The Asthma Center
Education and Research Fund
ADVISOR

OCCUPATIONAL Asthma

A. INTRODUCTION

Occupational Asthma (OA) is a form of asthma associated with work or a hobby involving inhalation of a chemical, allergen, or irritant which is aerosolized as dust or fumes. Occupational asthma symptoms have been observed among workers (e.g., bakers, grain workers), even dating back to ancient times. OA may only affect a small percentage of the population; however, it is a serious problem which can lead to permanent lung damage.

Occupational asthma affects the bronchial tree, resulting in symptoms that mimic those of bronchial asthma (e.g., coughing, wheezing, dyspnea, and chest congestion) and is associated with airway obstruction and/or airway hyper-responsiveness. These symptoms may also be accompanied by typical allergy symptoms such as itchy eyes, itchy nose and sneezing when OA is IgE-mediated.

There are many types of OA, and it is now understood that there is more than one possible mechanism involved in its development.

Unlike most cases of bronchial asthma (which usually respond to treatment and may be reversible), OA with long-term exposure to workplace allergens and irritants can lead to a chronic, irreversible form of asthma that is unresponsive to medication, even when the patient is no longer exposed to the original offending agent.

The common form of allergic bronchial asthma is often provoked by common aeroallergens found at home and outdoors during the pollen season. In contrast, OA is associated with the inhalation of specific and potent airborne agents unique to the workplace.

Symptoms of OA can include:

Coughing	Itchy eyes
Wheezing	Itchy nose
Chest tightness	Sneezing
Shortness of breath	Congestion

In addition to a new onset of asthma symptoms at work in a previous non-asthmatic individual, some patients with pre-existing asthma may notice that their symptoms are triggered or worsened while at work. This may be due to exposure to non-specific airborne irritants or inhaled allergens to which the patient is already sensitive.

In addition, asthmatic patients may also develop new sensitivities or lung damage due to inhaled environmental agents unique to the workplace.

The following section details the known mechanisms at work in the development of OA.

B. CAUSES OF OA

There are at least two major mechanisms involved in the development of OA:

1. **The most common type of OA** occurs after prolonged exposure to workplace allergens. During this time, the patient becomes sensitized to the inhaled workplace agent. The initial period in which the patient is symptom-free is called the *latency phase*, which can sometimes last for years. During this period, the patient has no asthma symptoms as the immunologic hypersensitivity to the workplace allergen is developing. The mechanism is mostly IgE-mediated, and the patient may also develop typical allergy-like symptoms that include itchy eyes, itchy nose and sneezing prior to or during the presentation of asthma symptoms. Early in the course of OA, asthma symptoms usually lessen or resolve when the patient is not at work, especially during evenings, weekends, and vacations.

Immunologic sensitization to a workplace agent in this form of OA is mostly due either to **high molecular weight (HMW) agents** (e.g., flour, animal protein), or less often, to **low molecular weight (LMW) agents** (e.g., chemicals such as isocyanates). The mechanism for HMW sensitization is usually IgE-mediated, while the mechanism for LMW sensitization is often a result of T-cell mediation (cellular hypersensitivity).

2. **The less common type of OA** results from exposure to high levels of airborne irritants in the workplace. Symptoms begin soon after entering the new work environment, with little to no latency period. Since there is no underlying immunologic mechanism or sensitization (latency) period, symptoms result from direct irritation or damage to the airway. This presentation is often referred to as reactive airway dysfunction syndrome (RADS), or irritant-induced asthma (IrIA), which is mentioned in the next section.

C. MECHANISMS OF OA

■ ***Immunologic: IgE-mediated sensitization***
HMW agents (e.g., animal proteins) have the size and molecular weight to act as complete allergens; therefore, they can elicit a specific IgE response to a workplace allergen (for example, baker's asthma is a specific IgE response to airborne flour). In this example, sensitization is not immediate, but it follows a latency period that can last years. Although IgE sensitization is usually the result of HMW allergen exposure, a few **LMW agents**, classified as *haptens* or incomplete allergens (e.g., platinum salts), can also cause a similar reaction. LMW haptens can act as sensitizers when they combine with body proteins to form complete allergens. Such allergens then behave as HMW allergens, thus eliciting the production of specific IgE against the offending workplace allergen.

