagnosis of immunologic OA, the majority of cases are mild, but cigarette smoking is associated with a greater severity of disease (173).

Sex plays a role in the distribution of occupational lung diseases, because there are sex differences in specific jobs and therefore differences in exposure to agents causing these diseases (174). Women report significantly more exposure to cleaning products, biological agents, and textile fibers than men. In addition, one study reported that the risk of OA in the service sector was higher for women (175). A case-control study performed in Göteborg by Toren and coworkers (176) showed that among women, the risk of adult asthma was increased after exposure to paper dust and textile dust, whereas among men, the risk of adult asthma was increased after exposure to flour dust, welding fumes, man-made mineral fibers, and solvents. Because a strong association has been found between welding metal fume fever and welding-related respiratory symptoms suggestive of OA, it has been proposed that welding metal fume fever be viewed as a premarker of welding-induced OA (177).

Genetics

Genetic markers of occupational asthma have begun to be explored (178–182). As Apter (183) stated, genetic predisposition might be both a confounder and an effect modifier. Understanding of the interaction between genes and the environment is facilitated by the ability to precisely characterize the phenotype of an individual with OA. Also facilitated is the ability to assess and estimate exposure to the causal occupational agent, which in turn makes it possible to compare sensitized and nonsensitized individuals working in the same workplace with similar exposure.

Of interest is the pool of major histocompatibility complex genes on chromosome 6p, which encode the HLA class II molecules required for presentation of an antigen to a T-cell receptor to initiate the cascade of events that lead to an antibody response. Data obtained in occupational studies indicate that major histocompatibility complex class II proteins are important factors for the specificity of the response to occupational agents such as acid anhydrides, diisocyanates, western red cedar, complex platinum salts, natural rubber latex, and animal proteins (184–189). The largest study of the association of HLA molecules, which assessed specific symptoms and sensitization to rat lipocalin allergens, showed that about 40% of OA in the population examined could be attributed to an HLA-DRβ1*07 phenotype; the attributable proportions for atopy and daily work in an animal housing facility were 58 and 74%, respectively (189). The HLA associations identified in that study might be found for other major animal allergens, in light of the similarities between lipocalin animal allergens. The HLA phenotype is also a significant determinant of sensitization to complex platinum salts, because the strength of the HLA association varied with the intensity of exposure to the sensitizing agent (190). Evidence of HLA associations has not been confirmed for diisocyanates by some investigations (191, 192), but in these studies, accurate phenotypes of the subjects were not provided. Even though HLA class II molecules are involved in immune recognition of occupational agents, HLA associations are not strong enough to be used for prevention. A significant association could be due to a causal relationship, but it could also occur by chance (multiple comparisons without a prior hypothesis) or by linkage disequilibrium. Despite these limitations, especially for asthma induced by low-molecular-weight agents, for which the absence of a specific IgE might challenge the immunologic mechanism, HLA associations indicate that HLA class II molecules contribute to individual susceptibility to low-molecular-weight agents, and provide evidence of a specific immunologic response in asthma induced by these agents. For other occupational agents, such as natural rubber latex, HLA associations confirm the importance of T cells in the regulation of IgE responses (193).

A second pool of genes that could be involved in OA is the superfamily of glutathione *S*-transferase (GST), a family that is critical for protecting cells from oxidative stress products, including lipid peroxides. Evidence of the involvement of GST is that among subjects who were exposed to toluene diisocyanate (TDI) for 10 years or more, the frequency of the *GSTP1 Val/Val* genotype was lower in those who had asthma and in those with moderate to severe airway hyperresponsiveness to methacholine (194). Conversely, because the protective effect of homozygosity for the *GSTP1* Val* allele increases in proportion to the duration of exposure to TDI, one might argue that the role of GST and its allelic variants could lie in determining which subjects will have persistent asthma (180). Moreover, individuals lacking this genotype may, over time, exhibit ongoing TDI-induced proinflammatory processes and consequent airway remodeling, leading to irreversible asthma symptoms. However, a study of GST genotypes in workers exposed to various diisocyanates showed no significant association between the *GSTP1* genotype and the risk of asthma (195). A possible explanation for the differences between these two studies is that a protective effect might be observed only in subjects exposed to diisocyanates for at least 10 years.

More recently, the same investigators showed that, in addition to GST, *N*-acetyltransferase genotypes may play a role in diisocyanate-induced asthma, especially TDI-induced asthma, in which the *N*-acetyltransferase slow acetylator genotypes posed a 7.77-fold risk of asthma (196). In this common type of OA, by contrast, HLA class I antigens and the tumor necrosis factor α A-308G are not associated with susceptibility or resistance to the development of TDI-induced asthma (197). Similarly, in potroom asthma, no associations have been found between this type of OA and genotyping for the β_2-adrenoreceptor, high-affinity IgE receptor, and tumor necrosis factor, confirming that the mechanisms involved in potroom asthma remain poorly understood (198).

Because genes affect virtually all human characteristics and diseases, what lesson can be learned by identifying a genetic predisposition to OA? It seems clear that the patient needs to receive information about the health risks. However, because asthma is considered a disease caused by complex interactions over time between genes and environment (7, 199), efforts should be made to use the genetic information appropriately.

Moreover, any reported association between a genetic marker and risk for disease cannot be considered definitive until the findings of the study have been replicated (200, 201). A complete review of the ethical, legal, and social implications of genomic medicine has been published (202). Wisely, the author writes that the "DNA sequence is not the Book of Life."

PATHOPHYSIOLOGY

Immunologic OA: IgE Dependent and IgE Independent

The pathophysiology of immunologic OA usually involves an IgE-dependent mechanism. OA induced by IgE-dependent agents is similar to allergic asthma that is unrelated to work (203–210). Most high-molecular-weight agents (e.g., flour and animal proteins) induce asthma by producing specific IgE antibodies. Certain low-molecular-weight agents (e.g., platinum salts, trimellitic anhydride, and other acid anhydrides) also induce specific IgE antibodies, probably acting as haptens and combining with a body protein to form functional antigens (211, 212). Cross-linking of allergens with a specific IgE antibody on the surface of mast cells, basophils, and possibly macrophages, dendritic cells, eosinophils, and platelets, gives rise to a cascade of events that result in the influx and activation of inflammatory cells and in the release of preformed and newly formed inflammatory mediators that orchestrate the inflammatory process.

Other low-molecular-weight agents, such as diisocyanates and plicatic acid, cause OA that has the clinical and pathologic features of immunologic asthma, but do not consistently induce specific IgE antibodies (206, 213–215). It has been suggested that, when specific antibodies to plicatic acid are present, they may be markers of exposure and not causes of disease (216). However, even though an IgE antibody to diisocyanates, which has strong positive response levels (an RAST score of 3 or greater) is present and exhibits high specificity (217), it has no sensitivity in detecting OA. The sensitivity increases when a blood sample is taken less than 30 days from the last exposure, which is consistent with the observed approximate 6 months of half-life of IgE.

Specific inhalation challenge with these low-molecular-weight agents in sensitized subjects induces various patterns of asthmatic reactions, including isolated early or late asthmatic reactions, a biphasic reaction, a progressive reaction, or atypical reactions (218). Atypical reactions have been reported principally after exposure to isocyanates. These reactions are uncommon after exposure to high-molecular-weight agents (219, 220).

The airway inflammation process is similar in IgE-dependent and IgE-independent asthma (221–223) and is characterized by the presence of eosinophils, lymphocytes, mast cells, and thickening of the reticular basement membrane (Figure 1) (222, 224). In the bronchial airways, inflammatory cells are not only increased in number but are also activated (224), resulting in the secretion of a wide range of proinflammatory mediators and proteins; these mediators and proteins have a variety of harmful effects, such as toxic damage to epithelial cells. In the airway inflammatory process of OA, eosinophilia is associated with an increased number of T cells, especially $CD4^+$ cells, which exhibit signs of activation (224). Increased expression of lymphocyte markers, such as IL-2 receptor and very late activation antigen-1, has also been found (225). Along with the increased expression of lymphocyte activation markers, in asthma induced by low-molecular-weight agents (e.g., diisocyanates) an increased number of cells producing proinflammatory cytokines has been reported (225, 226). These proinflammatory cytokines, produced primarily by mononuclear phagocytes, may contribute to airway inflammation by several mechanisms, including increased expression of adhesion molecules, chemotaxis, and stimulation of inflammatory leukocytes. Together with these findings, antigen stimulation of monocyte chemoattractant protein 1 and tumor necrosis factor α has been shown in isocyanate-induced asthma, suggesting that isocyanate-specific cellular immune reactions result in activation of macrophages, which may be important in the pathogenesis of this type of OA (227).

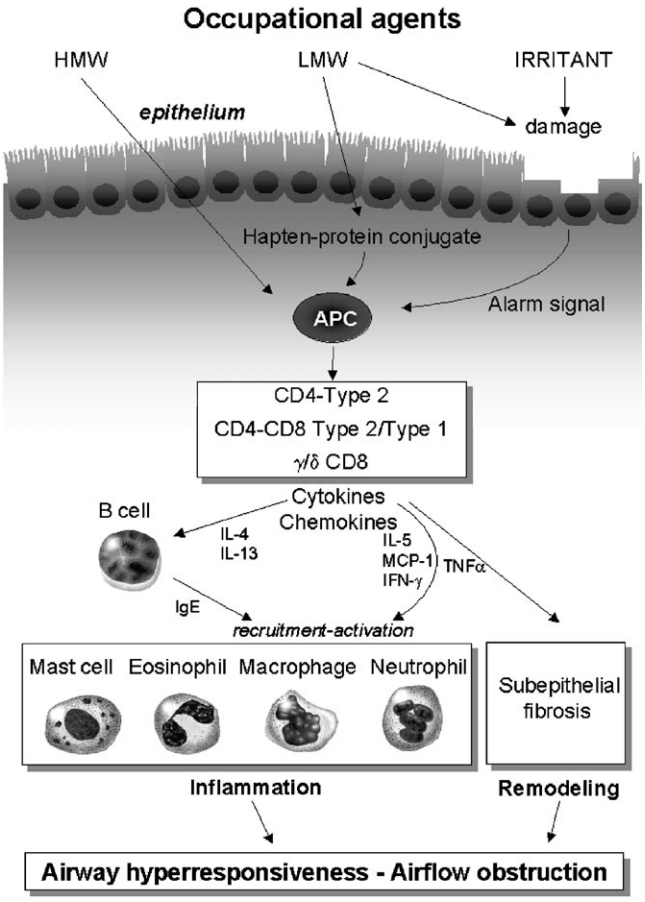

Figure 1. Schematic summary of possible mechanisms in occupational asthma (OA). Causal agents of OA are categorized into high-molecular-weight (HMW) and low-molecular-weight (LMW) agents. Exposure to high levels of respiratory irritants can induce irritant-induced asthma. HMW agents are recognized by antigen-presenting cells (APCs) and mount a CD4 type 2 immunologic response leading to production of specific IgE antibodies by interleukin (IL)-4/IL-13–stimulated B cells. Certain LMW agents also induce specific IgE antibodies, probably acting as haptens and combining with a body protein to form functional antigens. However, most LMW agents do not consistently induce specific IgE antibodies. In this type of OA, a mixed CD4/CD8 type 2/type 1 immunologic response or induction of γ/δ-specific CD8 may play a role. Inhalation of high levels of irritants may damage airway epithelium. In subjects who develop irritant-induced asthma, alarm signals from damaged epithelial cells might in turn activate immunocompetent cells. Binding of IgE to their receptors, Th2 (IL-5) and Th1 (IFN-γ) cytokines, and other proinflammatory chemokines (monocyte chemoattractant protein 1 [MCP-1]; tumor necrosis factor α [TNF-α]) induce recruitment and activation of inflammatory cells. These cells (mast cells, eosinophils, macrophages, and, in some instances, neutrophils) characterize airway inflammation, which contributes to the functional alterations of OA, that is, airway hyperresponsiveness and airflow obstruction. Subepithelial fibrosis due to thickening of the reticular basement membrane is considered a histopathologic feature of OA. However, the role of this remodeling of the airways in lung function is obscure.

It has been suggested that $CD8^+$ cells are key cells in OA with an IgE-independent mechanism (e.g., diisocyanate-induced asthma), because one study found that the majority of T cells obtained from bronchial biopsy specimens of subjects with diisocyanate-induced asthma showed the CD8 phenotype and produced IFN-γ and IL-5, with few clones producing IL-4 (228). Ott and coworkers (229) reported that a mediator important for the recruitment of effector $CD8^+$ T cells to sites of inflammation could be leukotriene B_4, produced by activated peripheral leukocytes. This observation is particularly important, because we have shown that leukotriene B_4 is involved in late asthmatic reactions induced by toluene diisocyanate (230). However, in a mouse model, it has been shown that the lung inflammatory response to inhaled hexamethylene diisocyanate (HDI) depends primarily on the effective generation of a $CD4^+$ helper T-cell type 2 response (231), as in the case of atopic asthma. $CD4^+$ and not $CD8^+$ T cells mediate the airway eosinophilic response in HDI-sensitized mice. The authors suggested that the type of response induced after exposure to diisocyanates might be genetically influenced and that the generation of an HDI-specific $CD4^+$ T-cell response must occur for the development of airway disease. Much research in humans and with different diisocyanates remains to be performed before this interesting hypothesis can be proved or disproved. Among the several animal models of OA, a mouse model developed using TDI showed a role for matrix metalloproteinase (MMP) activity in the inflammatory cells and lumen (232). Most of the inflammatory changes were inhibited by administration of an MMP inhibitor, suggesting a possible role for MMP inhibitors in treating OA.

Irritant-induced Asthma

The mechanism of asthma induced by irritants is unknown (233). Many reports indicate that unintentional high-level respiratory irritant exposures can induce the new onset of asthma (39). Because this type of OA occurs after inhalation of high levels of irritants, the main target for the initial injury could be the bronchial epithelium, which becomes denuded and loses its protective properties. Consequences of the damage in the bronchial epithelium are the loss of relaxing factors derived from epithelium, the exposure of nerve endings leading to neurogenic inflammation, and the release of inflammatory mediators and cytokines after the nonspecific activation of mast cells (234). A further consequence of the disruption of the epithelium accompanied by the secretion of growth factors for epithelial cells, smooth muscle, and fibroblasts, together with matrix degradation, is a tissue-regenerative and remodeling response (234). Pathologic changes consist of marked fibrosis of the bronchial wall and denudation of the mucosa with fibrinohemorrhagic exudates in the submucosa (235). In an animal model, chlorine exposure causes functional and pathologic changes in the airways resulting from oxidative stress (236).

Controversial Issues

Specific antibodies and OA. Controversial issues exist regarding the pathophysiology of OA. One of these controversies is the role of specific antibodies in asthma induced by low-molecular-weight agents, such as diisocyanates and western red cedar. In clinical practice, a test for the diagnosis of this type of asthma would be appreciated. Many laboratories have investigated the usefulness of specific antibodies, for example, in diisocyanate-induced asthma, with conflicting results. Specific IgE antibodies to TDI in a range of 0 to 50% of workers have been reported (237–240). If these antibodies have an RAST score below 3, they are not highly specific (217). However, if these antibodies have an RAST score of 3 or greater, they exhibit high specificity and therefore are diagnostic of isocyanate-induced asthma. An explanation for the variable results in prevalence studies of serum-specific IgE antibody to TDI–human serum albumin conjugate in TDI-induced asthma has been proposed by Park and coworkers (241–243). These investigators found that the specific IgE binding to a new antigenic determinant of TDI–human serum albumin conjugate can be heterogeneous and can differ between one individual and another.

It is still not clear whether IgE-mediated responses contribute to the development of asthmatic symptoms in workers exposed to TDI. In fact, specific IgE responses to isocyanates are detected in a minority of isocyanate-induced asthma. The half-life of specific IgE differs in published studies on diisocyanate-induced asthma, ranging from a few months to several years (239, 240, 244). Moreover, it has been reported that the presence of high levels of serum-specific IgE at initial diagnosis may indicate a better prognosis (244, 245). Because the more convincing evidence for a role for specific IgE comes from studies conducted on subjects living in Korea, a country where TDI is the most common cause of asthma, it would be reasonable to investigate the possible differences that exist between this population and other populations regarding antibody-mediated immunity in this type of asthma. To complicate the picture, the results of specific IgE responses to other diisocyanates, such as methylene diisocyanate and HDI, may be different from the responses to TDI (246).

If the role of specific IgE responses in asthma induced by low-molecular-weight agents looks uncertain, the role of specific IgG responses to occupational agents seems even more complex. Serum-specific IgG may persist for many years after the last exposure to TDI (244). Because the sensitivity of specific IgG in the diagnosis of TDI-induced asthma based on the results of specific inhalation challenge is higher than that of specific IgE, but the specificity is poor, it has been suggested that IgG could be used to monitor the effect of exposure to diisocyanates before clinical disease appears (247). For other occupational agents, conflicting results have been reported, showing that the prevalence of specific IgG is significantly higher in symptomatic workers, with no correlation with the level and duration of exposure (248), or that the presence of specific IgG may be a response to high levels of exposure but is unrelated to the development of respiratory symptoms (249, 250).

Neutrophils and OA. Another controversial issue is the role of neutrophils in OA. In the model of TDI-induced asthma, which has been widely investigated because diisocyanates are an important cause of OA in many countries, the role of neutrophils is unclear. Neutrophilia was found in the bronchoalveolar lavage fluid of subjects with TDI-induced asthma, especially in those exhibiting a late asthmatic response after specific inhalation challenge (251); however, the levels of TDI used in the challenge were higher than those used in the studies that followed. In nonoccupational asthma, the presence of neutrophils is considered a marker of the severity of the disease (252). What is unclear in OA is whether neutrophilia can also be considered a marker of severe disease due, perhaps, to higher levels of exposure, or whether, for unknown reasons, the same level of exposure may produce an inflammatory airway infiltrate in which eosinophils or neutrophils are the predominant cells (253, 254). Park and coworkers, by examining bronchial biopsies, serum, and induced sputum, found that, in TDI-induced asthma, neutrophils play a role (255, 256). They proposed a role for IL-8 released after exposure to TDI in the activation of neutrophils. Mast cells or basophils could be the origin of the neutrophil chemotactic activity found after TDI challenge (257).

Similarly, in grain dust–induced asthmalike disorder, the number of neutrophils in the bronchial mucosa is higher than that in allergic asthma, and the levels of IL-8 in induced sputum are significantly higher after inhalation challenge with grain dust

extract than at baseline (258). The actual cause for these higher levels is currently unknown. Some of the clinical, functional, and pathologic features of grain dust asthmalike disorder may be reproduced by endotoxin inhalation.

Endotoxin levels tend to be highest in environments where there are farm animals, because the fecal flora of larger mammals is a major source of endotoxin. Chronic exposure to significant levels of endotoxin is associated with the development and/or progression of many diseases, including asthma and chronic bronchitis (259, 260). Because work-related asthma symptoms in workers exposed to laboratory animals occur even in those not sensitized to occupational antigens, other factors in the workplace may explain these symptoms, including endotoxin. The few investigations on the role of endotoxins in respiratory symptoms observed in technicians handling small animals gave controversial results (97, 261, 262).

