Occupational asthma – The past 50 years

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It was indeed a great honour for me to be this year's Christie Memorial Lecturer. Although I have not been fortunate enough to have had personal contact with Professor Christie, one of the greatest lung physiologists of our time, I have had the opportunity over the years of interacting with and learning from the group working in the laboratory named after him – the Meakins-Christie Laboratories – as a member of the Respiratory Health Network of Centres of Excellence, Canada.

I have chosen to discuss the advances and development of occupational asthma in the following areas in the past 50 years: agents responsible and pathogenic mechanisms, diagnostic methods, natural history, epidemiology, compensation and impairment evaluation issues, and prevention.

Occupational disease came of age when Ramazzini (1) published his great classic – *De Morbis Artificum Diatriba* – in 1713. It contained important contributions to occupational respiratory disease. He was often attributed to be the first one to describe grain dust asthma, although as early as 1555, Olaus Magus wrote about disease due to the threshing of grain (2).

If Ramazzini was known as the 'father' of occupational medicine, Jack Pepys should be called the 'father' of occupational asthma. By using a simulated, occupational-type of exposure testing, he identified and confirmed many agents responsible for asthma. In addition to his academic achievements, Jack Pepys also trained several students who have successfully carried on with his research in asthma and occupational asthma, and they have chosen Canada to be their home. Among them are Freddy Hargreave, Jean-Luc Malo, Dan McCarthy and myself.

AGENTS AND THEIR PATHOGENIC MECHANISMS

Many agents responsible for occupational asthma have been described since the time of Ramazzini. By 1999, over 300 agents have been found that can cause occupational asthma (3). Two agents of special interest are diisocyanates and plicatic acid. Both diisocyanates and plicatic acid are small molecular weight compounds, and the pathogenic mechanisms responsible for asthma arising from these two compounds are almost identical. They are of interest because diisocyanates are the most common agents responsible for occupational asthma, and as a result, an investigator may encounter a number of cases for which careful investigations must be carried out. Plicatic acid is the chemical compound responsible for Western red cedar

asthma (4). I have studied Western red cedar asthma for a good part of my research career. For this reason, I have drawn heavily on the findings of the model of Western red cedar asthma in the following discussion.

The Western red cedar tree is prevalent in the Pacific Northwest. Plicatic acid has a molecular weight of 400 daltons (5) and is found uniquely in the Western red cedar (*Thuja plicata*). Workers in sawmills, the construction industry and furniture factories in the Pacific Northwest are commonly exposed to the dust of this wood. It has been known for a long time that asthma is common among these workers. Typically, they present with a history of cough and difficulty breathing after working hours and at night, with improvement of symptoms during weekends and holidays during the early stages of the illness. As the disease becomes more advanced, there is no remission of symptoms, even when the patient has been away from work for a long period of time (6).

In 1970, my colleagues and I challenged the first patient with Western red cedar dust using the simulated type of occupational exposure testing – he developed a typical isolated asthmatic reaction, thus reproducing the symptoms experienced by the patient. As a control test, he did not react to challenge testing with Douglas fir dust (7).

The major nonvolatile component of Western red cedar extractives is plicatic acid, which accounts for about 70% to 80% of the weight (5). To find out which component in the wood causes asthma, my colleagues and I were able to obtain relatively pure plicatic acid from Western Forest Laboratories (Vancouver, British Columbia) for inhalation testing. Patients who reacted to crude cedar dust extract on inhalation testing reacted in the same way to plicatic acid. On the other hand, asthmatic patients with no history of exposure to cedar dust did not react to either the crude cedar dust extract or the plicatic acid. We concluded that plicatic acid is probably the most important chemical responsible for cedar dust asthma (4).

