A large number of agents in the workplace have been shown to give rise to occupational asthma. With the rapid introduction of new compounds into industries, it is likely that the prevalence of occupational asthma will continue to increase. This condition may well exceed pneumoconiosis as the most important cause of occupational lung disease. During the past two decades, there have been many studies which advanced our knowledge of occupational asthma: many causes have been identified, diagnostic techniques developed and the pathogenetic mechanisms investigated. The purpose of this review is to highlight some of the recent advances in this area.

DEFINITION

Occupational asthma is defined as variable airflow obstruction caused by a specific agent in the workplace. There is considerable controversy on the classification of occupational asthma. Some authorities attempt to classify this condition according to pathogenetic mechanisms: reflex, acute inflammatory, pharmacologic and allergic bronchoconstriction; however, the actual mechanism is often unknown.

Patients with pre-existing asthma often develop reflex bronchoconstriction on exposure to low levels of noxious gases and fumes. These patients should not be considered as suffering from occupational asthma since the reaction is nonspecific, due to a temporary aggravating factor.

Asthma sometimes develops for the first time within hours of accidental exposure to high levels of irritant gases such as chlorine, ammonia, smoke and fumes. In some such patients, symptoms of asthma may persist for years after one single heavy exposure. Gandevia first described it as occupational asthma due to acute inflammatory process; later Brooks and Lockey coined the term "reactive airway disease syndrome" since these patients demonstrate hyperresponsive airways. Many researchers would not regard this condition as true occupational asthma.

There are a number of agents which can give rise to acute bronchoconstriction through a pharmacologic mechanism, eg, cotton dust. There is considerable controversy whether byssinosis constitutes a form of occupational asthma since affected individuals do not have nonspecific bronchial hyperresponsiveness (NSBHR) or eosinophilia.

By far the greatest number of occupational agents causing asthma have been divided into those with high molecular weight, eg, proteins and polysaccharides and those with low molecular weight (<1,000 daltons), such as toluene diisocynate and plicatic acid in Western red cedar. With high molecular weight compounds, specific IgE and sometimes specific IgG antibodies to the appropriate allergens have been found indicating that these compounds indeed act as allergens. However, with low molecular compounds, in most instances, specific IgE antibodies or IgG antibodies cannot be identified to the appropriate compound when conjugated to a carrier protein, even though the clinical picture presented by the patients is suggestive of allergen-induced reaction.

DIAGNOSIS

Some compensation boards or similar agencies accept the diagnosis of occupational asthma if this condition develops after entering an industry known to give rise to occupational asthma, such as toluene diisocynate exposure; others, however, require the demonstration of specific bronchial reactivity to the workplace inhalant. Moreover, when a patient develops asthma after entering an exposure not previously known to given rise to occupational asthma, specific provocation test is necessary. There are very few centers where inhalation provocation tests or occupational type of exposure tests are regularly carried out for investigation of such patients. For practicing physicians without access to such facilities, establishing...
causal relationship can be difficult. The following methods are often used:

1. “Stop-resume” work test with monitoring of lung function when the patient has been off work for a period of time and when the patient returns to work. Improvement in symptoms and lung function tests when away from work, recurrence of symptoms and deterioration in lung function tests on returning to work confirm that the symptoms are due to an adverse work environment; furthermore, in “advanced” cases, recovery may be incomplete during the period away from exposure.

2. Measurement of lung function before and after a work shift. Unfortunately, patients with occupational asthma may not show a significant drop in FEV to over one work shift, and control subjects without any symptoms may have a significant drop in FEV over the course of one work shift in the same environment. This test is generally not very helpful in establishing causal relationship between symptoms and work exposure.

3. Recording peak expiratory flow rate by the patient at home and at work, over a long period. This has been proposed by some investigators as a good method of establishing causal relationship. The patient is asked to do readings every two hours from waking to sleep; the record should be kept for at least a week at work followed by ten days off work and then two weeks at work. Different patterns of changes in peak flow rate have been described. The criteria for establishing a positive response have yet to be worked out. One of the major criticisms of peak flow rate recordings is that the worker may falsify the results since he is making the readings himself.