■ ***Immunologic: Non-IgE mediated sensitization***
LMW chemicals (e.g., isocyanates, plicatic acid/western cedar) that induce OA are not usually associated with specific IgE production. Although IgE and IgG antibodies have been detected against some LMW agents, a cellular immunologic reaction involving T-cell activation appears to be more commonly associated with LMW sensitization to workplace agents.

■ ***Non-immunologic***
Irritant-induced asthma (IrIA) or reactive airway dysfunction syndrome (RADS) can occur after a single dose or multiple exposures to high concentrations of non-specific irritants (e.g., acids). While the exact mechanism is unknown, epithelial damage to the bronchi is common early in the disease process, leading to airway narrowing and typical symptoms of asthma. In other words, a previously non-asthmatic individual can develop OA following a single exposure to a strong irritant or chemical. An example of this would be the first responders present at the collapse of the World Trade Center on 9/11. This often occurs following an intense irritant or chemical exposure, as with a chemical spill.

■ ***Combined immunologic and non-immunologic***
Some agents (e.g., toluene diisocyanate/TDI) can cause OA through both immunologic and non-immunologic mechanisms, causing epithelial damage in addition to sensitization.

D. THE OA HISTORY

The possibility of OA should always be considered with a new onset of asthma symptoms or a recent worsening of asthma symptoms or recent worsening of asthma. Beyond current employment and hobbies, the physician should consider the patient's past work history and exposure experiences to assess prior risk of OA.

Diagnostic clues

- Type of symptoms (wheezing, etc. prominent in the workplace)
- Relationship of symptoms to workplace
- Risk factors at workplace due to known sensitizers
- Past medical and occupational history
- History of lung disease
- Chemicals, processes, and exposure incidence, as well as potential agent exposure risks within the profession or industry
- Location of patient within the work environment

Material safety data (MSD) sheets obtained from the patient's employer can help identify the offending agent. However, the MSD is not required by law in work environments where the offending chemical is present in concentrations of less than 1%. Therefore, information on a suspected agent must be obtained directly from its manufacturer.

Identifying high-risk agents in the work environment may require detective work by the patient with the guidance of an allergist or other specialist. He/she will need to gather information regarding the duration and frequency of agent exposure, concentration of exposure, preventive measures used in the workplace (e.g., masks, ventilation methods, air cleaners, etc.), and location of the worker in relation to agent exposure. These bits of information may offer clues in detecting the presence of OA.

In the development of OA, the occurrence of symptoms of allergic rhinitis and conjunctivitis in the workplace often precede chest symptoms, especially when HMW agents are involved (e.g., animal protein, grains). Workers with OA frequently notice that chest symptoms begin early in their shift, progress in severity during the shift, and later extend into the hours after the shift has ended. Improvement in asthma symptoms when not at work is suggestive of OA, but not conclusive.

In the early stages of OA, symptoms usually resolve during weekends and holidays. However, with continued exposure to the offending agent, the disease process and symptoms become chronic, often persisting outside of the workplace.

For many patients with longstanding OA, symptoms may not resolve even when the patient discontinues work completely and is no longer exposed to the allergen. Therefore, early detection of OA and removal of the individual from the workplace before permanent changes occur may prevent chronic lung symptoms. It has been reported that early intervention may result in resolution of asthma symptoms in one third or more of OA patients.

Agent exposure history may not always be obvious. For example, a bookkeeper in an office connected to a warehouse or factory may be exposed to high levels of an allergen or irritant via a common ventilation system. Therefore, such a clerical worker may develop OA symptoms without awareness of his or her exposure to a high-risk agent.

In contrast, awareness of high-risk occupational exposure to agents with the potential to cause OA (see Tables 1 and 2) will help the physician reach an early diagnosis in the development of OA symptoms. This is no simple matter since there are more than 400 known sensitizers or irritants which can cause asthma in the workplace. One compilation of these triggers can be found at the following web address: **www.remcomp.fr/asmanet/asmapro/agents.htm#start**.