In the following years, my colleagues and I were able to amass a list of over 100 patients with Western red cedar asthma confirmed by inhalation challenge testing. A clear clinical picture then emerged. In contrast to patients with allergic asthma, patients with Western red cedar asthma were mostly nonatopic and nonsmokers. Isolated, late asthmatic reactions occurred in 43% of the patients, biphasic reactions occurred in approximately one-half of the patients and isolated, immediate asthmatic reactions occurred in less than 10% of the patients (6).

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Figure 1) Classification of occupational asthma. HMW High molecular weight; IgE Immunoglobulin E; LMW Low molecular weight; RADS Reactive airways dysfunction syndrome

Patients with diisocyanate-induced asthma share the same clinical picture (8).

My colleagues and I began to investigate how this small chemical compound induces asthma. We found that it combines with human serum albumin or bovine serum albumin to form a conjugate. Using this conjugate, we were able to detect specific immunoglobulin (Ig) E antibodies in approximately only 20% of patients proven to have a specific reaction to plicatic acid, but not in unexposed controls nor in those with a negative reaction to challenge testing (9). Skin testing using the crude extract or the conjugate did not produce any positive skin test reaction. Despite the high proportion of patients with negative specific IgE antibodies and negative skin test reactions to the conjugate, we thought that the mechanism was likely to be an immunological one because of the latency period between the onset of exposure and the onset of symptoms, as well as the specificity of the reaction.

By the 1980s, fiber optic bronchoscopy became available. My colleagues and I performed bronchoalveolar lavage (BAL) during late asthmatic reactions in patients with Western red cedar asthma and found that there were significantly higher percentages of eosinophils, epithelial cells and degenerated cells in the BAL of these patients compared with healthy subjects. These findings are similar to patients with allergic asthma after inhalation challenge testing (10). Bronchial biopsy of a patient during a late asthmatic reaction showed cellular infiltration with eosinophils, sloughing of the epithelium and marked thickening of the basement membrane, as in patients with allergic asthma. In a later study, we stained bronchial mucosa with monoclonal antibodies and demonstrated significantly increased CD3 and CD4 cells compared with patients with atopic asthma or healthy controls, suggesting that T lymphocytes may be important in the pathogenesis of occupational asthma due to low molecular weight compounds (11). In addition, stimulation of peripheral mononuclear cells of Western red cedar asthma patients with plicatic acid-human serum albumin conjugate led to proliferation of lymphocytes (12). The above pathological findings were also described in patients with

diisocyanate-induced asthma (13). The fact that certain human leukocyte antigens confer predisposition, while others confer protection, further suggests the involvement of T cells in the pathogenesis of asthma due to these compounds (14,15).

Agents causing occupational asthma could be classified into two groups with distinct clinical features: one group produces specific IgE antibodies while the other is probably mediated by T lymphocytes.

In 1985, Brooks and colleagues (16) described, for the first time, reactive airway dysfunction syndrome, which occurs in patients after a single exposure to a high level of irritant. Because the disease cannot be reproduced in the laboratory, the diagnosis was based on clinical criteria: a history of exposure to high levels of irritants; symptoms occurring within 24 h of exposure, lasting for more than three months; objective evidence of air flow obstruction and presence of nonspecific airway hyper-responsiveness; and no previous history of lung disease.

The classification of occupational asthma now also included this nonimmunological group of agents (Figure 1) (17).

DEVELOPMENT OF DIAGNOSTIC METHODS

The first step in making the diagnosis of occupational lung disease is to ask the question, "What is your occupation?". Ramazzini taught that as early as 1713. For the diagnosis of occupational asthma, one must add, "What are you exposed to at work now and in the past?" (1). Few knew, however, that Charles Thackrah had written during the Industrial Revolution in 1832 that "scientific treatment of a malady requires a knowledge of its nature, and the nature is imperfectly understood without knowledge of the cause" (18). How important this observation is in occupational asthma, in which the exact etiological agent should be identified! He also described the usefulness of measurement of air flow obstruction using a "pulmometer", an early version of the spirometer. Even presently, the importance of confirmation of the diagnosis of occupational asthma by objective means is emphasized.