Potroom asthma. Potroom asthma has been recognized for many years in workers employed in the production of aluminum smelting, where the alumina is partially dissolved in an electrolyte of molten cryolite at about 960°C (263–265). Only one study has documented a dual asthmatic reaction with an associated increase in nonspecific airway responsiveness after exposure to the potroom workplace (266). Bronchial biopsies obtained in workers with potroom asthma have shown that pathologic alterations are similar to those described in other types of asthma (171). Often, this occupational environment has not been included among causal agents of OA because different mechanisms could be involved including an immunologically mediated reaction against trace amounts of metals, or an irritant effect resulting from exposure to hydrogen fluoride and sulfur dioxide. A dose–response relationship has been described for fluoride exposure and airway hyperresponsiveness in potroom workers (267), but whether fluorides are the causative agents, coagents, or simply markers for the causative agent(s) of potroom asthma remains to be determined.

NATURAL HISTORY AND LONG-TERM CONSEQUENCES

Chan-Yeung and Malo (6, 268) have provided a "schema" of the natural history of OA with a latency period. For each stage (the onset of exposure; the development of sensitization and asthmatic symptoms; the occurrence, in some cases, of rhinoconjunctivitis symptoms; the onset of airway inflammation; the development of OA; the cessation of exposure; and the cure or persistence of asthma), one might investigate the role of modulating factors, including host markers, characteristics of both the occupational agent and exposure, and the effect of therapy.

To summarize the natural history of OA and the role of specific agents, the risk of OA is highest soon after the first exposure, because most subjects develop asthma within 1 to 2 years of exposure. Nevertheless, the latency period can vary from months to years (6). The rate of acquiring both sensitization and asthmatic symptoms may differ according to the nature of the agent (268), and the intensity of exposure. For example, workers exposed to proteins of laboratory animals usually develop sensitization during the first 2 years after the first exposure, but bakers exposed to flour do not, suggesting that animal allergens are more potent sensitizers than flour (102). In workers exposed to laboratory animals, rhinoconjunctivitis symptoms usually occur in years 1 and 2 after the first exposure, but the incidence of respiratory symptoms is greater in years 2 and 3 (269). However, Rodier and coworkers (270) reported on a high incidence of occupational rhinitis among new recruits to animal laboratories. Rhinoconjunctivitis symptoms often precede the onset of asthma symptoms in workers exposed to high-molecular-weight agents but less frequently in those exposed to low-molecular-weight agents (271). It should be underlined that patients with occupationally induced rhinitis have a high risk of asthma. In fact, in a study of 3,637 patients with work-induced rhinitis, the risk of asthma was highest in the first year after notification of occupational rhinitis, and a roughly threefold risk persisted for several years thereafter (272).

OA is a potentially fatal condition: death from asthma has been reported for a subject exposed to diisocyanates, for a baker, and for a subject exposed to shark cartilage dust (273–275).

Most subjects who develop OA after a latency period do not recover, even several years after cessation of exposure. Symptoms and nonspecific airway hyperresponsiveness persist in about 70% of affected workers. The percentages of those with persistent nonspecific airway hyperresponsiveness after removal from exposure are lower for electronic (276) and aluminum potroom workers (277). Moreover, removal from exposure is associated with worse socioeconomic outcome (278).

Important determinants of recovery are the total duration of exposure, the duration of symptoms, the severity of asthma, the lung function, the degree of airway hyperresponsiveness at the time of diagnosis, and the duration of follow-up. Workers who, after diagnosis of OA, continue to be exposed to the same causal agent worsen with time. The most effective treatment of immunologic OA is complete avoidance of exposure, which is associated with improvement in asthma symptoms (wheezing, shortness of breath, cough) and functional variables (airway hyperresponsiveness). However, Vandenplas and coworkers (279) showed that workers allergic to natural rubber latex were able to function when exposure was reduced, improving in symptoms and keeping their jobs.

Once a worker is sensitized to an occupational agent, bronchial reactivity usually persists. Most workers with OA retain specific bronchial reactivity to the occupational causal agent even two or more years after removal from exposure (280). Some individuals show an asthmatic reaction to occupational agents despite the normalization of nonspecific airway responsiveness. This finding has practical implications, because some subjects who are considered cured and return to their previous jobs are at risk for an asthmatic reaction when reexposed to the causal agent. Following up this observation, Lemière and coworkers (281, 282) showed that, despite treatment, the absence of asthmatic symptoms, and normal nonspecific airway responsiveness, subjects with OA induced by exposure to high-molecular-weight agents (e.g., flour, psyllium, and guar gum) and with high levels of specific IgE reacted to the causal agent within a few minutes of exposure. Thus, persistent immunologic sensitization appears to be a key factor in the persistence of specific bronchial reactivity to occupational agents. This finding emphasizes the importance for subjects with OA caused by high-molecular-weight agents to avoid exposure, even if they are asymptomatic and have normal airway responsiveness. Similarly, in workers exposed to isocyanates, despite removal from exposure to the offending agent, persistence of specific bronchial reactivity to these low-molecular-weight agents has been reported (283, 284). Is persistent immunologic sensitization the unique factor in causing persistence of sensitization to occupational agents? Does this factor also cause the persistence of asthmatic symptoms in subjects with OA? And how must we consider subjects who have airway hyperresponsiveness but are asymptomatic: as "sensitized" or as "asthmatics"? One might argue that these asymptomatic subjects are, of course, still sensitized but that they also have "latent disease," because it is likely that if they return to work and are exposed to the same causal agent, their asthma will again become clinically detectable.

Consistent with persistent symptoms and nonspecific airway hyperresponsiveness in about 70% of workers with immunologic

OA, studies of the outcome of OA indicate that resolution is a slow process that continues for years (285). In general, cessation of exposure is associated with an improvement in symptoms, and when glucocorticoids are used the asthma is further improved but not cured (286). Only a few longitudinal studies of airway pathology in subjects with OA after cessation of exposure have been conducted (287–291). In a follow-up study of diisocyanate-induced asthma, although subepithelial collagen deposition decreased, airway eosinophilia persisted (289). It is still not known whether the persistence of OA is related to genetic susceptibility or to persistence of an inflammatory process in the airways. These two possibilities are not mutually exclusive, because genetic susceptibility may affect the capability of an individual to deal with airway inflammation (194).

Airway inflammation is considered to be the cause of asthma, whereas the role of airway remodeling in the pathogenesis and severity of the disease remains controversial (292). Some investigators think that thickening of the airway wall causes airway hyperresponsiveness whereas others think it protects against airway narrowing and attenuates airway reactivity in individuals with asthma (293). However, airway remodeling provides an explanation for many conditions observed in subjects with asthma, such as corticosteroid-resistant airway hyperresponsiveness (294) and the accelerated decline in lung function that occurs over time in adult asthma (295). The traditional view that airway remodeling is caused by longstanding inflammation needs to be changed. Studies of children with asthma showed that the remodeling begins early in the development of asthma and might occur in parallel with inflammation or even be required for the establishment of persistent inflammation (296). Thus, in adult-onset asthma, where both airway inflammation and airway remodeling are present, one might argue with the traditional view that airway inflammation occurs first and remodeling later.

What can we learn about the role of airway remodeling from studying the pathology of OA? A longitudinal study of airway pathology performed in subjects with OA caused by TDI showed that the histopathologic characteristics of asthma and the classic indicators of remodeling, such as a thickened reticular layer of the basement membrane, were present at diagnosis (289) and therefore may be considered part of the inflammatory response to the offending agent (297). However, because a thickened reticular layer of the basement membrane, even if reduced, was present 6 to 21 months after the cessation of exposure, it may also be considered a marker of long-lasting structural changes of the airway wall (298).

At the present time, it is difficult to establish the relative contributions of airway inflammation and remodeling to the chronicity of OA; probably, both are associated with the persistence of asthmatic symptoms and of nonspecific airway hyperresponsiveness. Epithelial cells, smooth muscle cells, bronchial vessels, eosinophils, myofibroblasts, macrophages, and sensory neuropeptides (299–301) may contribute to both processes, and the secretion of cytokines, chemokines (302–304), growth factors, and matrix metalloproteinases (305) may help to establish a particular tissue microenvironment that sustains the chronicity of the disease.

Diagnosis

Diagnosis of OA should be confirmed by objective testing for asthma and then by establishing the relation between asthma and work (306, 307). Physicians should consider the possibility of OA in all adults with asthma; therefore, an occupational history should be the first step in the initial evaluation of the patient. The diagnosis should be confirmed as soon as possible to prevent worsening of symptoms and should be investigated when workers are at the workplace, because a prolonged avoidance of exposure may influence the reliability of diagnostic procedures (308). More accurate criteria are required for medical purposes than for case identification in field surveys.

The diagnosis of asthma is based on a compatible history and the presence of variable airflow limitation or, if lung volumes are normal, of nonspecific airway hyperresponsiveness, which is generally assessed by means of a histamine or methacholine challenge test. The two protocols, recommended by the American Thoracic Society (309), should be expected to give different results. If greater sensitivity of the test is sought, deep breaths should be avoided (i.e., by using specific airway conductance), whereas if greater specificity is sought, a measurement requiring deep breaths (e.g., FEV_1) is recommended (310). Because measurements of nonspecific airway responsiveness are log-normally distributed in the population (311), an arbitrary cutoff (e.g., a PC_{20} FEV_1 of 8–16 mg/ml) has been selected in defining an abnormal test. Cut points are highly sensitive, but have low specificity. The test may be positive in cases of allergic rhinitis, cystic fibrosis, bronchiectasis, chronic obstructive pulmonary disease, sarcoidosis, and congestive heart failure (312). The strength of the methacholine inhalation challenge is its negative predictive value, because a negative response is unlikely to occur in subjects with asthma (313). However, in the occupational setting, normal methacholine test results have been reported in subjects with asthma induced by diisocyanates (314). These normal results could have been due to the avoidance of exposure for several days or more. In this common type of asthma, and, in general, in each type of sensitizer-induced OA, in the absence of changes in FEV_1 in response to specific inhalation challenge, nonspecific airway responsiveness should be assessed before and after the specific inhalation challenge (314–316).

The other diagnostic information, occupational history, should be accurate (317). The physician should ask the patient about the frequency and intensity of exposures and the frequency of exposures to peak concentrations of the potential causal agent, although many patients are not aware of the agents to which they are exposed at work. The physician should be aware of the potential exposures experienced in different occupations (Table 5). Additional information can be obtained from a visit to the workplace by experts in occupational hygiene, from material safety data sheets for workplace chemicals, and from the manufacturers of the workplace substances. Lists and databases of the etiologic agents are available (71). The physician should also be aware of the following: that the presentation of OA is variable, some subjects developing asthma symptoms immediately on exposure and others developing symptoms after several hours; that the absence of airway hyperresponsiveness does not rule out sensitization to an occupational sensitizer; and that not all symptomatic workers have "true" OA attributable to a specific agent (318).

There is considerable published literature on the diagnosis of OA (207, 306, 307, 319–325). Each investigative tool can have false-positive and false-negative outcomes. Therefore, comprehensive investigation requires the interpretation of a specialist, as suggested by the following details of patients' symptoms and clinical findings.

A history of improvement of symptoms during weekends and holidays and a worsening on return to work suggests OA. Rhinoconjunctivitis usually precedes the onset of asthma symptoms in the case of high-molecular-weight agents (271). However, in a study of laboratory animal workers, the positive predictive value of rhinoconjunctivitis for the development of OA was 11.4% (269). More studies are necessary to confirm this figure. Moreover, rhinitis is associated with an increased risk of asthma regardless of atopic status (326). Because occupational rhinoconjunctivitis can lead to OA (327–329), efforts should be made to increase the awareness of this poorly diagnosed condition

TABLE 5. MANAGEMENT OF WORK-RELATED ASTHMA

Characteristic	Sensitizer-induced OA	Irritant-induced OA	Aggravation of Preexisting or Coincident Asthma
Symptoms	Treat asthma*	Treat asthma*	Optimize treatment of asthma*
Exposure	Prevent further exposure to the causal agent	Prevent exposure to high levels of irritants, consider personal protection or change in work area	Reduce exposure to workplace irritants, consider personal protection or change in work area; reduce exposure to tobacco smoke and relevant environmental allergens
Stay in the same job	No†	Feasible with close medical follow-up‡	Feasible with close medical follow-up
Compensation	Initiate compensation claim; notify authorities of sentinel cases of OA to implement workplace hygiene measures and medical surveillance	Initiate compensation claim	Largely unsettled
Other measures	Prohibition of cigarette smoking in the workplace	Prohibition of cigarette smoking in the workplace	Prohibition of cigarette smoking in the workplace

Definition of abbreviation: OA = occupational asthma.

Adapted from Reference 52 by permission of the publisher, © 2003 CMA Media Inc.

* As in the asthma guidelines published in the Global Initiative for Asthma (397).

† For exposure to latex, reduction of exposure is associated with clinical improvement and fewer socioeconomic consequences than cessation of exposure (279).

‡ Especially after exposure to an irritant that is also a sensitizer.

(330–334). Preexisting airway inflammation or a preinflammatory condition marked by airway hyperresponsiveness to adenosine 5′-monophosphate is a predictor of new-onset nasal symptoms (335).

Some studies have evaluated the reliability of questionnaires in the diagnosis of OA (308, 336, 337). According to these studies, clinical history provides high sensitivity (87, 92, and 87%, respectively) but low specificity (22, 32, and 14%, respectively). For the recognition of bronchoconstriction, responses to respiratory questionnaires are less reliable than measurements of airway responsiveness to methacholine (338).

The strengths and limitations of specific tests again suggest the expertise needed to diagnose and treat patients with OA. One test, the monitoring of PEFR, is particularly useful in the investigation of OA (339). The patient is asked to record PEFR four times per day, and to record symptoms and medications during periods of work and periods off work (339). The sensitivity and specificity of serial PEFRs were found to be 73 and 100%, respectively, higher than for other objective tests (340), although there are no uniformly accepted criteria for the interpretation of PEFR recordings (341). It has been shown that serial PEFRs should be recorded for 4 weeks, because records spanning 4 weeks exhibit high sensitivity and specificity (342). Sensitivity and specificity were 81.8 and 93.8% for records spanning 4 weeks; they fell to 70 and 82.4% for those 2 weeks in duration. Accurate PEFR monitoring depends on patient compliance and honesty. If differences are found in PEFR readings between periods of exposure and periods off work, these readings could also reflect aggravation of preexisting asthma rather than true OA. Interpretation of the readings could be improved by the monitoring of nonspecific airway responsiveness at the end of a period of work and at the end of a period of holiday, even if the combination of the two tests is no more sensitive or specific than PEFR monitoring alone (343). Although airway hyperresponsiveness may persist for months or years, a threefold or greater decline in responsiveness to methacholine (i.e., an increase in PC_{20} or PD_{20}) after a period away from work indicates OA rather than an aggravation of preexisting asthma. Possible confounding factors in the interpretation of changes in PEFR or in PD_{20} or PC_{20} (methacholine or histamine) include a respiratory viral infection, exposure to nonoccupational allergens to which the patient is sensitized, and changes in the treatment of asthma.

Specific inhalation challenge tests with occupational agents (220) are performed in only a few specialized centers (318, 344–346); even if they are considered "gold standard" tests, they are not common practice and therefore should not be considered routine diagnostic tests. Moreover, only 50% of those who have a clinical diagnosis of OA exhibit a positive response to the challenge with the specific agent (318). These tests require the expertise of physicians to monitor the response of a patient in the laboratory and of engineers and occupational hygienists to generate and monitor exposure levels of the causal agent. Because these tests are time-consuming and can produce false-positive or false-negative responses (347), they should be performed in particular circumstances, such as the following: when a new agent is suspected of inducing OA, when the diagnosis is not certain based on the regular diagnostic tests, when there is disagreement between the results of PEFR and inhalation challenge with methacholine, and when it is necessary to confirm the diagnosis to manage the condition. In general, these tests should be recommended when the highest level of accuracy is required to demonstrate a causal relationship between asthma and occupational exposure. Alternatives to inhalation challenge tests have been proposed. One alternative was suggested in a review on whether the determinants of occupational agents cause early, late, or dual asthmatic responses (348). The author suggested that, likely, high-molecular-weight sensitizers behave as aeroallergens, with the consequence that early asthmatic responses can be predicted from skin-prick tests and the degree of airway responsiveness. The author also pointed out that, by contrast, responses to low-molecular-weight agents are difficult to predict because of the absence of a good measure of sensitization. It should be added that, in general, the pattern of response is also likely to be influenced by the length of time from the last exposure and by the use of medication. Previously (349), the same author recommended that clinical practice should use the area decrement summary method (350) and the serial FEV_1 method together, because each is sensitive to different aspects of a potential late asthmatic reaction. More recently, Malo and coworkers (351) recommended that for agents that can be generated using the closed-circuit method, use of this method results in a smaller proportion of exaggerated bronchoconstriction than does the realistic method, particularly for low-molecular-weight agents. This method is particularly important in workers with higher levels of airway hyperresponsiveness to methacholine.

Immunologic tests used in the diagnosis of OA have limited usefulness. These tests are limited by the lack of standardized and of commercially available reagents for skin tests, and by the lack of commercially available antigens for the determination of specific IgE antibodies in OA (352). Moreover, skin tests or *in vitro* assays alone are not diagnostic as a sole investigation.

A response to a skin test can be positive in up to 60% of asymptomatic workers exposed to enzymes (353). Immunologic tests are useful for demonstrating IgE antibodies to a high-molecular-weight agent, with high values of sensitivity and specificity (354). However, they are not useful in the diagnosis of sensitization and asthma due to low-molecular-weight agents, except for a few chemicals, such as trimellitic anhydride and platinum salts. Another limitation is that these tests are well standardized in only a few academic centers. Assessment of mediators such as chemokines may be useful in OA induced by isocyanates, because sensitivity, specificity, and test efficiency of monocyte chemoattractant protein 1 in peripheral blood mononuclear cells were higher than for specific IgG: 79, 91, and 87%, respectively, as compared with 47, 74, and 65% (355).

When using skin testing to common inhalants, the physician should be aware that in the occupational setting, incident cases of sensitization and of OA have been shown in nonatopic subjects exposed to high-molecular-weight agents (33, 34, 102, 356).

Another limitation of immunologic tests is that low molecular weight agents such as diisocyanates are complex chemicals, and there are many difficulties in using indirect biomarkers (e.g., antibodies) to assess exposure and to define thresholds between exposure to these agents and disease (357). The main issue concerns whether the marker represents a measure of exposure or disease.

Combining clinical history with immunologic testing has proved to be useful in ruling out the presence of OA in response to natural rubber latex, because the negative predictive value is 71% (337). Skin-prick testing with a commercial extract of natural rubber latex has high sensitivity (100%) but low specificity (21%) (337). In contrast, a proportion (25%) of workers with work-related respiratory symptoms, but with negative skin-prick test to platinum salts, experienced an asthmatic reaction after specific bronchial provocation test with platinum salts (358).