About 10% of adult workers with a prior diagnosis of asthma will experience a worsening of their asthma symptoms in the workplace. Such asthma symptoms may be due to either non-specific air pollution irritating a hyperreactive airway or result from allergic sensitivity to the presence of a specific airborne allergen or agent.

E. TYPICAL ONSET OF OA

For those exposed to HMW allergens, allergy symptoms such as conjunctivitis and rhinitis often precede or accompany the development of coughing, wheezing or dyspnea in cases of OA. The diagnosis may be complicated when exposure to a workplace allergen is intermittent or the patient has a history of asthma and airway hyperreactivity prior to beginning employment. In this latter instance, workplace exposure to non-specific pollution can trigger underlying asthma. On the other hand, the patient can have symptoms resulting from a workplace inhaled allergen, either as a result of a newly acquired sensitization or from prior sensitization.

The latency period for sensitization to a workplace allergen varies with the type of allergen inhaled. For example, the latency period is generally shorter with exposure to LMW substances (e.g., isocyanates) and longer with HMW substances (e.g., flour, animal protein). As discussed earlier, the latency period may persist for years with HMW sensitization.

F. DIAGNOSIS OF OA

Occupational asthma diagnosis is based on:

1) History of asthma-related symptoms in the workplace
2) Pulmonary function tests

A pulmonary function test performed during or after work that demonstrates an obstructive pattern with or without significant reversibility supports the diagnosis of OA.

If spirometric pulmonary functions do not clearly support the diagnosis of OA, then a methacholine challenge may be necessary. A positive methacholine challenge will demonstrate the presence of airway hyperreactivity supporting the diagnosis of OA. In contrast, a negative methacholine challenge rules out the diagnosis of OA. These objective clinical studies may aid in creating solid documentation supporting the diagnosis of OA and the need for modification of the workplace environment with regard to agent exposure. These studies may also be necessary for disability claims.

An agent-specific bronchoprovocation challenge with a suspected workplace agent is usually not necessary and should only be carried out in specialized laboratories with experienced personnel. Such centers may be found at Johns Hopkins University Hospital in Maryland, The National Institutes of Health in Maryland, and National Jewish Health Center in Denver, Colorado, and the College of Medicine at the University of Cincinnati, among others.

Inhalational challenges to specific agents should be performed

in a laboratory equipped to deliver precisely measured doses of the suspected agent in order to create a dose response curve. The challenge begins with a very tiny dose in order to avoid producing an irritant reaction or a serious flare of asthma symptoms. Specialized equipment—including a dosimeter (which precisely measures the dose of allergen to be inhaled) and an occupational challenge chamber—are used to quantify individual doses and provide a safe challenge area for both the patient and the testing personnel. Bronchoprovocation tests with allergens or workplace chemicals can result in significant broncho-pulmonary reactions leading to hospitalization and serious complications. Since most presentations of OA can be diagnosed accurately by combining history, serial pulmonary functions, allergy tests and/or evidence of sputum eosinophilia, the risks and additional benefits of bronchial provocation testing need to be carefully weighed. Finally, allergy skin testing can also be particularly valuable in detecting sensitivity to a HMW allergen in the workplace.

G. OBJECTIVE STUDIES

• ***Peak flow expiratory rate***—Serial measurements of peak flow rates can be performed on a regular basis before, during and after work, 4-6x per day over a few weeks. This should be done similarly for a period when not at work. In OA, peak flows will trend downward during the workday, often improving by the following morning, on weekends, and on vacation. This is not a specific test identifying the cause, but it may help support the diagnosis by demonstrating airway obstruction related to workplace exposure. However, a malingering patient can manipulate these studies.