In 1952, Collodah (19) started conducting bronchoprovocation testing using common allergens to induce an attack of asthma. In 1963, Gelfand (20) encountered patients with occupational asthma due to a variety of low molecular weight compounds. He used bronchoprovocation tests to confirm the diagnosis. However, the method used was rather crude, and he induced severe attacks in some subjects.

It was not until 1969, when Pepys first introduced the simulated occupational type of exposure testing, that a safe method became available to reproduce the patient's symptoms and confirm the etiological agent (21). These tests were performed in an exposure chamber with an extraction fan. For example, for toluene diisocyanate challenge, the patient was asked to paint a board with a brush using polyurethane varnish without activator the first day and with activator the following day. The patient's forced expiratory volume in 1 s was measured throughout both days at intervals. Using this method, Pepys and Hutchcroft (22) documented many different agents responsible for occupational asthma. They also described different types of asthmatic reactions that they had observed during these challenges: isolated immediate asthmatic reactions that came on immediately after a challenge, lasting for 1 h; isolated late asthmatic reactions that started 3 h to 4 h after

challenge, were maximal at 8 h to 12 h after challenge and lasted for 24 h or longer; and biphasic asthmatic reactions, with an immediate phase followed by a late phase.

Since 1980, Malo and his colleagues have continued to improve and standardize methods of challenge testing with various occupational agents, using a closed-circuit method to provide steady exposure, thus making challenge testing safer and more reproducible (23).

Unfortunately, few centres outside of Montreal have the sophisticated machines and trained personnel to do these types of testing. Confirmation of diagnosis of occupational asthma remains problematic for many physicians.

The next landmark in the diagnosis of occupational asthma was the use of serial monitoring of peak expiratory flow (PEF) rate (24). Patients were asked to measure their PEF at least four times daily at work and away from work for a period of 10 days to two weeks, to document changes in airway calibre during these periods. PEF monitoring, when performed well, has been found to be both sensitive and specific compared with the results of specific challenge testing, which is the gold standard (25). PEF monitoring has its drawbacks, which are not discussed here (26). Despite its drawbacks, PEF monitoring is being used widely for confirmation of the diagnosis of occupational asthma.

Recently, the use of induced sputum to document the occurrence of eosinophilia, as well as the demonstration of increased exhaled nitric oxide during challenge tests, have been proposed as adjunct diagnostic tests (27,28). These methods require further evaluation.

With the various diagnostic methods available, an algorithm was developed for the investigation of occupational asthma, which remains useful today (29).

NATURAL HISTORY OF OCCUPATIONAL ASTHMA

After making the diagnosis of Western red cedar asthma, patients were advised to find alternative employment, because it was believed, at that time, that these patients should recover after removal from exposure. In a follow-up study, I found that in those who were no longer exposed, their asthma improved, but a proportion did not recover completely (30). Those who continued to be employed in the same job for financial reasons deteriorated and had to take more medications for the control of their symptoms; their lung function decreased (31). These results were confirmed in later studies involving more patients with this disease (32,33). Since then, the observations have been observed in patients with occupational asthma due to a number of other agents (8,34-38). The single most important determinant for recovery is the duration of exposure before diagnosis and how long the patient with symptoms stayed exposed to the causative agent (33). Those who recovered were those who were diagnosed and removed from exposure early.

Although most patients with occupational asthma did not recover completely, they improved with time. Lung function and nonspecific bronchial hyper-responsiveness decreased gradually with cessation of exposure and plateaued after about two to three years (37). For this reason, assessment of respiratory impairment should take place two to three years after a patient with occupational asthma has been away from exposure (38).

Figure 2) Natural history of occupational asthma.