In the case of irritant-induced asthma, symptoms usually follow an accidental exposure to an irritant. The diagnosis of this type of OA is based on the clinical history and on the demonstration of variable airflow limitation, persistent airway hyperresponsiveness, or both; no previous known lung disease; documentation of high-level exposure to a respiratory irritant; and the onset of symptoms shortly after the exposure. In the case of irritant-induced asthma due to an agent with both irritant and sensitizing properties, history and objective tests should be repeatedly assessed, because immunologic OA may develop after the diagnosis of irritant-induced asthma (141, 359).

In addition to assessment of airway hyperresponsiveness, noninvasive assessment of airway inflammation can be used to diagnose OA. Commonly, functional changes in FEV_1 and PD_{20} or PC_{20} methacholine induced by exposure to occupational agents at the workplace or in the laboratory have been used as indicators of airway hyperresponsiveness. However, because there is no significant association between airway inflammation and airway hyperresponsiveness as measured by PC_{20} and PD_{20} methacholine, the results of methacholine challenge cannot be taken as an index of airway inflammation (310). An alternative is to assess airway inflammation by using invasive diagnostic procedures, such as bronchoalveolar lavage and bronchial biopsy, but the use of these procedures in clinical practice is limited.

Several objective, noninvasive methods of assessing airway inflammation to diagnose OA are available (reviewed carefully in Lemière [360]). One objective, noninvasive tool for diagnosing OA is analysis of induced sputum. Analysis of induced sputum is a valid and reproducible method for studying airway inflammation (361). The method consists of inducing sputum production by having the patient inhale a hypertonic saline solution and then counting the number of eosinophils in the induced sputum. The validity of this method is attested to by several studies, which have shown that sputum inflammatory indices such as eosinophils and eosinophil cationic protein are increased by exposure to common allergens (362–364) and are reduced by inhaled corticosteroids (365). The finding of neutrophil inflammation, documented by an increase in neutrophils in induced sputum, after exposure to low-molecular-weight agents (253, 254, 366, 367) is less common.

After Maestrelli and coworkers (368) reported sputum eosinophilia in both early and late reactors 8 and 24 hours after inhalation challenge with diisocyanates, several studies confirmed the importance of eosinophils in asthma caused by both high- and low-molecular-weight occupational agents (e.g., Di Franco and coworkers [369] and Lemière and coworkers [370]). Eosinophilia is a reasonably good noninvasive index of airway inflammation, because, among individuals with asthma, there is fairly strong agreement between the number of eosinophils counted in induced sputum, in bronchial biopsy specimens, and in bronchoalveolar lavage (371). In addition, in another study, sputum eosinophils, eotaxin, and IL-5 were present on the day preceding an asthmatic reaction and therefore preceded the functional change; these findings were more pronounced after exposure to low-molecular-weight agents (372). Interestingly, circadian variability in pulmonary function in asthma could be related to changes in airway eosinophil recruitment, as shown by sputum analysis (373). Moreover, the addition of sputum cell counts to monitoring of PEFR increased the specificity of this test, by 18 or 26.8%, respectively, depending on whether an increase in sputum eosinophils greater than 1 or 2% when at work was considered significant (374). The results of this study indicate that monitoring airway inflammation by counting eosinophils in induced sputum improves the diagnosis of OA.

One caveat in the use of sputum eosinophils is that it is unclear whether eosinophil counts in induced sputum relate to airway hyperresponsiveness. One study showed that changes in sputum eosinophil counts are satisfactory predictors of significant airway responsiveness to occupational agents (375). Another study showed that, although sputum eosinophils correlated inversely with FEV_1, they did not correlate with airway responsiveness (376). Indeed, induced sputum may be useful in the diagnosis and follow-up of subjects with OA. Its utility in epidemiologic studies has not been evaluated.

Eosinophil counts in sputum may have other diagnostic uses. Sputum may be particularly helpful in differentiation between work-aggravated asthma and superimposed OA due to a workplace sensitizer, because two studies have shown that exposure to occupational agents in asthmatics not sensitized to the agents did not induce airway inflammation and did not change the sputum cell composition (375, 377). The analysis of induced sputum has also been found to be useful in the identification of occupational eosinophilic bronchitis (58, 59). This condition is characterized by cough on exposure to occupational agents, without any functional changes.

Another noninvasive tool for assessing airway inflammation as an indicator of OA is the measurement of exhaled nitric oxide (eNO) (378). NO is produced by various activated inflammatory cells. Its concentration is increased in the exhaled air from patients with asthma (379, 380) and decreased by corticosteroid therapy (381). A few occupational studies have investigated the role of eNO in assessing OA, but with inconsistent results (377, 381–385). It has been suggested that measurement of eNO can be used to indicate the development of airway inflammation accompanying late asthmatic reactions after specific inhalation challenges in patients with normal or slightly increased basal NO levels (386). However, the usefulness of eNO in the investigation of OA is limited by factors affecting its determination,

such as therapy with inhaled steroids and smoking (171, 381). Thus, whereas the sensitivity of this measurement is high, its specificity is low. More data are needed to be able to use the eNO test in assessing airway inflammation, because NO can be produced in large amounts by epithelial cells in the paranasal sinuses (387) and in the stomach (388). Moreover, in a cross-sectional study of respiratory health of bleachery workers, it has been shown that only atopic subjects who have recently been exposed to the relevant allergens have elevated levels of eNO, suggesting that eNO relates to airway inflammation in atopic subjects (389).

Another novel and noninvasive method for assessing airway inflammation is the detection of markers (e.g., isoprostanes and aldehydes) and mediators (e.g., prostaglandins and leukotrienes) in the exhaled breath condensate (390). Because serial measurements can be made with no harmful effects, it is possible that this tool could be useful in occupational medicine (391).

The nose is often forgotten in the diagnostic approach to a patient with suspected OA. Tools such as examination of nasal lavage fluid and rhinomanometry can provide useful cellular and biochemical information. In a study of diagnostic approaches to occupational airway allergy, eosinophils and basophils significantly increased 5 and 24 hours after specific challenge in patients with OA due to laboratory animal allergens, and the increase was correlated with expiratory nasal resistance (392).

Management

To prevent OA, removal of the offending agent and substitution of a nontoxic agent are the best approach because they eliminate the asthma hazard (14). If substitution is not possible, ongoing maintenance of engineering controls, such as enclosure of the industrial process and improving work area ventilation, are useful, particularly when the employee works at a constant location and does the same tasks (14). Changes in work practices and/or job organization may also be helpful. Management of patients with work-induced asthma depends on the type of work-induced asthma: sensitizer-induced OA, irritant-induced OA, or aggravation of preexisting or coincident asthma (Table 5).

When asthma is induced by a workplace sensitizer, strict exposure control is needed. For employees sensitized to low-molecular-weight agents (e.g., isocyanates), complete cessation of exposure is the most desirable intervention.

Although respirators have not usually been considered safe for sensitizer-induced asthma (14), there is evidence that the use of respirators and other environmental controls to lower exposures may be helpful in OA induced by exposure to sensitizers (393, 394). The use of respirators requires worker adherence, professional guidance to assure correct device selection, and user training (395).

For patients with OA induced by an acute exposure to an irritant at work, steps should be taken to prevent further exposure to high concentrations of the irritant (40).

Patients with preexisting asthma that is aggravated at work should limit exposure to irritants, tobacco smoke, and relevant environmental allergens. If asthma is mild, the employee can stay in the same job, provided that exposure to nonspecific triggers is reduced (e.g., by moving to a different work area, improving ventilation, or using a respirator for short-term exposures to irritants). In addition to these types of changes, the physician may recommend periodic monitoring of symptoms and objective criteria of lung function. By contrast, if the disease is severe, a job change may be necessary.

Smoking exacerbates preexisting asthma that is aggravated at work. In a study of the effect of smoking on the outcome of patient education, the authors concluded that, compared with not smoking, smoking was associated with lower health-related quality of life, a lower FEV_1, a greater need for rescue medication and general practitioner visits, and higher costs, even after patient education during the 1-year follow-up (396).

Pharmacologic treatment for patients with OA caused by a respiratory sensitizer and/or irritant should be the same as that for patients with nonoccupational asthma (397). Two studies state that if workers remain exposed to the offending agent, pharmacologic treatment does not prevent deterioration of lung function (398, 399). However, a 3-year longitudinal study of workers with mild to moderate persistent OA who were still exposed at work to the causal agent of their disease, suggested that regular treatment with inhaled glucocorticoids and long-acting bronchodilators does seem to prevent deterioration of lung function (400). The beneficial effects of inhaled glucocorticoids are more evident when treatment starts soon after diagnosis (286).

Patients with preexisting asthma that is aggravated at work should optimize antiasthmatic pharmacologic treatment. Like other chronic diseases, OA can cause loss of productivity, which can be reduced by pharmacologic treatment (401).

Immunotherapy with extracts of high-molecular-weight occupational allergens has been studied only for natural rubber latex. Chan-Yeung and Malo (6) suggested that this therapy seems unlikely to allow the subject to continue to work because continuous exposure has not led to improvement of symptoms. In two placebo-controlled studies in which latex-specific immunotherapy was given for treatment of latex allergy in sensitized workers (17 and 24 patients, respectively), asthma symptoms were not consistently improved (402, 403).

Because the socioeconomic consequences of OA are relevant (5, 404–408), proper assessment of impairment and proper management of patients with OA and with work-aggravated asthma are important. Early removal of the employee from exposure to the offending agent, although associated with a better medical outcome, has the worst socioeconomic outcome (409), unless compensation programs are satisfactory and offer adequate financial coverage. Even in the absence of demonstrable OA, work-related asthma symptoms have socioeconomic consequences (30). Alternatives to prolonged unemployment, such as the use of modified materials, improvement in workplace conditions, or relocation to jobs with less exposure to the causal agent, may be successful in some occupational settings. One example is the exposure to natural rubber latex among health professionals (410). When exposure to natural rubber latex was reduced, clinical symptoms improved and socioeconomic consequences were less frequent than when the employee was removed from exposure to the agent (279).

Clinicians should support the patient in the pursuit of appropriate compensation. The assessment for temporary disability should be performed immediately after the diagnosis of OA is made, and long-term assessment of impairment (405) should be performed for 2 years after cessation of exposure, because the maximum rate of improvement occurs in the first 2 years after cessation of exposure. The new American Medical Association guidelines (404), which are based on the 1993 American Thoracic Society statement guidelines (405), are helpful in evaluating impairment and in standardizing disability criteria. Airway responsiveness may take longer than 2 years to improve (285). The factors that predict the outcome are baseline airway responsiveness, the duration of exposure before diagnosis and the interval since removal, and specific sensitivity (285, 167). To rate impairment, physiologic variables (postbronchodilator FEV_1, reversibility of FEV_1, degree of airway hyperresponsiveness), the minimum medication required to control asthma, and quality of life should be considered. Sputum eosinophilia, a useful marker

of airway inflammation, is appropriate for monitoring the disease (376, 411).

In several countries, compensation systems for OA are unsatisfactory because they largely underestimate the social and occupational damages and should be revised. A study in France showed that factors significantly associated with a risk for becoming unemployed or having a new employer after the diagnosis of OA are claims for compensation, small size of the industry, low level of education, and young age at time of diagnosis (409).

In the guidelines of the American Thoracic Society for assessing asthma risk at work (14), work-related asthma encompasses both OA and asthma aggravated by work. This choice is perhaps due to the difficulty in clinical practice of making a diagnosis of work-aggravated asthma and/or of irritant-induced asthma. This difficulty is well illustrated in a retrospective review of 469 asthma claims accepted by the Ontario Workers' Compensation Board, which showed that some claims related to accidental high exposure to irritants at work were assigned to the category of work-aggravated asthma rather than to irritant-induced asthma (36).

Prevention and Surveillance

Strategies for preventing OA have been described by several authors including Malo and Blanc (412), Cullinan and coworkers (413), and Gordon and Preece (414). For primary prevention, host and environmental factors are taken into consideration; for secondary prevention, preclinical changes in the disease need to be identified; and for tertiary prevention, workers should be diagnosed in an early phase of the disease and appropriate management of the disease should be offered.

Primary prevention is designed to abate hazards before any damage or injury has occurred. An example of primary prevention is the use of powder-free and low-protein latex gloves in health care facilities. Elimination or substitution of the agents that cause OA are the most effective measures, but these activities are generally outside the control of chest physicians.

Host factors were described earlier in this review. With the exception of atopy and smoking, little is known about host susceptibility factors. Atopy has a low predictive value in workers exposed to high-molecular-weight agents. Although cigarette smoking is known to increase the risk of sensitization to only a few agents such as platinum salts and acid anhydrides, we wish to stress that smoking should be discouraged in all workplaces (415).

For environmental factors, risk identification is of paramount importance. Efforts to set permissible levels at which immunologic sensitization is unlikely to occur should be encouraged (416). Dissemination of information should be reinforced. To identify risk from low-molecular-weight agents, research on the relationship between the structure of these agents and their activity, on molecular interactions between chemical sensitizers and human airway proteins, and on the ability to detect and localize chemical adducts in human lung tissue should be improved (417–425).

The reduction of respiratory exposure has been achieved in some workplaces, such as in the manufacture of detergent enzymes by improved dust control and the encapsulation of the enzymes (426) and for natural rubber latex by the use of powder-free low-protein gloves (410, 427–429). However, improved dust control and the encapsulation of enzymes did not eliminate the problem of allergic diseases in the detergent industry, because in one factory immunologic sensitization occurred because of failure to perform recommended procedures (426) and in another factory an outbreak of asthma developed after a modification of the manufacturing process (430).

Secondary prevention addresses preclinical changes, namely the immunologic sensitization that generally precedes the development of OA. Although the positive predictive value of skin reactivity as an indicator of immunologic sensitization is low, those with positive skin tests to high-molecular-weight agents should be monitored closely. For these agents, rhinoconjunctivitis can be considered a predictor of the later development of OA.

Early detection of disease could be accomplished by periodic examination of workers employed in high-risk industries (431), but this procedure is costly. The aim is to detect immunologic sensitization or OA at an early stage, because early detection leads to a better prognosis.

Medical surveillance programs for sensitization and OA consist of a questionnaire given before employment and repeated periodically (432); in addition, immunologic tests (skin tests) and physiologic tests may be considered.

In workers exposed to complex platinum salts, a medical surveillance program has been beneficial (433). Similarly, in workers with diisocyanate-induced OA, medical surveillance programs improved outcome (434, 435). The excess of sensitization in bread bakers is largely due to IgE-mediated allergy to fungal amylase, contained in bread improvers. In bread bakeries, the strategy of targeting bread improver exposure is an effective approach for the prevention of new cases of symptomatic sensitization. Over the 10-year period of surveillance, there was an overall reduction in the incidence of new cases of symptomatic sensitization in the bread-baking sector, from 2,085 per million employees per year in the first 5 years of surveillance to 405 per million employees per year in the next 5 years (436). Monitoring a cohort of dental students who had a high atopic incidence and who were exposed to powder-free latex gloves showed absence of subsequent sensitization over 5 years in this population (437). However, these promising findings are not necessarily applicable to all occupational agents. For many sensitizers, especially low-molecular-weight agents, the mechanism of sensitization is not known, so skin tests are not helpful (438).

Health surveillance programs should focus on disease prevention without continuing to apply the same invalidated tools (e.g., follow-up questionnaires not validated; questionnaires inappropriately administered by the employees themselves, rather than by an interviewer as recommended) (439). The use of sensitive and specific tests is highly recommended.

Tertiary prevention aims at the prevention of permanent asthma. Examples of tertiary prevention include therapy with inhaled glucocorticoids, substitution of non–isocyanate-containing spray paints in the workplace of an employee with isocyanate-induced asthma, and strict avoidance of exposure to mice in an animal handler's asthma that resulted from an allergy to mice (440). Early recognition of the disease and early removal of the patient from exposure make it more likely that the patient will avoid permanent asthma.

Although effective primary preventive measures are most appropriate for reducing the development of sensitization and of OA, periodic assessments of symptoms and the use of objective criteria for evaluating lung function can help the physician in managing the disease and in assessing adequate control of exposure and adequate protection of the individual patient.

CONCLUSIONS AND FUTURE RESEARCH

For physicians caring for adult patients with asthma, an understanding of the contribution of occupational exposure to the pathogenesis and treatment of the disease is important. The first step should be the quick evaluation of causality and the demonstration of a relationship between exposure to the agent in the workplace and sensitization or the occurrence of asthma.

To maximize the efforts and opportunities to reduce the incidence of OA, and to improve the outcome of the disease, re-

search in basic asthma (occupational and nonoccupational) should drive the management and treatment of the disease, which creates a significant economic burden.

The different aspects of asthma research have often been constrained by a lack of funds, but it is time to return to vision and science (441). In the opinion of the authors the following specific issues relevant to the pathogenesis of OA need to be investigated further.

1. The relationship between exposure to a sensitizing agent (allergen, chemical), atopic status, and the development of asthma: Research should focus on the dose–response relationship of allergen exposure, on the measurement of allergen exposure, and on possible interactions (smoking, endotoxin, particulates, pollutants). In a cohort of laboratory animal workers, it was reported that the strongest and clearest exposure–response relationships for symptoms were observed among rat-sensitized workers whereas the nonsensitized workers showed only small increased risks of developing symptoms. Sensitized workers were almost four times more likely to go on to develop chest symptoms than nonsensitized workers (139).
2. The role of HLA class II molecules in the development of occupational sensitization and asthma, particularly to low-molecular-weight agents: Whether genetic susceptibility is a risk factor is an important issue, because it was shown that the *DQB1*0501* allele is involved in asthma induced by low-molecular-weight sensitizers such as organic acid anhydrides (442); the same allele is relevant for asthma induced by isocyanates (186) and plicatic acid (protective role) (187), suggesting various affinities of chemical sensitizers for the corresponding specific class II molecules.
3. The role of airway inflammation and remodeling in causing chronic asthma, bronchial obstruction, and airway hyperresponsiveness: Research should focus on understanding the cellular and molecular events leading to airway remodeling, and on the development and validation of noninvasive markers of matrix turnover.
4. The mechanisms of irritant-induced asthma and factors other than exposure that are relevant to this type of OA: Research should focus on prospective cohort studies of individuals with possible exposure to high or repeated low levels of irritants, using accurate definitions of the population baseline characteristics and of the exposure characteristics. Another focus of research should be on the use of an animal model(s) of irritant-induced asthma.
5. Establishment of structure–function relationships for causal agents of OA.
6. Identification of the biologically relevant antigenic forms of low-molecular-weight agents (e.g., isocyanates): This aspect of future research is important because it has been shown that HDI-albumin conjugates produced by a novel approach designed to model the air–liquid interface of the human airways are physiologically relevant and are useful in characterizing the immune responses associated with HDI exposures and asthma (423). Furthermore, in isocyanate-induced asthma it has been shown that TDI exposure can augment cytokeratin-19 expression from the bronchial epithelial cell, which may involve immune responses as an autoantigen to induce airway inflammation in this common type of OA (443).