• ***Spirometry***—Recording the FEV_1 on workdays and non-workdays is a standard objective study that can confirm the presence of asthma in the workplace. This test will not identify the specific agent, but it can support that asthma symptoms are occurring in the workplace. Although the FEV_1 is the most commonly used spirometric measurement, the FEF_{25-75} is actually a more sensitive measurement and less susceptible to patient manipulation. Another important advantage of measurement by spirometry versus peak flow measurement is that it is difficult, if not impossible, for the patient to manipulate the results without a skilled physician detecting such an attempt.

• ***Testing for airway hyperreactivity***—Another objective method for identifying changes in the airway induced by workplace exposure to an allergen or chemical is demonstrating the presence or increase in bronchial hyperresponsiveness with a methacholine challenge. This study can be performed at the end of the work period and at the end of a period away from work. A decrease by 50% or more in the amount of methacholine required to induce a 20% drop in FEV_1 following work would support the diagnosis of OA by revealing an increase in airway hyperreactivity.

In contrast, a lack of bronchial hyper-responsiveness when the subject is at work with asthma-like symptoms virtually excludes the diagnosis of OA. However, a negative methacholine challenge when the patient is not at work and asymptomatic does not rule out OA.

• ***Allergy skin testing***—Allergy skin test antigens are not available for documenting hypersensitivity to many occupational agents, since many are of low molecular weight and therefore unsuitable for skin testing. Allergy extracts suitable for skin testing can be developed for some HMW antigens, such as animal dander, insect parts and plant proteins. While a positive skin test would support the presence of IgE-mediated sensitization, in order to confirm an OA diagnosis, there must also be a concomitant history of asthma symptoms and pulmonary functions demonstrating obstruction and airway hypersensitivity. However, a negative allergy skin test with suspected HMW allergens (egg, flour or enzymes) probably rules out that those specific antigens are a cause of OA symptoms.

• ***Specific agent bronchoprovocation challenge***—Patients who have asthma symptoms in the workplace along with normal pulmonary functions in the workplace, negative methacholine challenges, and eosinophil-free sputum are unlikely to have occupational asthma as a cause of their symptoms. However, one can finalize a questionable diagnosis with a specific agent bronchoprovocation challenge. A negative challenge clearly rules out the presence of OA under these circumstances.

When the diagnosis of OA is suspected and yet not clearly defined, specific bronchoprovocation inhalation testing may be required to objectively finalize the diagnosis. The use of HMW agents in a bronchial challenge can be carried out in a single day because the reaction is immediate (IgE mediated). In contrast, LMW agents can induce a non-immediate or late response and daily challenges of increasing doses on subsequent days is often required to elicit a response.

In addition to spirometry, demonstration of bronchial hyperresponsiveness at the end of each day of the challenge and/or demonstration of eosinophils in sputum, or an increase in exhaled nitric oxide following the challenge adds support for the diagnosis of OA caused by the specific agent used in the challenge.

In asymptomatic workers, a positive methacholine challenge or presence of eosinophils in sputum after antigen exposure may predict the onset of occupational asthma and allow for an early and sensitive marker for the potential development of occupational asthma.

• ***Chest x-ray***—Will either be normal or reveal signs of asthma such as air trapping in patients with OA. The x-ray or CT scan of the chest in OA will not reveal signs of fibrosis, while the presence of fibrosis is more typical of hypersensitivity pneumonitis and other chronic

occupational lung diseases associated with interstitial pulmonary damage.

• ***Laboratory studies***—In allergy-induced occupational asthma, the eosinophil count can be elevated in the blood and/or sputum. A RAST assay/Immunocap may be positive for one sensitized to a HMW allergen.