At the time, this finding of persistent asthma caused by a single agent after removal from exposure aroused considerable interest among investigators. My colleagues and I performed BAL on a number of patients who did not recover and compared results with those who did recover. We found that patients who did not recover had an increase in eosinophils and neutrophils in the BAL fluid, suggesting the presence of continuous airway inflammation (39). Similar findings have been observed in patients with toluene diisocyanate-induced asthma (40,41). It is the current belief that persistent symptoms in asthma are not only the result of airway inflammation, but also airway remodelling, leading to permanent structural changes in the airway, including subepithelial fibrosis, an increase in extracellular matrix deposition and smooth muscle hyperplasia (42). The reason for the persistent airway inflammation, however, is not entirely clear.

Occupational asthma is an ideal model to study the natural history of asthma, because one can define several stages: when exposure starts, when sensitization occurs, when symptoms of asthma begin and what happens after removal from exposure. For each step, one can explore risk factors (environmental and host) for progression. This is not possible for the types of asthma in which the agent responsible is not known (Figure 2). Malo and his colleagues conducted prospective studies (43-47) on apprentices of various industries at high risk for occupational asthma to study the natural history of this disease. They found that sensitization to laboratory animals usually occurs during the first two years of exposure. This is followed by the development of occupational rhinokonjunktivitis and, later, asthma (46). The degree of exposure, previous sensitization to pets and increase in baseline, nonspecific bronchial hyper-responsiveness were significant determinants of occupational asthma (46). There is no doubt that important and relevant information were derived from these studies, not only in the understanding of occupation asthma, but of asthma in general.

EPIDEMIOLOGY OF OCCUPATIONAL ASTHMA

As the prevalence of asthma has increased in many developed countries, there is a great deal of interest in determining the contribution of occupational exposure to adult-onset asthma. Blanc and Toren (48) published an excellent review in 1999 and found that in one in 10 patients, adult-onset asthma could be attributed to work exposure. The prevalence of occupational asthma varies considerably in different industries – from 54% in platinum refineries to about 5% in Western red cedar sawmills (49). Although there are methodological differences in the prevalence

American Thoracic Society Guidelines for Impairment/Disability in patients with asthma *				
Score	Postbronchodilator FEV ₁	Reversibility of FEV ₁ % FEV ₁ change	Degree of NSBH PC20 mg/ml	Need for medication
0	> lower limit of N	< 10	> 8	no medication
1	70 % to lower limit of N	10-19	8 - > 0.5	occasional (not daily) BDT or cromolyn
2	60-69	20-29	0.5 - > 0.125	daily BDT or cromolyn or low dose (< 800 µg) beclomethasone
3	50-59	≥ 30	≤ 0.125	daily high dose (>800 µg) beclomethasone or occasional course (1-3/yr) of oral steroids
4	< 50	-	-	daily high dose (>800 µg) beclomethasone and daily oral steroids

Total Impairment :
class 0: total score = 0;
class I: total score = 1-3;
class II: total score = 4-6;
class III: total score = 7-9;
class IV: total score = 10-11;
class V: asthma not controlled despite maximal treatment.

Figure 3) Parameters for impairment/disability evaluation of a patient with asthma. BDT Bronchodilator; FEV₁ Forced expiratory volume in 1 s; N Normal; NSBH Nonspecific bronchial hyper-responsiveness; PC20 Provocative concentration for a 20% fall in FEV₁. Data from reference 57

studies mentioned above, there are other reasons that may account for the divergent prevalence of disease, such as the level of exposure, the nature of the agent and possibly the presence of cofactors.

Many studies have demonstrated a dose-dependent relationship between the level of exposure and the prevalence of sensitization or asthma (50). In the cedar sawmill, my colleagues and I found that the higher the level of exposure was, the higher the prevalence of asthma or persistent wheeze was (51). In the baking industries, the higher the level of exposure to flour dust or fungal amylase, the higher the prevalence of sensitization and asthma was found (52,53). These findings have been summarized by Baur and colleagues (50), and they presented the lowest effective dose for sensitization to these various agents. With these findings, one can begin to determine the threshold limit values for various occupational agents.