Other specific issues that could positively impact OA prevention and management include the following:

1. Reduction or elimination of risk factors that cause OA
2. Consideration of sputum induction as a noninvasive measurement for airway eosinophilia as an adjunct to the objective criteria of airway inflammation and monitoring
3. Collection of more data to consider measurement of eNO for airway inflammation and monitoring

Conflict of Interest Statement: None of the authors have a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

Acknowledgment: The authors thank Mimi Zeiger, M.A., Lecturer in Scientific Writing, Cardiovascular Research Institute, University of California, San Francisco, San Francisco, California, for meticulously helping to rewrite a part of this manuscript and for fine work throughout the revision of this manuscript. They also thank Elisa Veratelli for scientific secretarial assistance.

References

1. Meredith S, Nordman H. Occupational asthma: measures and frequency from four countries. *Thorax* 1996;51:435–440.
2. Mannino DM. How much asthma is occupationally related? *Occup Med* 2000;15:359–368.
3. Blanc PD, Toren K. How much asthma can be attributed to occupational factors? *Am J Med* 1999;107:580–587.
4. Balmes J, Becklake M, Blanc P, Henneberger P, Kreiss K, Mapp CE, Milton D, Schwartz D, Toren K, Viegi G. American Thoracic Society statement: occupational contribution to the burden of airway disease. *Am J Respir Crit Care Med* 2003;167:787–797.
5. Dewitte JD, Chan-Yeung M, Malo JL. Medicolegal and compensation aspects of occupational asthma. *Eur Respir J* 1994;7:969–980.
6. Chan-Yeung M, Malo JL. Natural history of occupational asthma. In: Asthma in the workplace. Bernstein IL, Chan-Yeung M, Malo JL, Bernstein DI, editors. New York: Marcel Dekker; 1999. p. 129–144.
7. Patino CM, Martinez FD. Interactions between genes and environment in the development of asthma. *Allergy* 2001;56:279–286.
8. Maestrelli P. Natural history of adult-onset asthma: insights from model of occupational asthma. *Am J Respir Crit Care Med* 2004;169:331–332.
9. Barbee RA, Murphy S. The natural history of asthma. *J Allergy Clin Immunol* 1998;102:S65–S72.
10. Bernstein IL, Bernstein DI, Chan-Yeung M, Malo JL. Definition and classification of asthma. In: Asthma in the workplace. Bernstein IL, Chan-Yeung M, Malo JL, Bernstein DI, editors. New York: Marcel Dekker; 1999. p. 1–3.
11. Malo JL, Ghezzo H, D'Aquino C, l'Archeveque J, Cartier A, Chan-Yeung M. Natural history of occupational asthma: relevance of type of agent and other factors in the rate of development of symptoms in affected workers. *J Allergy Clin Immunol* 1992;90:937–944.
12. Tarlo SM. Occupational asthma: a valid model for adult asthma? *Curr Opin Allergy Clin Immunol* 2003;3:91–94.
13. Frew AJ. What can we learn about asthma from studying occupational asthma? *Ann Allergy Asthma Immunol* 2003;90:7–10.
14. American Thoracic Society. Guidelines for assessing and managing asthma risk at work, school, and recreation. *Am J Respir Crit Care Med* 2004;169:873–881.
15. Vandenplas O, Malo JL. Definitions and types of work-related asthma: a nosological approach. *Eur Respir J* 2003;21:706–712.
16. Chan-Yeung M, American College of Chest Physicians. Assessment of asthma in the workplace: ACCP consensus statement. *Chest* 1995;108: 1084–1117.
17. Gautrin D, Bernstein IL, Brooks S. Reactive airways dysfunction syndrome or irritant induced asthma. In: Asthma in the workplace. Bernstein IL, Chan-Yeung M, Malo JL, Bernstein DI, editors. New York: Marcel Dekker; 1999. p. 565–593.
18. Tarlo SM, Broder I. Irritant induced asthma. *Chest* 1989;96:297–300.
19. Brooks SM, Weiss MA, Bernstein IL. Reactive airways dysfunction syndrome (RADS): persistent asthma syndrome after high level irritant exposures. *Chest* 1985;88:376–384.
20. Becklake MR, Malo JL, Chan-Yeung M. Epidemiological approaches in occupational asthma. In: Asthma in the workplace. Bernstein IL, Chan-Yeung M, Malo JL, Bernstein DI, editors. New York: Marcel Dekker; 1999. p. 27–65.
21. Matte TD, Hoffman RE, Rosenman KD, Stanbury M. Surveillance of occupational asthma under the SENSOR model. *Chest* 1990;98:173S–178S.
22. Jajosky RA, Harrison R, Reinisch F, Flattery J, Chan J, Tumpowsky C, Davis L, Reilly MJ, Rosenman KD, Kalinowski D, *et al.* Surveillance of work-related asthma in selected US states using surveillance guidelines for state health departments. California. Massachusetts,

Michigan, and New Jersey, 1993–1995. *MMWR CDC Surveill Summ* 1999;48:1–20.
23. Malo JL, Chan-Yeung M. Comment on the editorial: "Occupational asthma: prevention by definition." *Am J Ind Med* 1999;35:L207.
24. Maestrelli P, Saetta M, Mapp CE, Fabbri LM. Regulatory issues and environmental control. *Eur Respir Monogr* 1999;11:124–135.
25. Milton DK, Solomon GM, Rosiello RA, Herrick RF. Risk and incidence of asthma attributable to occupational exposure among HMO members. *Am J Ind Med* 1998;33:1–10.
26. Wagner GR, Wegman DH. Occupational asthma: prevention by definition. *Am J Ind Med* 1998;33:427–429.
27. Tarlo SM, Leung K, Broder I, Silverman F, Holness DL. Asthmatic subjects symptomatically worse at work: prevalence and characterization among a general asthma clinic population. *Chest* 2000;118:1309–1314.
28. Saarinen K, Karjalainen A, Martikainen R, Uitti J, Tammilehto L, Klaukka T, Kurppa K. Prevalence of work-aggravated symptoms in clinically established asthma. *Eur Respir J* 2003;22:305–309.
29. Cannon J, Cullinan P, Newman Taylor A. Consequences of occupational asthma. *BMJ* 1995;311:602–603.
30. Larbanois A, Jamart J, Delwiche JP, Vandenplas O. Socioeconomic outcome of subjects experiencing asthma symptoms at work. *Eur Respir J* 2002;19:1107–1113.
31. Lau S, Illi S, Sommerfeld C, Niggemann B, Bergmann R, von Mutius E, Wahn U, Multicentre Allergy Study Group. Early exposure to house-dust mite and cat allergens and development of childhood asthma: a cohort study. *Lancet* 2000;356:1392–1397.
32. Grad R. Risk of asthma in children with exposure to mite and cat allergens. *Lancet* 2000;356:1369–1370.
33. Cullinan P, Cook A, Gordon S, Nieuwenhuijsen MJ, Tee RD, Venables KM, McDoanld JC, Newman Taylor AJ. Allergen exposure, atopy and smoking as determinants of allergy to rats in a cohort of laboratory employers. *Eur Respir J* 1999;13:1139–1143.
34. Gautrin D, Infante-Rivard C, Ghezzo H, Malo JL. Incidence and host determinants of probable occupational asthma in apprentices exposed to laboratory animals. *Am J Respir Crit Care Med* 2001;163:899–904.
35. Petsonk EL, Wang ML, Lewis DM, Siegel PD, Husberg BJ. Asthma-like symptoms in wood product plant workers exposed to methylene diphenyl diisocyanate. *Chest* 2000;118:1183–1193.
36. Chatkin JM, Tarlo SM, Liss G, Banks D, Broder I. The outcome of asthma related to workplace irritant exposures: a comparison of irritant-induced asthma and irritant aggravation of asthma. *Chest* 1999;116:1780–1785.
37. Testud F, Lambert-Chlum R. Reactive airway dysfunction syndrome: more flexible application of diagnostic criteria are important for occupational accident victims. *Rev Pneumol Clin* 2004;60:154–157.
38. Alberts WM, do Pico GA. Reactive airways dysfunction syndrome. *Chest* 1996;109:1618–1626.
39. Tarlo SM. Workplace respiratory irritants and asthma. *Occup Med* 2000;15:471–484.
40. Tarlo SM, Boulet LP, Cartier A, Cockcroft D, Cote J, Hargreave FE, Holness L, Liss G, Malo JL, Chan-Yeung M. Canadian Thoracic Society guidelines for occupational asthma. *Can Respir J* 1998;5:289–300.
41. Chan-Yeung M, Lam S, Kennedy SM, Frew A. Persistent asthma after repeated exposure to high concentrations of gases in pulpmills. *Am J Respir Crit Care Med* 1994;149:1676–1680.
42. Tarlo SM. Workplace irritant exposures: do they produce true occupational asthma? *Ann Allergy Asthma Immunol* 2003;90:19–23.
43. Andersson E, Olin AC, Hagberg S, Nilsson R, Nilsson T, Toren K. Adult-onset asthma and wheeze among irritant-exposed bleachery workers. *Am J Ind Med* 2003;43:532–538.
44. Quirce S, Gala G, Perez-Camo I, Sanchez-Fernandez C, Pacheco A, Losada E. Irritant-induced asthma: clinical and functional aspects. *J Asthma* 2000;37:267–274.
45. Prezant DJ, Weiden M, Banauch GI, McGuinness G, Rom WN, Aldrich TK, Kelly KJ. Cough and bronchial responsiveness in firefighters at the World Trade Center site. *N Engl J Med* 2002;347:806–815.
46. Scanlon PD. World Trade Center cough: a lingering legacy and a cautionary tale. *N Engl J Med* 2002;347:840–842.
47. Nemery B. Reactive fallout of World Trade Center dust. *Am J Respir Crit Care Med* 2003;168:2–3.
48. Kern DG. Outbreak of the reactive airways dysfunction syndrome after a spill of glacial acetic acid. *Am Rev Respir Dis* 1991;144:1058–1064.
49. Cone JE, Wugofski L, Balmes JR, Das R, Bowler R, Alexeeff G, Shusterman D. Persistent respiratory health effects after a metam sodium pesticide spill. *Chest* 1994;106:500–508.
50. Banaunch GI, Alleyne D, Sanchez R, Olender K, Cohen HW, Weiden M, Kelly KJ, Prezant DJ. Persistent hyperreactivity and reactive airway dysfunction in firefighters at the World Trade Center. *Am J Respir Crit Care Med* 2003;168:54–62.
51. Landrigan PJ, Lioy PJ, Thurston G, Berkpwitz G, Chen LC, Chillrud SN, Gavett SH, Georgopoulos PG, Geyh AS, Levin S, *et al.* NIEHS World Trade Center Working Group. Health and environmental consequences of the World Trade Center disaster. *Environ Health Perspect* 2004;112:731–739.
52. Tarlo SM, Liss GM. Occupational asthma: an approach to diagnosis and management. *CMAJ* 2003;168:867–871.
53. Banks DE. Workplace irritant exposures: do they produce true occupational asthma? *Curr Opin Allergy Clin Immunol* 2001;1:163–168.
54. Jenkins HS, Devalia JL, Mister RL, Bevan AM, Rusznak C, Davies RJ. The effect of exposure to ozone and nitrogen dioxide on the airway response of atopic asthmatics to inhaled allergen: dose- and time-dependent effects. *Am J Respir Crit Care Med* 1999;160:33–39.
55. de Meer G, Kerkhof M, Kromhout H, Schouten JP, Heederik D. Interaction of atopy and smoking on respiratory effects of occupational dust exposure: a general population-based study. *Environ Health* 2004;3:6.
56. Chan-Yeung M, Kennedy SM, Schwartz D. Grain dust-induced lung diseases. In: Bernstein IL, Chan-Yeung M, Malo JL, Bernstein DI, editors. Asthma in the workplace. New York: Marcel Dekker; 1999. p. 617–634.
57. Gibson PG, Fujimura M, Niimi A. Eosinophilic bronchitis: clinical manifestations and implications for treatment. *Thorax* 2002;57:178–182.
58. Lemière C, Efthimiadis A, Hargreave FE. Occupational eosinophilic bronchitis without asthma: an unknown occupational airway disease. *J Allergy Clin Immunol* 1997;100:852–853.
59. Quirce S, Fernandez-Nieto M, de Miguel J, Sastre J. Chronic cough due to latex-induced eosinophilic bronchitis. *J Allergy Clin Immunol* 2001;108:143.
60. Quirce S. Eosinophilic bronchitis in the workplace. *Curr Opin Allergy Clin Immunol* 2004;4:87–91.
61. Gibson PG, Fujimura M, Niimi A. Eosinophilic bronchitis: clinical manifestations and implications for treatment. *Thorax* 2002;57:178–182.
62. Kanazawa H, Nomura S, Yoshikawa J. Role of microvascular permeability on physiologic differences in asthma and eosinophilic bronchitis. *Am J Respir Crit Care Med* 2004;169:1125–1130.
63. Park SW, Lee YM, Jang AS, Lee JH, Hwangbo Y, Kim do J, Park CS. Development of chronic airway obstruction in patients with eosinophilic bronchitis: a prospective follow-up study. *Chest* 2004;125:1998–2004.
64. Brightling CE, Symon FA, Birring SS, Bradding P, Wardlaw AJ, Pavord ID. Comparison of airway immunopathology of eosinophilic bronchitis and asthma. *Thorax* 2003;58:528–532.
65. Berry MA, Parker D, Neale N, Woodman L, Morgan A, Monk P, Bradding P, Wardlaw AJ, Pavord ID, Brightling CE. Sputum and bronchial submucosa IL-13 expression in asthma and eosinophilic bronchitis. *J Allergy Clin Immunol* 2004;114:1106–1109.
66. Chan-Yeung M, Malo JL. Tables of major inducers of occupational asthma. In: Bernstein IL, Chan-Yeung M, Malo JL, Bernstein DI, editors. Asthma in the workplace. New York: Marcel Dekker; 1999. p. 683–720.
67. Bernstein DI. Allergic reactions to workplace allergens. *JAMA* 1997;278:1907–1913.
68. Cullinan P, Newman Taylor AJ. Aetiology of occupational asthma. *Clin Exp Allergy* 1997;27:41–46.
69. Van Kampen V, Merget R, Baur X. Occupational airway sensitizers: an overview on the respective literature. *Am J Ind Med* 2000;38:164–218.
70. Mapp CE. Agents, old and new, causing occupational asthma. *Occup Environ Med* 2001;58:354–360.
71. www.asmanet.com. Date last updated: continuous.
72. www.asthme.csst.qc.ca. Date last updated: continuous.
73. Fransman W, McLean D, Douwes J, Demers PA, Leung V, Pearce N. Respiratory symptoms and occupational exposures in New Zealand plywood mill workers. *Ann Occup Hyg* 2003;47:287–295.
74. Liss GM, Tarlo SM, Doherty J, Purdham J, Greene J, McCaskell L, Kerr M. Physician diagnosed asthma, respiratory symptoms, and associations with workplace tasks among radiographers in Ontario, Canada. *Occup Environ Med* 2003;60:254–261.
75. Gautrin D, Newman Taylor AJ, Nordman H, Malo J-L. Controversies in epidemiology of occupational asthma. *Eur Respir J* 2003;22:551–559.
76. Reijula K, Haahtela T, Klaukka T, Rantanen J. Incidence of occupational asthma and persistent asthma in young adults has increased in Finland. *Chest* 1996;110:58–61.