Increased NSBHR has been found in patients who develop late asthmatic reaction to inhalation challenge with allergens or to chemicals. Serial measurements of NSBHR in addition to prolonged recording of peak flow rate have been suggested to provide objective evidence of “sensitization.” The demonstration of increase in bronchial responsiveness on return to work and a decrease in bronchial responsiveness when away from work, associated with appropriate changes in peak flow readings, suggests the occupational relationship.

Inhalation Challenges in Diagnosis

Specific inhalation challenge tests to identify the industrial agent responsible for asthma are time-consuming and not devoid of danger. They should be performed by experienced personnel in the hospital setting where resuscitation facilities are available and frequent observations can be made. They are indicated for medicolegal purposes and when a new agent is suspected to cause occupational asthma. The methods of specific challenge test and the types of asthmatic reaction induced have been described in detail by Pepys and Hutchcroft.

On inhalation tests with occupational agents, a large proportion of patients develop either isolated late asthmatic reaction or dual asthmatic reaction. It is important to measure lung function tests before and at intervals after challenge for at least 8 to 10 hours and again at 24 hours to detect the late response. There is good correlation between the clinical history given by the patient and the result of inhalation challenge test; those with a history of asthmatic symptoms starting toward the end of a work shift usually develop isolated late asthmatic reaction, while those with a history of symptoms occurring immediately on exposure and persistent throughout the day develop dual or continuous asthmatic reaction.

Bronchial provocation tests with methacholine or histamine to measure NSBHR are relatively easy to perform and can be done in the office setting. Measurement of NSBHR is a useful diagnostic tool in patients suspected of having occupational asthma. Firstly, the presence of NSBHR supports the diagnosis of asthma if the presentation of the patient is atypical and his lung function is found to be normal. It should be pointed out that a negative methacholine or histamine challenge test does not always exclude the diagnosis of asthma, particularly when the patient has been away from exposure for a period of time. Lam and coworkers have shown a progressive decrease in NSBHR in patients who recovered from red cedar asthma after they left the industry. Some patients with TDI-induced asthma were found to have normal bronchial responsiveness.

Secondly, as discussed earlier, serial measurements of NSBHR in conjunction with prolonged recording of peak expiratory flow rate provide objective evidence of “sensitization.” Thirdly, measurement of NSBHR is a good guide to the initial dose of allergen that can be safely given during specific bronchial provocation test. When the allergen is a high molecular weight compound and positive immediate skin reaction is induced by the allergen, the initial dose of allergen to be used for the bronchial provocation test can readily be determined by skin tests with serial dilutions of the allergen. When occupational asthma is due to low molecular weight compounds or when the responsible agent has not been identified, skin tests cannot be done. Lam et al found a good correlation between the severity of reaction to plicatic acid challenge (red cedar “antigen”) and the degree of NSBHR. For patients with a high degree of NSBHR, it is important to start with a small dose of the offending agent to avoid a severe reaction. Fourthly, measurement of NSBHR
may add another dimension in the evaluation of respiratory impairment/disability in patients with persistent asthma after removal from exposure, to be discussed later.