The structure of the agent appears to be an important determinant for its potential as a respiratory sensitizer. For high molecular weight compounds, studies have shown that those with enzymatic activities are potent sensitizers (54). This is probably the reason that detergent and food enzymes are common occupational agents. For low molecular weight compounds, those with the N=C=O molecular configuration, such as those present in isocyanates, are also potent sensitizers (55).

COMPENSATION ISSUES

Because more than one-half of the patients with occupational asthma do not recover, the question of compensation for permanent disability arises. Compensation for occupational asthma varies considerably between countries, as well as within countries and between provinces or states. For a long time compensation boards dealt with disability assessments for pneumoconiosis and did not consider asthma as an entity of permanent disability. When occupational asthma was finally recognized as a disease

with permanent disability, guidelines for pneumoconiosis based entirely on lung function level were used for assessing impairment or disability in asthma. However, asthma is a disease characterized by variable air flow obstruction, rather than fixed irreversible air flow obstruction. Lung function results can be within normal limits while the patient is taking medications. Asthma is also characterized by the presence of airway hyper-responsiveness, and workers may not be able to work in industries that expose them to low levels of irritants. Using lung function levels alone to determine the degree of impairment or disability is therefore not appropriate in patients with asthma (56).

In 1993, the American Thoracic Society published guidelines for impairment evaluation in asthma, taking into consideration not only lung function level, but also nonspecific airway hyper-responsiveness or airway reversibility and the use of medication (Figure 3) (57). For each of these three parameters, scores were given based on objective measures. The total score is then calculated, and the class of impairment determined based on the total scores. These guidelines were developed by a committee of American and Canadian researchers in the field of occupational asthma.

PREVENTION

A great deal has been achieved in the area of prevention. Reduction of exposure is the key to primary prevention, while medical and environmental surveillance programs are the keys to secondary prevention. An excellent example is the reduction of occupational asthma seen in the detergent enzyme industry when the detergent enzyme is produced in granulated rather than powder form, together with improvement in ventilation (58). Similarly, improvement in ventilation and screening of atopic subjects for employment in the platinum refinery industry has successfully reduced the number of patients with occupational asthma (59). In Canada, there has been a progressive reduction in the number of claims of isocyanate-induced asthma during the past decade in Ontario due to good environmental and medical surveillance programs (60). As well, the same group of researchers reported a reduction in the number of patient visits for latex asthma since the introduction of powder-free gloves (61).

FUTURE RESEARCH

A great deal of advances have been made in the past 50 years through the work of many researchers in the development of diagnostic methods, pathogenesis, epidemiology, natural history and prevention of occupational asthma. There are, however, many areas that require further research.

- Determination of structure and activity relationships for agents causing occupational asthma to avoid introducing respiratory sensitizers in the workplace;
- Development of newer diagnostic techniques that are simple, accurate and readily accessible. Specific inhalation challenge testing is only available in very few centres, and monitoring of PEF has limitations;
- Understanding the pathogenesis of occupational asthma, as well as the interaction between irritants and allergens in the workplace;

- Establishment of threshold limit values for occupational agents and standardization of the technique of measurement of exposure and reduction of exposure; and
- Standardization of methods of assessment of respiratory impairment and disability for patients with asthma in different provinces and countries.