77. Blanc P. Occupation and asthma: through a glass darkly. *Chest* 1997; 110:3–4.
78. Vermeulen R, Heederik D, Kromhout H, Smit HA. Respiratory symptoms and occupation: a cross-sectional study in the general population. *Environ Health* 2002;1:5.
79. Le Moual N, Kennedy SM, Kauffmann F. Occupational exposures and asthma in 14,000 adults from the general population. *Am J Epidemiol* 2004;160:1108–1116.
80. Zock JP, Cavalle N, Kromhout H, Kennedy SM, Sunyer J, Jaen A, Muniozguren N, Payo F, Almar E, Sanchez JL, *et al.* Evaluation of specific occupational asthma risks in a community-based study with special reference to single and multiple exposures. *J Expo Anal Environ Epidemiol* 2004;14:397–403.
81. Brisman J, Jarvholm B, Lillienberg L. Exposure–response relations for self reported asthma and rhinitis in bakers. *Occup Environ Med* 2000;57:335–340.
82. Barker R, Tongeren MV, Harris J, Gardiner K, Venables K, Newman Taylor AJ. Risk factors for sensitisation and respiratory symptoms among workers exposed to acid anhydrides: a cohort study. *Occup Environ Med* 1998;55:684–691.
83. Cullinan P, Cook A, Nieuwenhyijsen M, Sandiford C, Tee RD, Venables KM, McDonald JC, Newman Taylor AJ. Allergen and dust exposure as determinants of work-related symptoms and sensitisation in a cohort of flour-exposed workers; a case-control analysis. *Ann Occup Hyg* 2001;45:97–103.
84. Newman Taylor AJ. Asthma and work. *Ann Occup Hyg* 2002;46:563–574.
85. Meredith S, Bugler J, Clark R. Isocyanate exposure and occupational asthma: a case-referent study. *Occup Environ Med* 2000;57:830–836.
86. Hollander A, Heederik D, Doekes G. Respiratory allergy to rats: exposure–response relationships in laboratory animal workers. *Am J Respir Crit Care Med* 1997;155:562–567.
87. Cartier A, Malo J-L, Forest F, Lafrance M, Pineau L, St-Aubin JJ, Dubois JY. Occupational asthma in snow crab processing workers. *J Allergy Clin Immunol* 1984;74:261–269.
88. Malo JL, Cartier A. Occupational asthma in workers of a pharmaceutical company processing spiramycin. *Thorax* 1988;43:371–377.
89. Malo JL, Cartier A, L'Archeveque J, Ghezzo H, Soucy F, Somers J, Dolovich J. Prevalence of occupational asthma and immunologic sensitization to guar gum among employees at a carpet-manufacturing plant. *J Allergy Clin Immunol* 1990;86:562–569.
90. Marks GB, Salome CM, Woolcock AJ. Asthma and allergy associated with occupational exposure to ispaghula and senna products in a pharmaceutical work force. *Am Rev Respir Dis* 1991;144:1065–1069.
91. Malo JL, Cartier A, L'Archeveque J, Trudeau C, Courteau JP, Bherer L. Prevalence of occupational asthma among workers exposed to eastern white cedar. *Am J Respir Crit Care Med* 1994;150:1697–1701.
92. Mastrangelo G, Paruzzolo P, Mapp CE. Asthma due to isocyanates: a mail survey in a 1% sample of furniture workers in the Veneto region. *Med Lav* 1995;86:503–510.
93. Desjardins A, Malo JL, L'Archeveque J, Cartier A, McCants M, Lehrer SB. Occupational IgE-mediated sensitization and asthma caused by clam and shrimp. *J Allergy Clin Immunol* 1995;96:608–617.
94. Rees D, Nelson G, Kielkwowski D, Wasserfall C, da Costa A. Respiratory health and immunological profile of poultry workers. *S Afr Med J* 1998;88:1110–1117.
95. Danuser B, Weber C, Kunzli N, Schindler C, Nowak D. Respiratory symptoms in Swiss farmers: an epidemiological study of risk factors. *Am J Ind Med* 2001;39:410–418.
96. Ortega HG, Daroowalla F, Petsonk EL, Lewis D, Berardinelli S Jr, Jones W, Kreiss K, Weissman DN. Respiratory symptoms among crab processing workers in Alaska: epidemiological and environmental assessment. *Am J Ind Med* 2001;39:598–607.
97. Lieutier-Colas F, Meyer P, Pons F, Hedelin G, Larsson P, Malmberg P, Pauli G, De Blay F. Prevalence of symptoms, sensitisation to rats, and airborne exposure to major rat allergen (Rat n 1) and to endotoxin in rat-exposed workers: a cross-sectional study. *Clin Exp Allergy* 2002; 32:1424–1429.
98. Di Lorenzo G, Vitale F, Pacor ML, Pellitteri ME, Drago A, Cucchiara R, Seroni G, Intonazzo V, Romano N, Caruso C. Prevalence of latex sensitization in health care workers of a general hospital in Palermo, Sicily. *J Investig Allergol Clin Immunol* 2002;12:114–119.
99. Medina-Ramon M, Zock JP, Kogevinas M, Sunyer J, Anto JM. Asthma symptoms in women employed in domestic cleaning: a community based study. *Thorax* 2003;58:950–954.
100. Akpinar-Elci M, Elci OC, Odabasi A. Work-related asthma-like symptoms among florists. *Chest* 2004;125:2336–2339.
101. Brant A, Berriman J, Sharp C, Welch J, Zekveld C, Nieuwenhuijsen M, Elms J, Newman Taylor A, Cullinan P. The changing distribution of occupational asthma: a survey of supermarket bakery workers. *Eur Respir J* 2005;25:303–308.
102. Gautrin D, Ghezzo H, Infante-Rivard C, Malo JL. Incidence and determinants of IgE-mediated sensitization in apprentices: a prospective study. *Am J Respir Crit Care Med* 2000;162:1222–1228.
103. El-Zein M, Malo JL, Infante-Rivard C, Gautrin D. Incidence of probable occupational asthma and changes in airway calibre and responsiveness in apprentice welders. *Eur Respir J* 2003;22:513–518.
104. Contreras GR, Rosseau R, Chan-Yeung M. Occupational respiratory disease in British Columbia, Canada in 1991. *Occup Environ Med* 1994;51:710–712.
105. Toren K. Self reported rate of occupational asthma in Sweden 1990–2. *Occup Environ Med* 1996;53:757–761.
106. Provencher S, Labreche FP, De Guire L. Physician based surveillance system for occupational respiratory diseases: the experience of PROPULSE, Quebec, Canada. *Occup Environ Med* 1997;54:272–276.
107. Rosenman KD, Reilly MJ, Kalinowski DJ. A state-based surveillance system for work-related asthma. *J Occup Environ Med* 1997;39:415–425.
108. Henneberger PK, Kreiss K, Rosenman KD, Reilly MJ, Chang YF, Geidenberger CA. An evaluation of the incidence of work-related asthma in the United States. *Int J Occup Environ Health* 1999;5:1–8.
109. Cherry NM, Meyer JD, Holt DL, Chen Y, McDonald JC. Surveillance of work-related diseases by occupational physicians in the UK: OPRA 1996–1999. *Occup Med (Lond)* 2000;50:496–503.
110. Karjalainen A, Kurppa K, Virtanen S, Keskinen H, Nordman H. Incidence of occupational asthma by occupation and industry in Finland. *Am J Ind Med* 2000;37:451–458.
111. Walls C, Crane J, Gillies J, Wilsher M, Wong C. Occupational asthma cases notified to OSH from 1996 to 1999. *N Z Med J* 2000;113:491–492.
112. Meyer JD, Holt DL, Chen Y, Cherry NM, McDonald JC. SWORD'99: surveillance of work-related and occupational respiratory disease in UK. *Occup Med (Lond)* 2001;51:204–208.
113. Karjalainen A, Kurppa K, Martikainen R, Klaukka T, Karjalainen J. Work is related to a substantial portion of adult-onset asthma incidence in the Finnish population. *Am J Respir Crit Care Med* 2001; 164:565–568.
114. Reinisch F, Harrison RJ, Cussler S, Athanasoulis M, Balmes J, Blanc P, Cone J. Physician reports of work-related asthma in California, 1993–1996. *Am J Ind Med* 2001;39:72–83.
115. Esterhuizen TM, Hnizdo E, Rees D. Occurrence and causes of occupational asthma in South Africa: results from SORDSA's occupational asthma registry, 1997–1999. *S Afr Med J* 2001;91:509–513.
116. Ameille J, Pauli G, Calastreng-Crinquand A, Vervloet D, Iwatsubo Y, Popin E, Bayeux-Dunglas MC, Kopferschmitt-Kubler MC, Observatoire National des Asthmes Professionnels. Reported incidence of occupational asthma in France, 1996–99: the ONAP programme. *Occup Environ Med* 2003;60:136–141.
117. Di Stefano F, Siriruttanapruk S, McCoach J, Di Gioacchino M, Burg PS. Occupational asthma in a highly industrialized region of UK: report from a local surveillance scheme. *Allerg Immunol (Paris)* 2004;36:56–62.
118. Elder D, Abramson M, Fish D, Johnson A, McKenzie D, Sim M. Surveillance of Australian workplace based respiratory events (SABRE): notifications for the first 3.5 years and validation of occupational asthma cases. *Occup Med* 2004;54:395–399.
119. Viegi G, Prediletto R, Paoletti P, Carrozzi L, Di Pede F, Vellutini M, Di Pede C, Giuntini C, Lebowitz MD. Respiratory effects of occupational exposure in a general population sample in north Italy. *Am Rev Respir Dis* 1991;143:510–515.
120. Kogevinas M, Anto JM, Soriano JB, Tobias A, Burney P, Spanish Group of the European Asthma Study. The risk of asthma attributable to occupational exposures: a population-based study in Spain. *Am J Respir Crit Care Med* 1996;154:137–143.
121. Kogevinas M, Anto JM, Sunyer J, Tobias A, Kromhout H, Burney P, European Community Respiratory Health Survey Study Group. Occupational asthma in Europe and other industrialised areas: a population-based study. *Lancet* 1999;353:1750–1754.
122. Eagan TM, Gulsvik A, Eide GE, Bakke PS. Occupational airborne exposure and the incidence of respiratory symptoms and asthma. *Am J Respir Crit Care Med* 2002;166:933–938.
123. Blanc PD, Burney P, Janson C, Toren K. The prevalence and predictors of respiratory-related work limitation and occupational disability in an international study. *Chest* 2003;124:1153–1159.
124. McDonald JC, Keynes HL, Meredith SK. Reported incidence of occupa-

tional asthma in the UK, 1989–97. *Occup Environ Med* 2000;57:823–829.
125. Seta JA, Young RO, Pedersen DH, Bernstein IL, Bernstein DI. The United States National Occupational Exposure Survey (NOES) data base. In: Asthma in the workplace. Bernstein IL, Chan Yeung M, Malo JL, Bernstein DI, editors. New York: Marcel Dekker; 1999. p. 721–728.
126. Ross DJ. Ten years of the SWORD project. *Clin Exp Allergy* 1999;29: 750–753.
127. Malo JL, Gautrin D. How often does it occur? Proceedings of the first Jack Pepys Occupational Asthma Symposium. *Am J Respir Crit Care Med* 2003;167:452–453.
128. Arif AA, Whitehead LW, Delclos GL, Tortorelo SR, Lee ES. Prevalence and risk factors of work related asthma by industry among United States workers: data from the third national health and nutrition examination survey (1988–94). *Occup Environ Med* 2002;59:505–511.
129. Jaakkola JJ, Piipari R, Jaakkola MS. Occupation and asthma: a population-based incident case-control study. *Am J Epidemiol* 2003;158:981–987.
130. Meijer E, Grobbee DE, Heederik D. A strategy for health surveillance in laboratory animal workers exposed to high molecular weight allergens. *Occup Environ Med* 2004;61:831–837.
131. Henneberger PK, Derk SJ, Davis L, Tumpowsky C, Reilly MJ, Rosenman KD, Schill DP, Valiante D, Flattery J, Harrison R, *et al.* Work-related airways dysfunction syndrome cases from surveillance in selected US states. *J Occup Environ Med* 2003;45:360–368.
132. Reijula K, Patterson R. Occupational allergies in Finland in 1981–91. *Allergy Proc* 1994;15:163–168.
133. Rosenman KD, Reilly MJ, Schill DP, Valiante D, Flattery J, Harrison R, Reinisch F, Pechter E, Davis L, Tumpowsky CM, *et al.* Cleaning products and work-related asthma. *J Occup Environ Med* 2003;45: 556–563.
134. Balmes JR. Occupational airways diseases from chronic low-level exposure to irritants. *Clin Chest Med* 2002;23:727–735.
135. Goe SK, Henneberger PK, Reilly MJ, Rosenman KD, Schill DP, Valiante D, Flattery J, Harrison R, Reinisch F, Tumpowsky C, *et al.* A descriptive study of work aggravated asthma. *Occup Environ Med* 2004;61:512–517.
136. Chan-Yeung M, Malo JL. Occupational asthma. *N Engl J Med* 1995; 333:107–112.
137. Chan-Yeung M. Occupational asthma. *Chest* 1990;98:148S–161S.
138. Venables KM, Newman Taylor AJ. Exposure–response relationships in asthma caused by tetrachlorophthalic anhydride. *J Allergy Clin Immunol* 1990;85:55–58.
139. Nieuwenhuijsen MJ, Putcha V, Gordon S, Heederik D, Venables KM, Cullinan P, Newman Taylor AJ. Exposure–response relations among laboratory animal workers exposed to rats. *Occup Environ Med* 2003;60:104–108.
140. Heederik D, Houba R. An exploratory quantitative risk assessment for high molecular weight sensitizers: wheat flour. *Ann Occup Hyg* 2001;45:175–185.
141. Leroyer C, Perfetti L, Cartier A, Malo JL. Can reactive airways dysfunction syndrome (RADS) transform into occupational asthma due to "sensitization" to isocyanates? *Thorax* 1998;53:152–153.
142. Johnson VJ, Matheson JM, Luster MI. Animal models of diisocyanate asthma: answers for lingering questions. *Curr Opin Allergy Clin Immunol* 2004;4:105–110.
143. Newman Taylor AJ, Cullinan P, Lympany PA, Harris JM, Dowdeswell RJ, duBois RM. Interaction of HLA phenotype and exposure intensity in sensitization to complex platinum salts. *Am J Respir Crit Care Med* 1999;160:435–438.
144. Droste J, Myny K, van Sprundel M, Kusters E, Bulat P, Braeckman L, Vermeire P, Vanhoorne M. Allergic sensitization, symptoms, and lung function among bakery workers as compared with a nonexposed work population. *J Occup Environ Med* 2003;45:648–655.
145. Baur X, Chen Z, Liebers V. Exposure–response relationships of occupational inhalative allergens. *Clin Exp Allergy* 1998;28:537–544.
146. Baur X. Are we closer to developing threshold limit values for allergens in the workplace? *Ann Allergy Asthma Immunol* 2003;90:11–18.
147. Heederik D, Thorne PS, Doekes G. Health-based occupational exposure limits for high molecular weight sensitizers: how long is the road we must travel? *Ann Occup Hyg* 2002;46:439–446.
148. Newman Taylor A. Asthma and Work: The Colt Lecture, delivered at the Ninth International Symposium on Inhaled Particles, Cambridge, September 2001. *Ann Occup Hyg* 2002;46:563–574.
149. Heederik D, Venables KM, Malmberg P, Hollander A, Karlsson AS, Renstrom A, Doekes G, Nieuwenhijsen M, Gordon S. Exposure–response relationships for work-related sensitization in workers exposed to rat urinary allergens: results from a pooled study. *J Allergy Clin Immunol* 1999;103:678–684.
150. Houba R, Heederik DJ, Doekes G, van Run PE. Exposure–sensitization relationship for α-amylase allergens in the baking industry. *Am J Respir Crit Care Med* 1996;154:130–136.
151. Merget R, Kulzer R, Dierkes-Globisch A, Breitstadt R, Gebeler A, Kniffka A, Artelt S, Koenig HP, Alt F, Vormberg R, *et al.* Exposure–effect relationship of platinum salt allergy in a catalyst production plant: conclusions from a 5-year prospective cohort study. *J Allergy Clin Immunol* 2000;105:364–370.
152. Welinder H, Nielsen J, Rylander L, Stahlbom B. A prospective study of the relationship between exposure and specific antibodies in workers exposed to organic acid anhydrides. *Allergy* 2001;56:506–511.
153. Kristiansson MH, Lindh CH, Jonsson BA. Correlations between air levels of hexahydrophthalic anhydride (HHPA) and HHPA-adducted albumin tryptic peptides in nasal lavage fluid from experimentally exposed volunteers. *Rapid Commun Mass Spectrom* 2004;18:1592–1598.
154. Swanson MC. Immunochemical measurement of occupational aeroallergenic bioaerosols: determination of permissible exposure limits? Proceedings of the first Jack Pepys Occupational Asthma Symposium. *Am J Respir Crit Care Med* 2003;167:456–458.
155. Occupational Safety and Health Administration. OSHA Safety and Health Standards. 29 CFR 1910.1025. Revised March 1983.
156. Arts J, de Koning M, Bloksma N, Kuper C. Respiratory allergy to trimellitic anhydride in rats: concentration–response relationships during elicitation. *Inhal Toxicol* 2004;16:259–269.
157. Reed CE, Swanson MC, Li JTC. Environmental monitoring of protein aeroallergens. In: Bernstein IL, Chan-Yeung M, Malo JL, Bernstein DI, editors. Asthma in the workplace. New York: Marcel Dekker; 1999. pp. 235–255.
158. Quirce S, Swanson MC, Fernandez-Nieto M, de las Heras M, Cuesta J, Sastre J. Quantified environmental challenge with absorbable dusting powder aerosol from natural rubber latex gloves. *J Allergy Clin Immunol* 2003;111:788–794.
159. Perrault G, Lesage J. Exposure to chemical agents. Proceedings of the first Jack Pepys Occupational Asthma Symposium. *Am J Respir Crit Care Med* 2003;167:458–459.
160. Lesage J, Perrault G. Environmental monitoring of chemical agents. In: Bernstein IL, Chan-Yeung M, Malo JL, Bernstein DI, editors. Asthma in the workplace. New York: Marcel Dekker; 1999. pp. 257–277.
161. Heederik D, Doekes G, Nieuwenhuijsen MJ. Exposure assessment of high molecular weight sensitizers: contribution to occupational epidemiology and disease prevention. *Occup Environ Med* 1999;56:735–741.
162. Malo JL. Prevention of occupational asthma. Proceedings of the first Jack Pepys Occupational Asthma Symposium. *Am J Respir Crit Care Med* 2003;167:463–464.
163. Chan-Yeung M, Ashley MJ, Corey P, Wilson G, Dorken E, Grzybowski A. A respiratory survey of cedar mill workers. I. Prevalence of symptoms and pulmonary function abnormalities. *J Occup Med* 1978;20: 323–327.
164. Mapp CE, Boschetto P, Dal Vecchio L, Maestrelli P, Fabbri LM. Occupational asthma due to isocyanates. *Eur Respir J* 1988;1:273–279.
165. Gautrin D, Ghezzo H, Malo JL. Rhinoconjunctivitis, bronchial responsiveness, and atopy as determinants for incident non-work-related asthma symptoms in apprentices exposed to high-molecular-weight allergens. *Allergy* 2003;58:608–615.
166. Nguyen B, Ghezzo H, Malo JL, Gautrin D. Time course of onset of sensitization to common and occupational inhalants in apprentices. *J Allergy Clin Immunol* 2003;111:807–812.
167. Perfetti L, Hébert J, La Palme Y, Grezzo H, Gautrin D, Malo JL. Changes in IgE-mediated allergy to ubiquitous inhalants after removal from or diminution of the exposure to the agent causing occupational asthma. *Clin Exp Allergy* 1998;28:66–73.
168. Venables KM, Dally MB, Nunn AJ, Stevens JF, Stephens R, Farrer N, Hunter JV, Stewart M, Hughes EG, Newman Taylor AJ. Smoking and occupational allergy in workers in a platinum refinery. *BMJ* 1989; 299:939–942.
169. Venables KM, Topping MD, Howe W, Luczynska CM, Hawkins R, Newman Taylor AJ. Interaction of smoking and atopy in producing specific IgE antibody against a hapten protein conjugate. *BMJ* 1985; 290:201–204.
170. Calverely AE, Rees D, Dowdeswell RJ, Linnett PJ, Kielkowski D.