FATE OF PATIENTS WITH OCCUPATIONAL ASTHMA

Several follow-up studies of patients with occupational asthma suggest that the majority of them fail to recover completely several years after removal from exposure.13-18 In an earlier study13 of 75 patients with Western red cedar asthma proven by inhalation challenge test, we found that only half of the patients recovered completely after removal from exposure. The remaining half continued to have recurrent attacks of asthma after a mean period of three years (range one to nine years) away from exposure. The severity of asthma varied considerably from an occasional attack relieved by the use of aerosol bronchodilators to persistent chronic asthma requiring systemic corticosteroid therapy. These patients had persistent NSBHR. These findings were subsequently confirmed in a larger follow-up study of 232 patients.14 Of the 136 patients who left exposure, 60 percent failed to recover an average period of four years after leaving exposure. Patients who remained in the same job had deterioration in their symptoms, and increase of airflow obstruction and bronchial responsiveness despite taking regular medications. Paggiaro and coworkers15 studied all 27 patients with toluene diisocyanate (TDI) induced asthma after a period of two years. They also found that eight of 12 patients (66 percent) who left exposure failed to recover. In a more recent report, Lozewicz et al16 found that 41 of 50 patients (82 percent) with proven isocyanate-induced asthma continued to have respiratory symptoms and required treatment after they left exposure for at least four years. Only six of the original 56 patients were lost to follow-up. Burge17 reviewed 45 electronic workers with asthma caused by colophony fumes after a period of one to four years. Only six workers in this group were lost to follow-up. Of the 20 workers who left exposure, only two were symptom-free. Furthermore, Moller et al18 reported that some patients with TDI-induced asthma retained their specific TDI sensitivity as shown by inhalation challenge test, years after removal from exposure.

It has been suggested that those individuals available for follow-up are more likely to be symptomatic. Paggiaro et al15 had a 100 percent participation in their follow-up study, and only 10 percent of individuals were lost to follow-up in the study of Lozewicz et al16 and Burge.17 The high proportion of patients with occupational asthma who failed to recover is unlikely to be due to a clinical bias.

The persistence of asthma after removal from exposure is not confined to asthma due to low molecular weight compounds. Hudson and colleagues19 showed that the majority of patients with asthma caused by snow-crab processing failed to recover. As these individuals did not have asthma before they entered the industry, one can reasonably assume that their symptoms are the result of occupational exposure. In these individuals, exposure to these offending agents permanently alters the responsiveness of the airways.

It is often said that workers with occupational asthma are all predestined to develop late onset or “intrinsic” asthma and that occupational exposure merely un masks the predisposition. There are several points of evidence against such an argument. First, in industries known to give rise to occupational asthma, the prevalence of asthma is usually much higher than expected.1 In British Columbia, the prevalence of asthma in red cedar sawmills is 10.4 percent which is significantly higher than the prevalence in office workers: 4.3 percent.20 The prevalence of asthma among animal handlers was reported to be around 10-30 percent.21-23 As many as half of the workers exposed to platinum salts24 or proteolytic enzymes developed asthma.25-27 There are very few prevalence studies of asthma in adult populations in “western” countries. In Britain, the prevalence of asthma in adults during 1944-47 was estimated to be less than 1 percent.28 Surveys of university students a few years later found the prevalence rate to be twice as high. The highest estimate of prevalence of current asthma in adults was 5.4 percent in a survey of a general practice in London; the criterion used to identify asthma was a demonstrable reversibility of airflow obstruction of at least 30 percent.29 The prevalence of asthma among the adult population is too low to account for the reported prevalence of occupational asthma in the industries or for the high proportion (60-80 percent) of patients who fail to recover. Secondly, some patients who failed to recover show not only NSBHR, they also retained their specific reactivity to the “sensitizing” agent.30 Thirdly, in patients who recovered from occupational asthma, NSBHR returned toward normal, re-exposure led to an increase in the degree of NSBHR suggesting that those sensitized acquire the disease from their job.31

Little is known about the factors that affect the prognosis of these patients. In our follow-up study of patients with red cedar asthma, we investigated a number of factors that might influence the prognosis. Smoking, atopy, race, alpha,-antitrypsin level and phenotype had no influence on the outcome of the disease. We found, however, that a favorable outcome was associated with a shorter duration of symptoms before diagnosis, relatively normal lung function and a lesser degree of nonspecific bronchial hyperresponsiveness at the time of diagnosis suggesting that they were diagnosed at an early stage of the disease.34 Persistent asthma after removal from exposure was associated with a significantly longer duration of symp-
toms before diagnosis, abnormal lung function and a more marked degree of NSBHR at the time of the diagnosis. Thus, early diagnosis and early removal from exposure are important factors in ensuring complete recovery.