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REFERENCES

- Ramazzini B. De Morbis Artificum Diatriba. Chicago: University of Chicago Press, 1940. (Translated by Wright WC)
- Pepys J, Bernstein IL. Historical aspects of occupational asthma. In: Bernstein IL, Chan-Yeung M, Malo JL, Bernstein DI, eds. Asthma in the Workplace. New York: Marcel Dekker Inc, 1999:5-26.
- Chan-Yeung M, Malo JL. Tables of major inducers of occupational asthma. In: Bernstein IL, Chan-Yeung M, Malo JL, Bernstein DI, eds. Asthma in the Workplace. New York: Marcel Dekker Inc, 1999:683-720.
- Chan-Yeung M, Barton G, MacLean L, Grzybowski S. Occupational asthma and rhinitis due to western red cedar (*Thuja plicata*). Am Rev Respir Dis 1973;108:1094-102.
- Gardener JA. Chemistry and Utilization of Western Red Cedar. Department of Forestry Publication, no 1023. Ottawa: Ottawa Department of Forestry, 1963.
- Chan-Yeung M, Lam S, Koerner S. Clinical features and natural history of occupational asthma due to western red cedar (*Thuja plicata*). Am J Med 1982;72:411-5.
- Chan-Yeung M, Barton GM, MacLean L, Grzybowski S. Bronchial reactions to western red cedar (*Thuja plicata*). CMAJ 1971;105:56-61.
- Paggiaro PL, Loi AM, Rossi O, et al. Follow-up study of patients with respiratory disease due to toluene diisocyanate (TDI). Clin Allergy 1984;14:463-9.
- Tse KS, Chan H, Chan-Yeung M. Specific IgE antibodies in workers with asthma due to western red cedar. Clin Allergy 1982;12:249-58.
- Lam S, Chan H, LeRiche J, Chan-Yeung M. Cellular and protein change in bronchial lavage fluid following late asthmatic reaction in patients with red cedar asthma. J Allergy Clin Immunol 1987;80:44-50.
- 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;151:340-73.
- Frew AJ, Chan H, Chang JH, et al. T lymphocyte response to plicatic acid-albumin conjugate in occupational asthma due to Western red cedar. J Allergy Clin Immunol 1998;108:841-7.
- Finotto S, Fabbri LM, Rado V, Mapp CE, Maestrelli P. Increase in numbers of CD8 positive lymphocytes and eosinophils in peripheral blood of subjects with late asthmatic reactions induced by toluene diisocyanate. Br J Ind Med 1991;48:116-21.
- Horne C, Quintana PJE, Keown P, Dimich-Ward H, Chan-Yeung M. Distribution of DRB1 and DQB1 HLA class II alleles in patients with western red cedar asthma. Eur Respir J 2000;15:911-4.
- Bignon JS, Aron Y, Ju LY, et al. HLA class II alleles in isocyanate-induced asthma. Am J Respir Crit Care Med 1994;149:71-5.
- Brooks S, Weiss MA, Bernstein IL. Reactive airways dysfunction syndrome: Persistent asthma syndrome after high level irritant exposure. Chest 1985;88:376-84.
- Bernstein IL, Bernstein DI, Chan-Yeung M, Malo JL. Definition and classification of asthma. In: Bernstein IL, Chan-Yeung M, Malo JL, Bernstein DI, eds. Asthma in the Workplace. New York: Marcel Dekker Inc, 1999:1-3.
- Thackrah CT. The Effects of the Principal Arts, Trades and Professions, and of Civic States and Habits of Living on Health and Longevity, with Suggestions for the Removal of Many Agents which Produce Disease and Shorten the Duration of Life. Edinburgh: Livingstone, 1957.
- Collodah H. Study of provocation tests on patients with bronchial asthma. Acta Allergol 1952;5:133-42.
- Gelfand HH. Respiratory allergy due to chemical compounds encountered in the rubber, lacquer, shellac, and beauty culture industries. J Allergy 1963;34:374-81.
- Pepys J. Inhalation challenge tests in asthma. N Engl J Med 1975;293:758-9.