Platinum salt sensitivity in refinery workers: incidence and effects of smoking and exposure. *Occup Environ Med* 1995;52:661–666.
171. Sjaheim T, Halstensen TS, Lund MB, Bjortuft O, Drablos PA, Malterud D, Kongerud J. Airway inflammation in aluminium potroom asthma. *Occup Environ Med* 2004;61:779–785.
172. Mapp CE, Newman Taylor AJ. Occupational asthma with latency (sensitizer-induced occupational asthma): factors predisposing to sensitization, development and persistence of symptoms. Proceedings of the first Jack Pepys Occupational Asthma Symposium. *Am J Respir Crit Care Med* 2003;167:454–456.
173. Moscato G, Dellabianca A, Maestrelli P, Paggiaro PL, Romano C, De Zotti R, Marabini A, Voltolini S, Crippa M, Previdi M, *et al.* Features and severity of occupational asthma upon diagnosis: Italian multicentric case review. *Allergy* 2002;57:236–242.
174. Wai Y, Tarlo SM. Occupational lung disease in women. *Eur Respir Monogr* 2003;25:131–145.
175. Mendonca EM, Algranti E, Freitas JB, Rosa EA, Freire JA, Santos U, Ude P, Pinto J, Bussacos MA. Occupational asthma in the city of Sao Paulo, 1995–2000, with special reference to gender analysis. *Am J Ind Med* 2003;43:611–617.
176. Toren K, Balder B, Brisman J, Lindholm N, Lowhagen O, Palmqvist M, Tunsater A. The risk of asthma in relation to occupational exposures: a case-control study from a Swedish city. *Eur Respir J* 1999;13: 496–501.
177. El-Zein M, Malo JL, Infante-Rivard C, Gautrin D. Prevalence and association of welding related systemic and respiratory symptoms in welders. *Occup Environ Med* 2003;60:655–661.
178. Mapp CE, Saetta M, Maestrelli P, Ciaccia A, Fabbri LM. Low molecular weight pollutants and asthma: pathogenetic mechanisms and genetic factors. *Eur Respir J* 1994;7:1559–1563.
179. Taylor AN. Role of human leukocyte antigen phenotype and exposure in development of occupational asthma. *Curr Opin Allergy Clin Immunol* 2001;1:157–161.
180. Park HS, Frew AJ. Genetic markers for occupational asthma. *J Allergy Clin Immunol* 2002;109:774–776.
181. Newman Taylor AJ. HLA phenotype and exposure in development of occupational asthma. *Ann Allergy Asthma Immunol* 2003;90:24–27.
182. Mapp CE. The role of genetic factors in occupational asthma. *Eur Respir J* 2003;22:173–178.
183. Apter AJ. Early exposure to allergen: is this the cat's meow, or are we barking up the wrong tree? *J Allergy Clin Immunol* 2003;111:938–946.
184. Young RP, Barker RD, Pile KD, Cookson WOCM, Newman Taylor AJ. The association of HLA Dr3 with specific IgE to inhaled acid anhydrides. *Am J Respir Crit Care Med* 1995;151:219–221.
185. Bignon JS, Aron Y, Ly J, Kopferschmitt MC, Garnier R, Mapp CE, Fabbri LM, Pauli G, Lockhart A, Charron D, *et al.* HLA class II alleles in isocyanate-induced asthma. *Am J Respir Crit Care Med* 1994;149:71–75.
186. Mapp CE, Beghè B, Balboni A, Zamorani G, Padoan M, Jovine L, Baricordi OR, Fabbri LM. Association between HLA genes and susceptibility to toluene diisocyanate-induced asthma. *Clin Exp Allergy* 2000;30:651–656.
187. Horne C, Quintana PJE, Keown PA, Dimich-Ward H, Chan-Yeung M. Distribution of HLA class II DQB1 alleles in patients with occupational asthma due to western red cedar. *Eur Respir J* 2000;15:911–914.
188. Rihs HP, Chen Z, Rueff F, Cremer R, Raulf-Heimsoth M, Baur X, Moneret-Vautrin DA, Bruning T. HLA-DQ8 and the HLA-DQ8–DR4 haplotype are positively associated with the hevein-specific IgE immune response in health care workers with latex allergy. *J Allergy Clin Immunol* 2002;110:507–514.
189. Jeal H, Draper A, Jones M, Harris J, Welsh K, Newman Taylor A, Cullinan P. HLA associations with occupational sensitisation to rat lipocalin allergens: a model for other animal allergies? *J Allergy Clin Immunol* 2003;111:795–799.
190. Newman Taylor AJ, Cullinan P, Lympany PA, Harris JM, Dowdeswell RJ, du Bois RM. Interaction of HLA phenotype and exposure intensity in sensitisation to complex platinum salts. *Am J Respir Crit Care Med* 1999;160:435–438.
191. Rihs HP, Barbalho-Krolls T, Huber H, Baur X. No evidence for the influence of HLA class II alleles in isocyanate-induced asthma. *Am J Ind Med* 1999;32:522–527.
192. Bernstein JA, Munson J, Lummus ZL, Balakrishnan K, Leikauf G. T-cell receptor Vb gene segment expression in diisocyanate-induced occupational asthma. *J Allergy Clin Immunol* 1996;99:245–250.
193. Frew AJ. Advances in environmental and occupational disorders. *J Allergy Clin Immunol* 2003;111:S824–S828.
194. Mapp CE, Fryer AA, de Marzo N, Pozzato V, Padoan M, Boschetto P, Strange RC, Hemmingsen A, Spiteri MA. Glutathione *S*-transferase *GSTP1* is a susceptibility gene for occupational asthma induced by isocyanates. *J Allergy Clin Immunol* 2002;109:867–872.
195. Piirila P, Wikman H, Luukkonen R, Kaaria K, Rosenberg C, Nordman H, Norpaa H, Vainio H, Hirvonen A. Glutathione *S*-transferase genotypes in allergic responses to diisocyanate exposure. *Pharmacogenetics* 2001;11:437–445.
196. Wikman H, Piirila P, Rosenberg C, Luukkonen R, Kaaria K, Nordman H, Norppa H, Vainio H, Hirvonen A. *N*-acetyltransferase genotypes as modifiers of diisocyanate exposure-associated asthma risk. *Pharmacogenetics* 2002;12:227–233.
197. Beghè B, Padoan M, Moss CT, Barton SJ, Holloway JW, Holgate ST, Howell WM, Mapp CE. Lack of association of HLA class I genes and TNFα-308 polymorphism in toluene diisocyanate-induced asthma. *Allergy* 2004;59:61–64.
198. Arnaiz NO, Kaufman JD, Daroowalla FM, Quigley S, Farin F, Checkoway H. Genetic factors and asthma in aluminium smelter workers. *Arch Environ Health* 2003;58:197–200.
199. Burke W. Genomic medicine: genomics as a probe for disease biology. *N Engl J Med* 2003;349:969–974.
200. Ioannidis JP, Ntzani EE, Trikalinos TA, Contopoulos-Ioannidis DG. Replication validity of genetic association studies. *Nat Genet* 2001;29: 306–309.
201. Hirschhorn JN, Lohmueller K, Byrne E, Hirschhorn K. A comprehensive review of genetic association studies. *Genet Med* 2002;4:45–61.
202. Clayton EW. Genomic medicine: ethical, legal, and social implications of genomic medicine. *N Engl J Med* 2003;349:562–569.
203. Fabbri LM, Boschetto P, Caramori G, Mapp CE. Pathophysiology. In: Bernstein IL, Chan-Yeung M, Malo JL, Bernstein DI, editors. Asthma in the workplace. New York: Marcel Dekker; 1999. pp. 81–110.
204. Mapp CE, Saetta M, Maestrelli P, Fabbri LM. Occupational asthma. *Eur Respir Monogr* 1999;11:255–285.
205. Mapp CE, Boschetto P. Occupational asthma. *Eur Respir Monogr* 2003; 23:249–259.
206. Sastre J, Vandenplas O, Park HS. Pathogenesis of occupational asthma. *Eur Respir J* 2003;22:364–373.
207. Hendrick DJ, Burge PS. Asthma. In: Hendrick DJ, Burge PS, Beckett WS, Churg A, editors. Disorders of the airways, parenchyma, and pleura. London: W.B. Saunders; 2002. pp. 33–76.
208. Malo JL, Lemiere C, Gautrin D, Labrecque M. Occupational asthma. *Curr Opin Pulm Med* 2004;10:57–61.
209. Bardana EJ Jr. Occupational asthma and allergies. *J Allergy Clin Immunol* 2003;111:S530–S539.
210. Frew AJ. Advances in environmental and occupational diseases 2003. *J Allergy Clin Immunol* 2004;113:1161–1166.
211. Baur X, Czuppon A. Diagnostic validation of specific IgE antibody concentrations, skin prick testing, and challenge tests in chemical workers with symptoms of sensitivity to different anhydrides. *J Allergy Clin Immunol* 1995;96:489–494.
212. Biagini RE, Bernstein IL, Gallagher JS, Moorman WJ, Brooks S, Gann PH. The diversity of reaginic immune responses to platinum and palladium metallic salts. *J Allergy Clin Immunol* 1985;76:794–802.
213. Karol MH, Tollerud DJ, Campbell TP, Fabbri LM, Maestrelli P, Saetta M, Mapp CE. Predictive value of airways hyperresponsiveness and circulating IgE for identifying types of responses to toluene diisocyanate inhalation challenge. *Am J Respir Crit Care Med* 1994;149:611–615.
214. Chan-Yeung M. Mechanisms of occupational asthma due to western red cedar (*Thuja plicata*). *Am J Ind Med* 1994;25:13–18.
215. Chan-Yeung M. 2003 Christie Memorial lecture: occupational asthma—the past 50 years. *Can Respir J* 2004;11:21–26.
216. Frew AJ, Chan H, Dryden P, Salari H, Lam S, Chan-Yeung M. Immunologic studies of the mechanisms of occupational asthma caused by western red cedar. *J Allergy Clin Immunol* 1993;92:466–478.
217. Tee RD, Cullinan P, Welch J, Burge PS, Newman Taylor AJ. Specific IgE to isocyanates: a useful diagnostic role in occupational asthma. *J Allergy Clin Immunol* 1998;101:709–715.
218. Mapp CE, Polato R, Maestrelli P, Hendrick DJ, Fabbri LM. Time course of the increase in airway responsiveness associated with late asthmatic reactions to toluene diisocyanate in sensitized subjects. *J Allergy Clin Immunol* 1985;75:568–575.
219. Vandenplas O, Malo JL. Inhalation challenges with agents causing occupational asthma. *Eur Respir J* 1997;10:2612–2629.
220. Cartier A, Malo JL. Occupational challenge tests. In: Bernstein IL, Chan-Yeung M, Malo JL, Bernstein DI, editors. Asthma in the workplace. New York: Marcel Dekker; 1999. pp. 211–233.

221. Turato G, Saetta M. Why does airway obstruction persist in asthma due to low-molecular-weight agents? *Occup Med* 2000;15:445–453.
222. Saetta M, Di Stefano A, Maestrelli P, De Marzo N, Milani GF, Pivirotto F, Mapp CE, Fabbri LM. Airway mucosal inflammation in occupational asthma induced by toluene diisocyanate. *Am Rev Respir Dis* 1992;145:160–168.
223. Bentley AM, Maestrelli P, Saetta M, Fabbri LM, Robinson DS, Bradley BL, Jeffery PK, Durham SR, Kay AB. Activated T-lymphocytes and eosinophils in the bronchial mucosa in isocyanate-induced asthma. *J Allergy Clin Immunol* 1992;89:821–829.
224. Frew AJ, Chan H, Lam S, Chan-Yeung M. Bronchial inflammation in occupational asthma due to western red cedar. *Am J Respir Crit Care Med* 1995;151:340–344.
225. Maestrelli P, Di Stefano A, Occari P, Turato G, Milani GF, Pivirotto F, Mapp CE, Fabbri LM, Saetta M. Cytokines in the airway mucosa of subjects with asthma induced by toluene diisocyanate. *Am J Respir Crit Care Med* 1995;151:607–612.
226. Maestrelli P, Occari P, Turato G, Papiris SA, Di Stefano A, Mapp CE, Milani GF, Fabbri LM, Saetta M. Expression of interleukin (IL)-4 and IL-5 proteins in asthma induced by toluene diisocyanate (TDI). *Clin Exp Allergy* 1997;27:1291–1298.
227. Lummus ZL, Alam R, Bernstein JA, Bernsetin DI. Diisocyanate antigen-enhanced production of monocyte chemoattractant protein-1, IL-8, and tumor necrosis factor-α by peripheral mononuclear cells of workers with occupational asthma. *J Allergy Clin Immunol* 1998;102: 265–274.
228. Maestrelli P, Del Prete GF, De Carli M, D'Elios MM, Saetta M, Di Stefano A, Mapp CE, Romagnani S, Fabbri LM. CD8 T-cell clones produce interleukin-5 and interferon-γ in bronchial mucosa of patients with asthma induced by toluene diisocyanate. *Scand J Work Environ Health* 1994;20:376–381.
229. Ott VL, Cmabier JC, Kappler J, Marrack P, Swanson BJ. Mast cell-dependent migration of effector $CD8^+$ T cells through production of leukotriene B4. *Nat Immunol* 2003;4:974–981.
230. Zocca E, Fabbri LM, Boschetto P, Plebani M, Masiero M, Milani GF, Pivirotto F, Mapp CE. Leukotriene B4 and late asthmatic reactions induced by toluene diisocyanate. *J Appl Physiol* 1990;68:1576–1580.
231. Herrick CA, Das J, Xu L, Wisnewski AV, Redlich CA, Bottomly K. Differential roles for CD4 and CD8 T cells after diisocyanate sensitization: genetic control of T_H2-induced lung inflammations. *J Allergy Clin Immunol* 2003;111:1087–1094.
232. Lee YC, Song CH, Lee HB, Oh JL, Rhee YK, Park HS, Koh GY. A murine model of toluene diisocyanate-induced asthma can be treated with matrix metalloproteinase inhibitor. *J Allergy Clin Immunol* 2001; 108:1021–1026.
233. Malo JL. Irritant-induced asthma and reactive airways dysfunction syndrome. *Can Respir J* 1998;5:66–67.
234. Gautrin D, Boulet LP, Boutet M, Dugas M, Bhérer L, l'Archeveque J, Laviolette M, Cote J, Malo JL. Is reactive airways dysfunction syndrome a variant of occupational asthma? *J Allergy Clin Immunol* 1994;93:12–22.
235. Lemière C, Malo JL, Boutet M. Reactive airways dysfunction syndrome due to chlorine: sequential bronchial biopsies and functional assessment. *Eur Respir J* 1997;10:241–244.
236. Martin JG, Campbell HR, Iijma H, Gautrin D, Malo JL, Eidelman DH, Hamid Q, Maghni K. Chlorine-induced injury to the airways in mice. *Am J Respir Crit Care Med* 2003;168:568–574.
237. Karol MH, Loset HH, Alarie YC. Tolyl-specific IgE antibodies in workers with hypersensitivity to toluene diisocyanate. *Am Ind Hyg Assoc J* 1978;39:454–458.
238. Baur X, Dewier M, Fruhmann G. Detection of immunologically sensitised isocyanate workers by RAST and intracutaneous skin tests. *J Allergy Clin Immunol* 1984;73:610–618.
239. Park HS, Nahm DH. Isocyanate-induced occupational asthma: challenge and immunologic studies. *J Korean Med Sci* 1996;11:314–318.
240. Piirila PL, Nordman H, Keskinen HM, Luukkonen R, Salo SP, Tuomi TO, Tuppurainen M. Long-term follow-up of hexamethylene diisocyanate, diphenylmethane diisocyanate, and toluene diisocyanate-induced asthma. *Am J Respir Crit Care Med* 2000;162:516–522.
241. Son M, Lee M, Kim YT, Yoon JK, Park HS. Heterogeneity of IgE response to TDI–HSA conjugates by ELISA in toluene diisocyanate (TDI)-induced occupational asthma patients. *J Korean Med Sci* 1998; 13:147–152.
242. Park HS, Kim HY, Lee SK, Kim SS, Nahn DH. Diverse profiles of specific IgE response to toluene diisocyanate (TDI)–human serum albumin (HSA) conjugate in TDI-induced asthma patients. *J Korean Med Sci* 2000;16:57–61.
243. Park HS, Cho SH, Hong CS, Kim YY. Isocyanate-induced occupational asthma in far-east Asia: pathogenesis to prognosis. *Clin Exp Allergy* 2002;32:198–204.
244. Park HS, Lee SK, Lee YM, Kim SS, Nahm DH. Longitudinal study of specific antibodies to toluene diisocyanate (TDI)–human serum albumin (HSA) conjugate in patients with TDI-induced asthma. *Korean J Intern Med* 2002;17:249–251.
245. Park HS, Lee SK, Kim HY, Nahm DH, Kim SS. Specific immunoglobulin E and immunoglobulin G antibodies to toluene diisocyanate–human serum albumin conjugate: useful markers for predicting long-term prognosis in toluene diisocyanate-induced asthma. *Clin Exp Allergy* 2002;32:551–555.
246. Redlich CA, Stowe MH, Wisnewski AV, Eisen EA, Karol MH, Lemus R, Holm CT, Chung JS, Sparer J, Liu Y, *et al.* Subclinical immunologic and physiologic responses in hexamethylene diisocyanate-exposed autobody shop workers. *Am J Ind Med* 2001;39:587–597.
247. Park HS, Kim HY, Nahm DH, Son JW, Kim YY. Specific IgG, but not specific IgE, antibodies to toluene diisocyanate–human serum albumin conjugate are associated with toluene diisocyanate bronchoprovocation test results. *J Allergy Clin Immunol* 1999;104:847–851.
248. Park HS, Hong CS. The significance of specific IgG and IgG4 antibodies to a reactive dye in exposed subjects. *Clin Exp Allergy* 1991;21:357–362.
249. Zock JPG, Doekes D, Heederik D, van Zuylen M, Wielard P. Airborne dust antigen exposure and specific IgG response in the potato processing industry. *Clin Exp Allergy* 1996;26:542–548.
250. Yokata K, Yamaguchi K, Takeshita T, Morimoto K. The significance of specific IgG4 antibodies to methyltetrahydrophthalic anhydride in occupational exposed subjects. *Clin Exp Allergy* 1998;28:694–701.
251. Fabbri LM, Boschetto P, Zocca E, Dilani GF, Pivirotto F, Plebani M, Burlina A, Licata B, Mapp CE. Bronchoalveolar neutrophilia during late asthmatic reactions induced by toluene diisocyanate. *Am Rev Respir Dis* 1987;136:36–42.
252. Jatakanon A, Uasuf C, Maziak W, Lim S, Chung KF, Barnes PJ. Neutrophilic inflammation in severe persistent asthma. *Am J Respir Crit Care Med* 1999;160:1532–1539.
253. Lemière C, Romeo P, Chaboillez S, Tremblay C, Malo JL. Airway inflammation and functional changes after exposure to different concentrations of isocyanates. *J Allergy Clin Immunol* 2002;110:641–646.
254. Anees W, Huggins V, Pavord ID, Robertson AS, Burge PS. Occupational asthma due to low molecular weight agents: eosinophilic and non-eosinophilic variant. *Thorax* 2002;57:231–236.
255. Park HS, Hwang SC, Nahm DH, Yim HE. Immunohistochemical characterization of cellular infiltrate in airway mucosa of toluene diisocyanate-induced asthma. *J Korean Med Sci* 1998;13:12–16.
256. Park HS, Jung KS, Hwang SC, Nahm DH, Yim HE. Neutrophil activation following TDI bronchial challenges to the airway secretion from subjects with TDI-induced asthma. *Clin Exp Allergy* 1999;29:1395–1401.
257. Sastre J, Banks DE, Lopez M, Barkman HW, Salvaggio JE. Neutrophil chemotactic activity in toluene diisocyanate (TDI)-induced asthma. *J Allergy Clin Immunol* 1990;85:567–572.
258. Park HS, Jung KS, Hwang SC, Nahm DH, Yim HE. Neutrophil infiltration and release of IL-8 in airway mucosa from subjects with grain dust-induced occupational asthma. *Clin Exp Allergy* 1998;28:724–730.
259. Eduard W, Douwes J, Omenaas E, Heederik D. Do farming exposures cause or prevent asthma? Results from a study of adult Norwegian farmers. *Thorax* 2004;59:381–386.
260. Alwis KU, Mandryk J, Hocking AD. Exposure to biohazards in wood dust: bacteria, fungi, endotoxins, and (1→3)-β-D-glucans. *Appl Occup Environ Hyg* 1999;14:598–608.
261. Pacheco KA, McCammon C, Liu AH, Thorne PS, O'Neill ME, Martyny J, Newman LS, Hamman RF, Rose CS. Airborne endotoxin predicts symptoms in non-mouse-sensitized technicians and research scientists exposed to laboratory mice. *Am J Respir Crit Care Med* 2003;167:983–990.
262. Omland O. Exposure and respiratory health in farming in temperate zones: a review of the literature. *Ann Agric Environ Med* 2002;9:119–136.
263. Kongerud J, Boe J, Soyseth V, Naalsund A, Magnus P. Aluminum potroom asthma: the Norwegian experience. *Eur Respir J* 1994;7:165–172.
264. Kongerud J, Soyseth V, Burge S. Serial measurements of peak expiratory flow and responsiveness to methacholine in the diagnosis of aluminium potroom asthma. *Thorax* 1992;47:292–297.
265. Soyseth V, Kongerud J, Boe J, Fonneland T. Bronchial responsiveness and work-related asthma in aluminium potroom workers: effect of removal from exposure. *Eur Respir J* 1992;5:829–833.