**Evaluation of Respiratory Impairment in Patients with Asthma**

Since a large proportion of patients with occupational asthma fail to recover after removal from exposure, the issue of compensation for permanent disability arises. There are no appropriate guidelines for assessment of impairment/disability in patients with asthma. In assessing these patients, the compensation boards or similar agencies use the recommendations of the American Medical Association (AMA) for evaluation of impairment/disability secondary to respiratory diseases. These recommendations require that the patient be evaluated after receiving optimal therapy or when he is in optimal health. If wheezing or other evidence of bronchospasm is evident at the time of the examination, the ventilatory studies are done before and after the administration of a bronchodilator. The spirogram indicating the best effort, either before or after administration of the bronchodilator, is used to calculate the FVC and FEV1. The degree of respiratory impairment is determined from the highest FEV1, and FVC. Such guidelines are inappropriate for patients with asthma who have variable airflow obstruction. Their lung function may be normal at the time of evaluation while taking medications; such patients would not be considered impaired according to the AMA criteria. In addition, patients with asthma have NSBHR which renders them unable to work in an environment in which they are exposed to irritants or cold air even though they are not exposed to the initial sensitizing agent.

The AMA has a specific guideline for asthmatics which states an asthmatic is considered severely impaired if the examiner can document attacks of bronchospasm severe enough to require treatment in an emergency room of a hospital at least once every two months or on the average of six times per year despite optimal therapy from an allergist or pulmonary physician. This individual should also have prolonged expiration with wheezing or rhonchi between attacks.

This guideline is unsatisfactory, as very few physicians experienced in the treatment of asthma would allow their patients to have six severe attacks per year requiring emergency treatment since such attacks can be life-threatening. Consequently, many patients with severe asthma, which is suppressed by daily medications, including steroids, would not qualify as impaired under this special guideline.

The recent American Thoracic Society (ATS) Statement on Evaluation of Impairment/Disability Secondary to Respiratory Disorders also attempts to address the issue of asthma. It recognizes the variability of airflow obstruction in these patients and recommends periodic evaluation of these patients. This represents a major improvement in assessment of functional impairment in asthma. However, it also includes the unsatisfactory specific AMA guideline discussed above.

It has been shown previously that there is good correlation between the degree of NSBHR and the severity of asthma as measured by the amount of medications required to control the symptoms. In our follow-up study of patients with red cedar asthma, we found that 62 percent of the patients who failed to recover had normal FEV1 (greater than 80 percent predicted) while taking antiasthma medications. They would not be considered impaired according to AMA criteria. However, all but two of these patients had evidence of NSBHR. In this group we found excellent correlation between the severity of asthma as measured by symptoms and medication requirement, and the degree of NSBHR. The above findings imply that in symptomatic patients with normal lung function, the presence of NSBHR provides objective evidence of abnormality; when measurement of NSBHR is not available, documented minimal amount of medication required to control asthma reflects the severity of asthma.

In establishing guidelines for assessment of impairment in patients with asthma, one should include lung function tests and periodic re-evaluation as recommended by the American Thoracic Society. In addition, it would be appropriate to include the measurement of NSBHR. Further research into evaluation of functional impairment in patients with asthma is urgently needed.

**Conclusion**

There are still many unanswered questions in the field of occupational asthma. What is the incidence of occupational asthma in industry? In what proportion of patients with asthma is it due to occupational exposure? Is there a level of exposure below which no one becomes "sensitized"? What are the predisposing host factors? Can affected workers return to the same job with reduced levels of exposure without detriment to their health?

The pathogenetic mechanisms of many causes of occupational asthma are unknown. The methods used in confirmation of diagnosis are also somewhat unsatisfactory. Finally, it is important to have appropriate criteria for evaluation of impairment/disability in patients with asthma.

It is hoped that this review will help to focus on some of the areas in which further research is needed.

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