- Pepys J, Hutchcroft BJ. Bronchial provocation tests in etiologic diagnosis and analysis of asthma. Am Rev Respir Dis 1975;112:829-59.
- Cartier A, Malo JL. Occupational challenge tests. In: Bernstein IL, Chan-Yeung M, Malo JL, Bernstein DI, eds. Asthma in the Workplace, 2nd edn. New York: Marcel Dekker Inc, 1999:211-33.
- Burge PS, Moscato G. Physiologic assessment: Serial measurements of lung function. In: Bernstein IL, Chan-Yeung M, Malo JL, Bernstein DI, eds. Asthma in the Workplace, 2nd edn. New York: Marcel Dekker Inc, 1999:193-210.
- Cote J, Kennedy S, Chan-Yeung M. Sensitivity and specificity of PC20 and PEFr in diagnosis of cedar asthma. J Allergy Clin Immunol 1990;85:592-8.
- Quirce S, Contreras G, DyBuncio A, Chan-Yeung M. Brief communication: Peak expiratory flow monitoring is not a reliable method in establishing the diagnosis of occupational asthma. Am J Respir Crit Care Med 1995;152:1100-2.
- Lemière C, Pizzichini MMM, Balkissoon R, et al. Diagnosing occupational asthma: Use of induced sputum. Eur Respir J 1999;13:482-8.
- Obata H, Dittrick M, Chan H, Chan-Yeung M. Sputum eosinophils and exhaled nitric oxide during late asthmatic reaction in patients with Western red cedar asthma. Eur Respir J 1999;13:489-95.
- Chan-Yeung M, Malo JL. Occupational asthma. N Engl J Med 1995;333:107-12.
- Chan-Yeung M. Fate of occupational asthma: A follow-up study of patients with occupational asthma due to western red cedar (*Thuja plicata*). Am Rev Respir Dis 1977;116:1023-9.
- Cote J, Kennedy S, Chan-Yeung M. Outcome of patients with cedar asthma with continuous exposure. Am Rev Respir Dis 1990;141:373-6.
- Chan-Yeung M, MacLean L, Paggiaro PL. Follow-up study of 232 patients with occupational asthma due to western red cedar (*Thuja plicata*). J Allergy Clin Immunol 1987;79:792-6.
- Chan-Yeung M, Malo JL. Natural history of occupational asthma. In: Bernstein IL, Chan-Yeung M, Malo JL, Bernstein DI, eds. Asthma in the Workplace. New York: Marcel Dekker Inc, 1999:129-43.
- Malo JL, Cartier A, Ghezzi H, Lafrance M, McCants M, Lehrer SB. Patterns of improvement of spirometry, bronchial hyperresponsiveness, and specific IgE antibody levels after cessation of exposure in occupational asthma caused by snow-crab processing. Am Rev Respir Dis 1988;138:807-12.
- Perfetti L, Cartier A, Ghezzi H, Gautrin D, Malo JL. Follow-up of occupational asthma after removal from or diminution of exposure to the responsible agent. Chest 1998;114:398-403.
- Burge PS. Occupational asthma in electronic workers caused by colophony fumes: Follow up of affected workers. Thorax 1982;37:348-53.
- Malo JL, Cartier A, Boulet LP, et al. Bronchial hyperresponsiveness can improve while spirometry plateaus two to three years after repeated exposure to chlorine causing respiratory symptoms. Am J Respir Crit Care Med 1994;150:1142-5.
- Johnson A, Chan-Yeung M. Nonspecific bronchial hyperresponsiveness in occupational asthma. In: Bernstein IL, Chan-Yeung M, Malo JL, Bernstein DI, eds. Asthma in the Workplace. New York: Marcel Dekker Inc, 1999:173-92.
- Chan-Yeung M, LeRiche J, Chan H, 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;18:359-65.
- Saetta M, Maestrelli P, DiStefano A, et al. Effect of cessation of exposure to toluene diisocyanate (TDI) on bronchial mucosa of subjects with TDI-induced asthma. Am Rev Respir Dis 1992;145:169-74.
- Boulet LP, Boutet M, Laviolette M, et al. Airway inflammation after removal from the causal agent in occupational asthma due to high and low molecular weight agents. Eur Respir J 1994;7:1567-75.