266. Desjardins A, Bergeron JP, Ghezzo H, Cartier A, Malo JL. Aluminium potroom asthma confirmed by monitoring of forced expiratory volume in one second. *Am J Respir Crit Care Med* 1994;150:1714–1717.
267. Soyseth V, Kongerud J, Ekstrand J, Boe J. Relation between exposure to fluoride and bronchial responsiveness in aluminium potroom workers with work-related asthma-like symptoms. *Thorax* 1994;49:984–989.
268. Malo JL. Occupational asthma. *J Allergy Clin Immunol* 2001;108:317–328.
269. Gautrin D, Ghezzo H, Infant-Rivard C, Malo JL. Natural history of sensitization, symptoms and diseases in apprentices exposed to laboratory animals. *Eur Respir J* 2001;17:904–908.
270. Rodier F, Bautrin D, Ghezzo H, Malo JL. Incidence of occupational rhinoconjunctivitis and risk factors in animal-health apprentices. *J Allergy Clin Immunol* 2003;112:1105–1111.
271. Malo JL, Lemière C, Desjardins A, Cartier A. Prevalence and intensity of rhinoconjunctivitis in subjects with occupational asthma. *Eur Respir J* 1997;10:1513–1515.
272. Karjalainen A, Martikainen R, Klaukka T, Saarinen K, Uitti J. Risk of asthma among Finnish patients with occupational rhinitis. *Chest* 2003;123:283–288.
273. Fabbri LM, Danieli D, Crescioli S, Bevilacqua P, Meli S, Saetta M, Mapp CE. Fatal asthma in a subject sensitized to toluene diisocyanate. *Am Rev Respir Dis* 1988;137:1494–1498.
274. Ehrlich RI. Fatal asthma in a baker: a case report. *Am J Ind Med* 1994;26:799–802.
275. Ortega HG, Kreiss K, Schill DP, Weissman DN. Fatal asthma from powdering shark cartilage and review of occupational asthma literature. *Am J Ind Med* 2002;42:50–54.
276. Burge PS. Occupational asthma in electronics workers caused by colophony fumes: follow-up of affected workers. *Thorax* 1982;37:348–353.
277. Soyseth V, Kongerud J, Boe J, Fonneland T. Bronchial responsiveness and work-related asthma in aluminium potroom workers: effect of removal from exposure. *Eur Respir J* 1992;5:829–833.
278. Moscato G, Dellabianca A, Perfetti L, Brame B, Galdi E, Niniano R, Paggiaro PL. Occupational asthma: a longitudinal study on the clinical and socioeconomic outcome in workers with occupational asthma. *Chest* 1999;115:249–256.
279. Vandenplas O, Jamart J, Delwiche JP, Evrard G, Larbanois A. Occupational asthma caused by natural rubber latex: outcome according to cessation or reduction of exposure. *J Allergy Clin Immunol* 2002;109:125–130.
280. Lemière C, Cartier A, Dolovich J, Chan-Yeung M, Grammer L, Ghezzo H, l'Archeveque J, Malo JL. Outcome of specific bronchial responsiveness to occupational agents after removal from exposure. *Am J Respir Crit Care Med* 1996;154:329–333.
281. Lemière C, Cartier A, Malo JL, Lehrer SB. Persistent specific bronchial reactivity to occupational agents in workers with normal nonspecific bronchial reactivity. *Am J Respir Crit Care Med* 2000;162:976–980.
282. Lemière C. Persistence of bronchial reactivity to occupational agents after removal from exposure and identification of associated factors. *Ann Allergy Asthma Immunol* 2003;90:52–55.
283. Mapp CE, Chiesura Corona P, De Marzo N, Fabbri LM. Persistent asthma due to isocyanates: a follow-up study of subjects with occupational asthma due to toluene diisocyanate (TDI). *Am Rev Respir Dis* 1988;137:1326–1329.
284. Paggiaro PL, Bacci E, Dente FL, Talini D, Giuntini C. Prognosis of occupational asthma induced by isocyanates. *Bull Eur Physiopathol Respir* 1987;23:565–569.
285. Padoan M, Pozzato V, Simoni M, Zedda L, Milan G, Bononi I, Piola C, Maestrelli P, Boschetto P, Mapp CE. Long-term follow-up of toluene diisocyanate-induced asthma. *Eur Respir J* 2003;21:637–640.
286. Malo JL, Cartier A, Coté J, Milot J, Lablanc C, Paquette L, Ghezzo H, Boulet LP. Influence of inhaled steroids on the recovery of occupational asthma after cessation of exposure: an 18-month double-blind cross-over study. *Am J Respir Crit Care Med* 1996;153:953–960.
287. Chan-Yeung M, Leriche J, McLean L, Lam S. Comparison of cellular and protein changes in bronchial lavage fluid of symptomatic and asymptomatic patients with red cedar asthma on follow up examination. *Clin Allergy* 1988;18:359–365.
288. Saetta M, Maestrelli P, di Stefano A, de Marzo N, Milani GF, Pivirotto F, Mapp CE, Fabbri LM. Effect of cessation of exposure to toluene diisocyanate (TDI), on the bronchial mucosa of subjects with TDI-induced asthma. *Am Rev Respir Dis* 1992;145:169–174.
289. Saetta M, Maestrelli P, Turato G, Mapp CE, Milani GF, Pivirotto F, Fabbri LM, di Stefano A. Airway wall remodeling after cessation of exposure to isocyanates in sensitized asthmatic subjects. *Am J Respir Crit Care Med* 1995;151:489–494.
290. Paggiaro PL, Bacci E, Paoletti P, Bernard P, Dente FL, Marchetti G, Talini D, Menconi GF, Giuntini C. Bronchoalveolar lavage and morphology of the airways after cessation of exposure in asthmatic subjects sensitized to toluene diisocyanate. *Chest* 1990;98:536–542.
291. Boulet LP, Boutet M, Laviolette M, Dugas M, Milot J, Leblanc C, Paquette L, Cote J, Cartier A, Malo JL. Airway inflammation after removal from the causal agent in occupational asthma due to high and low molecular weight agents. *Eur Respir J* 1994;7:1567–1575.
292. Chu HW, Halliday JL, Martin RJ, Leung DYM, Szefler SJ, Wenzel SE. Collagen deposition in large airways may not differentiate severe asthma from milder forms of the disease. *Am J Respir Crit Care Med* 1998;158:1936–1944.
293. Niimi A, Matsumoto H, Takemura M, Ueda T, Chin K, Mishima M. Relationship of airway wall thickness to airway sensitivity and airway reactivity in asthma. *Am J Respir Crit Care Med* 2003;168:983–988.
294. Sont JK, Willems LN, Bel EH, van Krieken JH, Vandenbrouche JP, Sterk PJ, AMPUL Study Group. Clinical control and histopathologic outcome of asthma when using airway hyperresponsiveness as an additional guide to long-term treatment. *Am J Respir Crit Care Med* 1999;159:1043–1051.
295. Lange P, Parner J, Vestbo J, Schnohr P, Jensen G. A 15-year follow-up study of ventilatory function in adults with asthma. *N Engl J Med* 1998;339:1194–1200.
296. Barbato A, Turato G, Baraldo S, Bazzan E, Calabrese F, Tura M, Zuin R, Beghé B, Maestrelli P, Fabbri LM, *et al.* Airway inflammation in childhood asthma. *Am J Respir Crit Care Med* 2003;168:798–803.
297. Holgate ST. The 1992 Cournand lecture. Asthma: past, present and future. *Eur Respir J* 1993;6:1507–1520.
298. Bousquet J, Chanez P, Lacoste JY, White R, Vic P, Godard P, Michel FB. Asthma: a disease remodelling the airways. *Allergy* 1992;47:3–11.
299. Barnes PJ. Pathophysiology of asthma. *Eur Respir Monogr* 2003;2:84–113.
300. Bai TR, Knight DA. Role of the airway nervous system in airway remodelling. In: Howart PH, Wilson JW, Bousquet J, Rak S, Pauwels R, editors. Airway remodelling. New York: Marcel Dekker; 2001. pp. 147–165.
301. Joos GF, Geppetti P. Neural mechanisms in asthma. *Eur Respir Monogr* 2003;23:138–163.
302. D'Ambrosio D, Mariani M, Panina-Bordignon P, Sinigaglia F. Chemokines and their receptors guiding T lymphocytes recruitment in lung inflammation. *Am J Respir Crit Care Med* 2001;164:1266–1275.
303. D'Ambrosio D, Panina-Bordignon P, Sinigaglia F. Chemokine receptors in inflammation: an overview. *J Immunol Methods* 2003;273:3–13.
304. Zimmermann N, Hershey GK, Foster PS, Rothenberg ME. Chemokines in asthma: cooperative interaction between chemokines and IL-13. *J Allergy Clin Immunol* 2003;111:227–242.
305. Park HS, Kim HA, Jung JW, Kim JK, Lee SK, Kim SS, Nahma DH. Metalloproteinase-9 is increased in the induced sputum from patients with toluene diisocyanate-induced asthma. *Clin Exp Allergy* 2003;33:113–118.
306. Anees W. Use of pulmonary function tests in the diagnosis of occupational asthma. *Ann Allergy Asthma Immunol* 2003;90:47–51.
307. Moscato G, Malo JL, Bernstein D. Diagnosing occupational asthma: how, how much, how far? *Eur Respir J* 2003;21:879–885.
308. Malo JL, Ghezzo H, l'Archieveque J, Lagier F, Perrin B, Cartier A. Is the clinical history a satisfactory means of diagnosing occupational asthma? *Am Rev Respir Dis* 1991;143:528–532.
309. American Thoracic Society. Guidelines for methacholine and exercise challenge testing: 1999. *Am J Respir Crit Care Med* 2000;161:309–329.
310. Brusasco V, Crimi E. Methacholine provocation test for diagnosis of allergic respiratory diseases. *Allergy* 2001;56:1114–1120.
311. Peat JK, Unger WR, Combe D. Measuring changes in logarithmic data, with special reference to bronchial responsiveness. *J Clin Epidemiol* 1994;47:1099–1108.
312. Ramsdell JW, Nachtwey FJ, Moser KM. Bronchial hyperreactivity in chronic obstructive bronchitis. *Am Rev Respir Dis* 1982;126:829–832.
313. Gilbert R, Auchncloss JH. Post-test probability of asthma following methacholine challenge. *Chest* 1990;97:562–565.
314. Mapp CE, Dal Vecchio L, Boschetto P, De Marzo N, Fabbri LM. Toluene diisocyanate-induced asthma without airway hyperresponsiveness. *Eur Respir J* 1996;68:89–95.
315. Sastre J, Fernandez-Nieto M, Novalbos A, de Las Heras M, Cuesta J, Quirce S. Need for monitoring nonspecific bronchial hyperresponsiveness before and after isocyanate inhalation challenge. *Chest* 2003;123:1276–1279.
316. Vandenplas O, Delwiche JP, Jamart J, Van de Weyer R. Increase in nonspecific bronchial hyperresponsiveness as an early marker of bron-

chial response to occupational agents during inhalation challenges. *Thorax* 1996;51:472–478.
317. Bernstein DI. Clinical assessment of occupational asthma. In: Bernstein IL, Chan-Yeung M, Malo JL, Bernstein DI, editors. Asthma in the workplace. New York: Marcel Dekker; 1999. pp. 1451–1457.
318. Banks DE. Use of the specific challenge in the diagnosis of occupational asthma: a "gold standard" test or a test not used in current practice of occupational asthma? *Curr Opin Allergy Clin Immunol* 2003;3:101–107.
319. Cartier A. Investigation of occupational asthma. *Can Respir J* 1998;5: 71A–76A.
320. Hendrick DJ. Diagnostic tests for occupational asthma. *Am J Respir Crit Care Med* 2002;166:436–437.
321. Tarlo S, Vandenplas O. Diagnosis and management of occupational asthma. Proceedings of the first Jack Pepys Occupational Asthma Symposium. *Am J Respir Crit Care Med* 2003;167:460–462.
322. Wild LG, Lopez M. Occupational asthma caused by high-molecular-weight substances. *Immunol Allergy Clin North Am* 2003;23:235–250.
323. Bernstein DI. Occupational asthma caused by exposure to low-molecular-weight chemicals. *Immunol Allergy Clin North Am* 2003;23:221–234.
324. Newman Taylor AJ, Nicholson PJ, Cullinan P, Boyle C, Burge PS. Guidelines for the prevention, identification and management of occupational asthma: evidence review and recommendations. London: British Occupational Health Research Foundation; 2004.
325. Campo P, Lummus ZL, Bernstein DI. Advances in methods used in evaluation of occupational asthma. *Curr Opin Pulm Med* 2004;10: 142–146.
326. Boulay ME, Boulet LP. The relationships between atopy, rhinitis and asthma: pathophysiological considerations. *Curr Opin Allergy Clin Immunol* 2003;3:51–55.
327. Grammer LC, Ditto AM, Tripathi A, Harris KE. Prevalence and onset of rhinitis and conjunctivitis in subjects with occupational asthma caused by trimellitic anhydride (TMA). *J Occup Environ Med* 2002; 44:1179–1181.
328. Karjalainen A, Martikainen R, Klaukka T, Saarinen K, Uitti J. Risk of asthma among Finnish patients with occupational rhinitis. *Chest* 2003;123:283–288.
329. Miralles JC, Negro JM, Alonso JM, Garcia M, Sanchez-Gascon F, Soriano J. Occupational rhinitis and bronchial asthma due to TBTU and HBTU sensitization. *J Investig Allergol Clin Immunol* 2003;13:133–134.
330. Slavin RG. Occupational rhinitis. *Ann Allergy Asthma Immunol* 2003; 90:2–6.
331. Drake-Lee A, Ruckley R, Parker A. Occupational rhinitis: a poorly diagnosed condition. *J Laryngol Otol* 2002;116:580–585.
332. Petrick MM, Slavin RG. Occupational rhinitis. *Immunol Allergy Clin North Am* 2003;23:193–203.
333. Pauli G, Birba NE. Recent developments in airways and nose occupational sensitizers. *Curr Opin Allergy Clin Immunol* 2003;3:95–100.
334. Dykewicz MS. Rhinitis and sinusitis. *J Allergy Clin Immunol* 2003;111: S520–S529.
335. De Meer G, Postma DS, Heederik D. Bronchial responsiveness to adenosine-5′-monophosphate and methacholine as predictors for nasal symptoms due to newly introduced allergens: a follow-up study among laboratory animal workers and bakery apprentices. *Clin Exp Allergy* 2003;33:789–794.
336. Baur X, Huber H, Degens PO, Allmers H, Ammon J. Relation between occupational asthma case history, bronchial methacholine challenge, and specific challenge test in patients with suspected occupational asthma. *Am J Ind Med* 1998;33:114–122.
337. Vandenplas O, Binard-Van Cangh F, Brumagne A, Caroyer JM, Thimpont J, Sohy C, Larbanois A, Jamart J. Occupational asthma in symptomatic workers exposed to natural rubber latex: evaluation of diagnostic procedures. *J Allergy Clin Immunol* 2001;107:542–547.
338. Stenton SC, Beach JR, Avery AJ, Hendrick DJ. Asthmatic symptoms, airway responsiveness and recognition of bronchoconstriction. *Respir Med* 1995;89:181–185.
339. Moscato G, Godnic-Cvar J, Maestrelli P, Malo JL, Burge PS, Coifman R, Subcommittee on Occupational Asthma of the European Academy of Allergy and Clinical Immunology. Statement on self-monitoring of peak expiratory flows in the investigation of occupational asthma. *Eur Respir J* 1995;8:1605–1610.
340. Leroyer C, Perfetti L, Trudeau C, l'Archeveque J, Chan-Yeung M, Malo JL. Comparison of serial monitoring of peak expiratory flow and FEV_1 in the diagnosis of occupational asthma. *Am J Respir Crit Care Med* 1998;158:827–832.
341. Baldwin DR, Gannon P, Bright P, Newton DT, Robertson A, Venables K, Graneek B, Barker RD, Cartier A, Malo JL, *et al.* Interpretation of occupational peak flow records: level of agreement between expert clinicians and Oasys-2. *Thorax* 2002;57:860–864.
342. Anees W, Gannon PF, Huggins V, Pantin CF, Burge PS. Effect of peak expiratory flow data quantity on diagnostic sensitivity and specificity in occupational asthma. *Eur Respir J* 2004;23:730–734.
343. Coté J, Kennedy S, Chan-Yeung M. Outcome of patients with cedar asthma with continuous exposure. *Am Rev Respir Dis* 1990;141:373–376.
344. Ortega HG, Weissman DN, Carter DL, Banks D. Use of specific inhalation challenge in the evaluation of workers at risk for occupational asthma: a survey of pulmonary, allergy and occupational medicine residency training programs in the United States and Canada. *Chest* 2002;121:1323–1328.
345. Tan RA, Spector SL. Provocation studies in the diagnosis of occupational asthma. *Immunol Allergy Clin North Am* 2003;23:251–267.
346. Tarlo SM. Laboratory challenge testing for occupational asthma. *J Allergy Clin Immunol* 2003;111:692–693.
347. Banks DE, Tarlo SM, Masri F, Rando R, Weissman DN. Bronchoprovocation tests in the diagnosis of isocyanate-induced asthma. *Chest* 1996;109:1370–1379.
348. Stenton SC. Determinants of whether occupational agents cause early, late, or dual asthmatic responses. *Occup Med* 2000;15:431–444.
349. Stenton SC, Avery AJ, Walters EH, Hendrick DJ. Statistical approach to the identification of late asthmatic reactions. *Eur Respir J* 1994;7: 806–812.
350. Matthews JNS, Altman DG, Campbell MJ, Royston P. Analysis of serial measurements in medical research. *BMJ* 1990;300:230–235.
351. Malo JL, Cartier A, Lemiere C, Desjardins A, Labrecque M, l'Archeveque J, Perrault G, Lesage J, Cloutier Y. Exaggerated bronchoconstriction due to inhalation challenges with occupational agents. *Eur Respir J* 2004;23:300–333.
352. Grammar L, Shaughnessy M, Kenamore B. Utility of antibody in identifying individuals who have or will develop anhydride-induced respiratory disease. *Chest* 1998;114:1199–1202.
353. Bernstein JA, Bernstein DI, Stauder T, Lummus Z, Bernstein IL. A cross-sectional survey of sensitization to *Aspergillus oryzae*-derived lactase in pharmaceutical workers. *J Allergy Clin Immunol* 1999;103: 1153–1157.
354. Hamilton RG, Adkinson NF. Diagnosis of natural rubber allergy: multicenter latex skin testing efficacy study. *J Allergy Clin Immunol* 1998;102:482–490.
355. Bernstein DI, Cartier A, Coté J, Malo JL, Boulet LP, Wanner M, Mi J, l'Archeveque J, Trudeau C, Lummus Z. Diisocyanate antigen-stimulated monocyte chemoattractant protein-1 synthesis has greater test efficiency than specific antibodies for identification of diisocyanate asthma. *Am J Respir Crit Care Med* 2002;166:445–450.
356. Gautrin D, Ghezzo H, Infante-Rivard C, Malo JL. Host determinants for the development of allergy in apprentices exposed to laboratory animnals. *Eur Respir J* 2002;19:96–103.
357. Brown WE, Burkert AL. Biomarkers of toluene diisocyanate exposure. *Appl Occup Environ Hyg* 2002;17:840–845.
358. Merget R, Schultze-Werninghaus G, Bode F, Bergmann EM, Zachgo W, Meier-Sydow J. Quantitative skin prick and bronchial provocation tests with platinum salts. *Br J Ind Med* 1991;48:830–837.
359. Perfetti L, Brame B, Ferrari M, Moscato G. Occupational asthma (OA) with sensitization to diphenylmethane diisocyanate (MDI) presenting at the onset as a reactive airways dysfunction syndrome (RADS). *Am J Ind Med* 2003;44:325–328.
360. Lemière C. Non-invasive assessment of airway inflammation in occupational lung diseases. *Curr Opin Allergy Clin Immunol* 2002;2:109–114.
361. Vignola AM, Rennar SI, Hargreave FE, Fah JV, Bonsignore MR, Djukanovic R, Sterk PJ. Standardized methodology of sputum induction and processing. *Eur Respir J Suppl* 2002;37:51s–55s.
362. Pizzichini E, Pizzichini MM, Efthimiadis A, Evans S, Morris M, Squillace D, Gleich GJ, Dolovich J, Hargreave FE. Indices of airway inflammation in induced sputum: reproducibility and validity of cell and fluid-phase measurements. *Am J Respir Crit Care Med* 1996;154:308–317.
363. Pavord ID, Pizzichini MM, Pizzichini E, Hargreave FE. The use of induced sputum to investigate airway inflammation. *Thorax* 1997;52: 498–501.
364. Kips JC, Kharitonov SA, Barnes PJ. Noninvasive assessment of airway inflammation in asthma. *Eur Respir Monogr* 2003;23:164–179.
365. Gibson PG, Saltos N, Kakes K. Acute anti-inflammatory effects of inhaled budesonide in asthma: a randomized controlled trial. *Am J Respir Crit Care Med* 2001;163:32–36.