42. Vignola AM, Kips J, Bousquet J. Tissue remodelling as a feature of persistent asthma. *J Allergy Clin Immunol* 2000;105:1041-53.
43. Gautrin D, Infante-Rivard C, Dao TV, Magnan-Larose M, Desjardins D, Malo JL. Specific IgE-dependent sensitization, atopy and bronchial hyperresponsiveness in apprentices starting exposure to protein-derived agents. *Am J Respir Crit Care Med* 1997;155:1841-7.
44. Monso E, Malo JL, Infante-Rivard C, et al. Individual characteristics and quitting in apprentices exposed to high-molecular-weight agents. *Am J Respir Crit Care Med* 2000;161:1508-12.
45. 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;162:1222-8.
46. Gautrin D, Ghezzo H, Infante-Rivard C, Malo JL. Host determinants for the development of symptoms, immunological sensitization and bronchial responsiveness in apprentices exposed to laboratory animals: Distinction by atopic status. *Eur Respir J*. (In press)
47. Archambault S, Malo JL, Infante-Rivard C, Ghezzo H, Gautrin D. Incidence of sensitization, symptoms and probable occupational rhinoconjunctivitis and asthma in apprentices starting exposure to latex. *J Allergy Clin Immunol* 2001;107:921-3.
48. Blanc PD, Toren K. How much asthma can be attributed to occupational factors? *Am J Med* 1999;107:580-7.
49. Becklake MR, Malo JL, Chan-Yeung M. Epidemiological approaches in occupational asthma. In: Bernstein IL, Chan-Yeung M, Malo JL, Bernstein DI, eds. *Asthma in the Workplace*. New York: Marcel Dekker Inc, 1999:27-65.
50. Baur X, Chen Z, Liebers V. Exposure-response relationships of occupational inhalative allergens. *Clin Exp Allergy* 1998;28:537-44.
51. Vedal S, Enarson D, Kus J, McCormack G, MacLean L, Chan-Yeung M. Symptoms and pulmonary function in Western red cedar workers related to duration of employment and dust exposure. *Arch Environ Health* 1986;41:179-84.
52. Heederik D, Newman-Taylor AJ. Occupational asthma in the baking industry. In: Bernstein DI, Chan-Yeung M, Malo JL, Bernstein DI, eds. *Asthma in the Workplace*. New York: Marcel Dekker Inc, 1999.
53. Houba R, Heederik D, Doekes G. Wheat sensitization and work-related symptoms in the baking industry are preventable. *Am J Respir Crit Care Med* 1998;158:1499-503.
54. Wan H, Winton HL, Soeller C, et al. Der p 1 facilitates transepithelial allergen delivery by disruption of tight junctions. *J Clin Invest* 1999;104:123-33.
55. Graham C, Rosenkranz HS, Karol MH. Structure-activity model of chemicals that cause human respiratory sensitization. *Regul Toxicol Pharmacol* 1997;26:296-306.
56. Chan-Yeung M. Pulmonary perspective. Evaluation of respiratory impairment/disability in patients with occupational asthma. *Am Rev Respir Dis* 1987;135:950-1.
57. Chan-Yeung M, Harber P, Balmes J, et al. American Thoracic Society Statement. Guidelines for the evaluation of impairment/disability in patients with asthma. *Am Rev Respir Dis* 1993;147:1056-61.
58. Sarlo K. Control of occupational asthma and allergy in the detergent industry. *Ann Allergy Asthma Immunol* 2003;90(5 Suppl 2):32-4.
59. Venables KM. Prevention of occupational asthma. *Eur Respir J* 1994;7:768-78.
60. Tarlo SM, Liss GM. Can medical surveillance measures improve the outcome of occupational asthma? *J Allergy Clin Immunol* 2001;107:583-5.
61. Tarlo SM, Sussman G, Contala A, Swanson MC. Control of airborne latex by use of powder-free latex gloves. *J Allergy Clin Immunol* 1994;93:985-9.