366. Park H, Jung K, Kim H, Nahm D, Kang K. Neutrophil activation following TDI bronchial challenges to airway secretion from subjects with TDI-induced asthma. *Clin Exp Allergy* 1999;29:1395–1401.
367. Jung KS, Park HS. Evidence for neutrophil activation in occupational asthma. *Respirology* 1999;4:303–306.
368. Maestrelli P, Calcagni P, Saetta M, di Stefano A, Hosselet J, Santonastaso A, Fabbri LM, Mapp CE. Sputum eosinophilia after asthmatic responses induced by isocyanates in sensitized subjects. *Clin Exp Allergy* 1994;24:29–34.
369. Di Franco A, Vagaggini B, Bacci E, Bartoli ML, Cianchetti S, Carnevali S, Dente FL, Giannini D, Macchioni P, Ruoco L, *et al.* Leukocyte counts in hypertonic saline-induced sputum in subjects with occupational asthma. *Respir Med* 1998;92:550–557.
370. Lemière C, Pizzichini MM, Balkissoon R, Clelland L, Efthimiadis A, O'Shaughnessy D, Dolovich J, Hargreave FE. Diagnosing occupational asthma: use of induced sputum. *Eur Respir J* 1999;13:482–488.
371. Maestrelli P, Saetta M, Di Stefano A, Calcagni PG, Turato G, Ruggieri MP, Roggeri A, Mapp CE, Fabbri LM. Comparison of leukocyte counts in sputum, bronchial biopsies and bronchoalveolar lavage. *Am J Respir Crit Care Med* 1995;152:1926–1931.
372. Lemière C, Chaboillez S, Trudeau C, Taha R, Maghni K, Martin JG, Hamid Q. Characterization of airway inflammation after repeated exposures to occupational agents. *J Allergy Clin Immunol* 2000;106: 1163–1170.
373. Panzer SE, Dodge AM, Kelly EAB, Jarjour N. Circadian variation of sputum inflammatory cells in mild asthma. *J Allergy Clin Immunol* 2003;111:308–312.
374. Girard F, Chaboillez S, Cartier A, Cote J, Hargreave FE, Labrecque M, Malo JL, Tarlo SM, Lemière C. An effective strategy for diagnosing occupational asthma: use of induced sputum. *Am J Respir Crit Care Med* 2004;170:845–850.
375. Lemière C, Chaboillez S, Malo JL, Cartier A. Changes in sputum cell counts after exposure to occupational agents: what do they mean? *J Allergy Clin Immunol* 2001;107:1063–1068.
376. Chan-Yeung M, Obata H, Dittrich M, Chan H, Abboud R. Airway inflammation, exhaled nitric oxide, and severity of asthma in patients with western red cedar asthma. *Am J Respir Crit Care Med* 1999; 159:1434–1438.
377. Obata H, Dittrich M, Chan H, Chan Yeung M. Sputum eosinophils and exhaled nitric oxide during late asthmatic reactions in patients with western red cedar asthma. *Eur Respir J* 1999;13:489–495.
378. Bates CA, Silkoff PE. Exhaled nitric oxide in asthma: from bench to bedside. *J Allergy Clin Immunol* 2003;111:256–262.
379. Alving K, Weitzberg E, Lundberg J. Increased amount of nitric oxide in exhaled air of asthmatics. *Eur Respir J* 1993;6:1368–1370.
380. Kharitonov S, O'Connor B, Evans D, Barnes P. Allergen-induced late asthmatic reactions are associated with elevation of exhaled nitric oxide. *Am J Respir Crit Care Med* 1995;151:1894–1899.
381. Baur X, Barbinova L. Latex allergen exposure increases exhaled nitric oxide in symptomatic healthcare workers. *Eur Respir J* 2005;25:309–316.
382. Adisesh LA, Kharitonov SA, Yates DH, Snashell DC, Newman Taylor AJ, Barnes PJ. Exhaled and nasal nitric oxide is increased in laboratory animal allergy. *Clin Exp Allergy* 1998;28:876–880.
383. Allmers H, Chen Z, Barbinova L, Marczynski B, Kirschmann V, Baur X. Challenge from methacholine, natural rubber latex, or 4,4-diphenylmethane diisocyanate in workers with suspected sensitization affects exhaled nitric oxide (change in exhaled NO levels after allergen challenges). *Int Arch Occup Environ Health* 2000;73:181–186.
384. Lund MB, Oksnel PI, Hamre R, Kongerud J. Increased nitric oxide in exhaled air: an early marker of asthma in non-smoking aluminium potroom workers? *Occup Environ Med* 2000;57:274–278.
385. Olin AC, Ljungkvist G, Bake B, Hagberg S, Henriksson L, Toren K. Exhaled nitric oxide among pulpmill workers reporting gassing incidents involving ozone and chlorine dioxide. *Eur Respir J* 1999;14:828–831.
386. Piipari R, Piirila P, Keskinen H, Tuppurainen M, Sovijarvi A, Nordman H. Exhaled nitric oxide in specific challenge tests to assess occupational asthma. *Eur Respir J* 2002;20:1532–1537.
387. Lundberg JO, Farkas-Szallasi T, Weitzberg E, Rinder J, Lidholm J, Anggaard A, Hokfelt T, Lundberg JM, Alving K. High nitric oxide production in human paranasal sinuses. *Nat Med* 1995;1:370–373.
388. Lundberg JO, Weitzberg E, Lundberg JM, Alving K. Intragastric nitric oxide production in humans: measurements in expelled air. *Gut* 1994; 35:1543–1545.
389. Olin AC, Alving K, Toren K. Exhaled nitric oxide: relation to sensitization and respiratory symptoms. *Clin Exp Allergy* 2004;34:221–226.
390. Corradi M, Folesani G, Andreoli R, Manini P, Bodini A, Piacentini G, Carraro S, Zanconato S, Baraldi E. Aldheydes and glutathione in exhaled breath condensate of children with asthma exacerbation. *Am J Respir Crit Care Med* 2003;167:395–399.
391. Antczak A, Gorski P. Markers of pulmonary diseases in exhaled breath condensate. *Int J Occup Med Environ Health* 2002;15:317–323.
392. Krakowiak A, Ruta U, Gorski P, Kowalska S, Palczynski C. Nasal lavage fluid examination and rhinomanometry in the diagnostics of occupational airway allergy to laboratory animals. *Int J Occup Med Environ Health* 2003;16:125–132.
393. Taivainen AI, Tukiainen HO, Terho EO, Husman KR. Powered dust respirator helmets in the prevention of occupational asthma among farmers. *Scand J Work Environ Health* 1998;24:503–507.
394. Obase Y, Shimoda T, Mitsuta K, Matsuse H, Kohno S. Two patients with occupational asthma who returned to work with dust respirators. *Occup Environ Med* 2000;57:62–64.
395. American Thoracic Society. Respiratory protection guidelines. *Am J Respir Crit Care Med* 1996;154:1153–1165.
396. Gallefoss F, Bakke PS. Does smoking affect the outcome of patient education and self-management in asthmatics? *Patient Educ Couns* 2003;49:91–97.
397. U.S. Department of Health and Human Services, National Institutes of Health, National Heart, Lung, and Blood Institute. Global Initiative for Asthma: Global Strategy for Asthma Management and Prevention. Washington, DC: U.S. Government Printing Office; 2002. NIH Publication No. 02-3659.
398. Marabini A, Ward H, Kwan S, Kennedy S, Wexler-Morrison N, Chan-Yeung M. Clinical and socioeconomical features of subjects with red cedar asthma: a follow-up study. *Chest* 1993;104:821–824.
399. Moscato G, Dellabianca A, Perfetti L, Brame B, Galdi E, Niniano R, Paggiaro PL. Occupational asthma: a longitudinal study on the clincal and socioeconomic outcome after diagnosis. *Chest* 1999;115:249–256.
400. Marabini A, Siracusa A, Stopponi R, Tacconi C, Abbritti G. Outcome of occupational asthma in patients with continuous exposure: a 3-year longitudinal study during pharmacologic treatment. *Chest* 2003;124: 2372–2376.
401. Burton WN, Morrison A, Wertheimer AI. Pharmaceuticals and worker productivity loss: a critical revision of the literature. *J Occup Environ Med* 2003;45:610–621.
402. Leynadier F, Herman D, Vervloet D, Andre C. Specific immunotherapy with a standardized latex extract versus placebo in allergic healthcare workers. *J Allergy Clin Immunol* 2000;106:585–590.
403. Sastre J, Fernadez-Nieto M, Rico P, Martin S, Barber D, Cuesta J, de Las Hera M, Quirce S. Specific immunotherapy with a standardized latex extract in allergic workers: a double-blind, placebo-controlled study. *J Allergy Clin Immunol* 2003;111:985–994.
404. American Medical Association. The respiratory system. In: Cocchiarella L, Andersson GBJ, editors. Guides to the evaluation of permanent impairment, 5th ed. Chicago, IL: American Medical Association Press; 2000.
405. American Thoracic Society. Guidelines for the evaluation of impairment/disability in patients with asthma. *Am Rev Respir Dis* 1993; 147:1056–1061.
406. Moscato G, Rampulla C. Costs of occupational asthma and of occupational chronic obstructive pulmonary disease. *Curr Opin Allergy Clin Immunol* 2003;3:109–114.
407. Leigh JP, Yasmeen S, Miller TR. Medical costs of fourteen occupational illnesses in the United States in 1999. *Scand J Work Environ Health* 2003;29:304–313.
408. Bernstein DI, Karnani R, Biagini RE, Bernstein CK, Murphy K, Berendts B, Bernstein JA, Bernstein L. Clinical and occupational outcomes in health care workers with natural rubber latex allergy. *Ann Allergy Asthma Immunol* 2003;90:209–213.
409. Ameille J, Parion JC, Bayeux MC, Brochard P, Choudat D, Conso F, Devienne A, Garnier R, Iwatsubo Y. Consequences of occupational asthma on employment and financial status: a follow-up study. *Eur Respir J* 1997;10:55–58.
410. Allmers H, Schmengler J, Skudlik C. Primary prevention of natural rubber latex allergy in the German health care system through education and intervention. *J Allergy Clin Immunol* 2002;110:318–323.
411. Maghni K, Lemière C, Ghezzo H, Yuquan W, Malo JL. Airway inflammation after cessation of exposure to agents causing occupational asthma. *Am J Respir Crit Care Med* 2004;169:367–372.
412. Malo JL, Blanc P. Occupational lung disease: issues in management. *Eur Respir Monogr* 1999;11:106–123.
413. Cullinan P, Tarlo S, Nemery B. The prevention of occupational asthma. *Eur Respir J* 2003;22:853–860.

414. Gordon S, Preece R. Prevention of laboratory animal allergy. *Occup Med* 2003;53:371–377.
415. Jaakkola MS, Samet JM. Summary: workshop on health risks attributable to ETS exposure in the workplace. *Environ Health Perspect* 1999;108:823–828.
416. Houba R, Heederik D, Doekes G. Wheat sensitization and work-related symptoms in the baking industry are preventable. An epidemiologic study. *Am J Respir Crit Care Med* 1998;158:1499–1503.
417. Graham C, Rosenkranz HS, Karol MH. Structure–activity model of chemicals that cause human respiratory sensitization. *Regul Toxicol Pharmacol* 1997;26:296–306.
418. Rodford R, Patlewicz G, Walker JD, Payne MP. Quantitative structure–activity relationships for predicting skin and respiratory sensitization. *Environ Toxicol Chem* 2003;22:1855–1861.
419. Kimber I, Dearman RJ. What makes a chemical an allergen? *Ann Allergy Asthma Immunol* 2003;90:28–31.
420. Dearman RJ, Skinner RA, Humphreys NE, Kimber I. Methods for the identification of chemical respiratory allergens in rodents: comparisons of cytokine profiling with induced changes in serum IgE. *J Appl Toxicol* 2003;23:199–207.
421. Lantz RC, Lemus R, Lange RW, Karol MH. Rapid reduction of intracellular glutathione in human bronchial epithelial cells exposed to occupational levels of toluene diisocyanate. *Toxicol Sci* 2001;60:348–355.
422. Redlich CA, Karol MH, Graham C, Homer RJ, Holm CT, Wirth JA, Cullen MR. Airway isocyanate adducts in asthma induced by exposure to hexamethylene diisocyanate. *Scand J Work Environ Health* 1997;23:227–231.
423. Wisnewski AV, Lemus R, Karol MH, Redlich CA. Isocyanate-conjugated human lung epithelial cell proteins: a link between exposure and asthma? *J Allergy Clin Immunol* 1999;104:341–347.
424. Wisnewski AV, Srivastava R, Herick C, Xu L, Lemus R, Chain H, Magoski NM, Karol MH, Bottomly K, Redlich CA. Identification of human lung and skin proteins conjugated with hexamethylene diisocyanate *in vitro* and *in vivo*. *Am J Respir Crit Care Med* 2000; 162:2330–2336.
425. Wisnewski AV, Stowe MH, Cartier A, Liu Q, Liu J, Chen L, Redlich CA. Isocyanate vapor-induced antigenicity of human albumin. *J Allergy Clin Immunol* 2004;113:1178–1184.
426. Liss GM, Kominsky JR, Gallagher JS, Melius J, Brooks SM, Bernstein IL. Failure of enzyme encapsulation to prevent sensitisation of workers in the dry bleach industry. *J Allergy Clin Immunol* 1984;73:348–355.
427. Tarlo SM, Sussman G, Contala A, Swanson M. Control of airborne latex by the use of powder-free latex gloves. *J Allergy Clin Immunol* 1994;93:985–989.
428. Charous BL, Blanco C, Tarlo S, Hamilton RG, Baur X, Beezhold D, Sussman G, Yunginger JW. Natural rubber latex allergy after 12 years: recommendations and perspectives. *J Allergy Clin Immunol* 2002;109: 31–34.
429. Charous BL, Tarlo SM, Charous MA, Kelly K. Natural rubber allergy in the occupational setting. *Methods* 2002;27:15–21.
430. Cullinan P, Harris JM, Newman Taylor AJ, Hole AM, Jones M, Barnes F, Jolliffe G. An outbreak for asthma in a modern detergent factory. *Lancet* 2000;356:1899–1900.
431. Malmberg P. Airway allergy and worklife: consensus report. *Scand J Work Environ Health* 2001;27:422–425.
432. Kraw M, Tarlo SM. Isocyanate medical surveillance: respiratory referrals from a foam manufacturing plant over a five year period. *Am J Ind Med* 1999;35:87–91.
433. Merget R, Caspari C, Dierkes-Globisch A, Kulzer R, Breitstadt R, Kniffa A, Degens P, Schultze-Werminghaus G. Effectiveness of a medical surveillance program for the prevention of occupational asthma caused by platinum salts: a nested case-control study. *J Allergy Clin Immunol* 2003;107:707–712.
434. Tarlo SM, Banks DE, Liss G, Broder I. Outcome determinants for isocyanate induced occupational asthma among compensation claimants. *Occup Environ Med* 1997;54:756–761.
435. Tarlo SM, Liss GM. Diisocyanate-induced asthma: diagnosis, prognosis, and effectiveness of medical surveillance measures. *Appl Occup Environ Hyg* 2002;17:902–908.
436. Smith TA. Preventing baker's asthma: an alternative strategy. *Occup Med* 2004;54:21–27.
437. Jones KP, Rolf S, Stingl C, Edmunds D, Davies BH. Longitudinal study of sensitization to natural rubber latex among dental school students using powder-free gloves. *Ann Occup Hyg* 2004;48:455–457.
438. Tarlo SM. Can medical surveillance measures improve the outcome of occupational asthma? *J Allergy Clin Immunol* 2001;107:583–585.
439. Murphy E, Harrison J, Beach J. Implementation of statutory occupational respiratory health surveillance. *Occup Med* 2002;52:497–502.
440. Goodno LE, Stave GM. Primary and secondary allergies to laboratory animals. *J Occup Environ Med* 2002;44:1143–1152.
441. Hallsworth MP, Major PJ, Barnes J, Lee TH. What are the priorities in basic asthma research? A UK perspective. *J Allergy Clin Immunol* 2003;111:251–255.
442. Jones MG, Nielsen J, Welch J, Harris J, Welinder H, Bensryd I, Skerfving S, Welsh K, Venables KM, Taylor AN. Association of HLA-DQ5 and HLA-DR1 with sensitisation to organic acid anhydrides. *Clin Exp Allergy* 2004;34:812–816.
443. Choi JH, Nahm DH, Kim SH, Kim YS, Suh CH, Park HS, Ahn SW. Increased levels of IgG to cytokeratin 19 in sera of patients with toluene diisocyanate-induced asthma. *Ann Allergy Asthma Immunol* 2004;93:293–298.