Table 1: SPECIFIC ALLERGY-CAUSING AGENTS

Agent	Workers at risk
Cereals (grains)	Bakers; millers
Animal-derived proteins	Animal handlers; veterinarians
Enzymes	Detergent users; pharmaceutical workers; bakers
Gums	Carpet makers; pharmaceutical workers
Latex	Health professionals; rubber workers
Seafoods	Seafood processors
Isocyanates	Spray painters; insulation installers; manufacturers of plastics; rubbers and foam
Wood dusts	Forest workers; carpenters; cabinet makers
Anhydrides	Plastics workers; epoxy resin
Fluxes, soldering resin	Electronics workers
Chloramine-T	Janitors; cleaners
Dyes	Textile workers; printers
Persulfate	Hairdressers
Formaldehyde, glutaraldehyde	Hospital staff
Acrylate	Adhesive handlers; refiners

Table 2: NON-ALLERGENIC AGENTS RESPONSIBLE FOR IRRITANT-INDUCED ASTHMA (IrIA):

Acids	Acetic acid Heated acid Sulfuric acid Hydrochloric acid
Ammonia	Floor sealant
Bleaching agents	Formalin
Chlorine	Metal remover
Chloropicrin	Mustard
Cleaning agents	Oxide (calcium)
Diesel exhaust	Paints (heated)
Dimethylaminoethanol	Perchloroethylene
Ethylene oxide	Spray paint
Fire/smoke	Sulfur dioxide

H. COMMON WORKPLACE ALLERGENS

Examples of HMW agents causing OA:

- Animal protein (animal lab researchers, veterinarians)
- Flour and grains
  Cereals (e.g., wheat flour, soya dust used in baking), enzymes (amylase, cellulose), yeast, and storage mites.
- Latex (healthcare workers, lab workers)
  Airborne latex allergens are often associated with the use of latex gloves. Sensitization to any of several different latex allergens may be involved. Aerosolization of latex often results from latex adhering to glove powder. Frequent changes of gloves will increase aerosolization and exposure to latex.

Examples of LMW agents causing OA:

- Diisocyanates (automobile painters, plastics manufacturers)
  Among the diisocyanates, toluenediisocyanate (TDI) is the most commercially used of these sensitizers. It is often used in the manufacture of automobiles, foam rubber, and molds for insulation. Hexamethylene diisocyanate (HDI) is used in spray paints. This agent can cause OA, RADS, and even hypersensitivity pneumonitis. These chemicals are strong sensitizers and can cause OA in up to 10% of exposed workers.
- Wood dust (loggers, sawmill workers, carpenters)
  Exposure to wood dust can cause OA as well as hypersensitivity pneumonitis. A common cause of OA in the Pacific northwestern United States is exposure to western red cedar dust, due to its content of plicatic acid. Plicatic acid as a hapten (LMW agent) can conjugate with body proteins to induce the production of specific IgE which is found in only 20% of exposed patients who developed OA. It appears that cellular hypersensitivity plays a more prominent role in sensitization than does IgE. Sensitization to western red cedar workers occurs in 5 -10% of this population of workers.

Occupational asthma must be differentiated from other **occupational lung diseases** which can also be immunologically mediated, but by a different mechanism than that seen in OA. Further, unlike OA in which the bronchi are primarily affected, other occupational lung diseases usually involve the parenchyma of the lung.

I. THREE DIFFERENT TYPES OF OCCUPATIONAL LUNG DISEASE

Occupational lung disease includes:

- **Occupational asthma**
- **Hypersensitivity pneumonitis**

■ Pneumoconiosis

Each of these three occupational lung diseases differs either in the site of lung damage or the nature of reaction causing the damage. Yet, they share a common element in that they all result from inhaling allergens, chemicals, or mineral dust in the workplace.

Occupational asthma is a disease of the bronchial tree resulting in an obstructive pattern on pulmonary function tests. OA is usually associated with symptoms of wheezing, coughing and shortness of breath. Early in the development of OA, symptoms may respond to bronchodilators and the pulmonary function test may reveal partial or total reversibility. In contrast, the two other occupational lung diseases involve damage to the parenchyma of the lung (interstitial tissue) resulting in shortness of breath without wheezing and eventually develop a restrictive pattern on pulmonary function tests.

1. HYPERSENSITIVITY PNEUMONITIS

This occupational lung disease results from an immunologic reaction to inhaled organic dust. The **organic dust** involved is often contaminated with mold or fungus which acts as an allergen. The resulting immunologic reaction that occurs in the lung is not IgE-mediated in hypersensitivity pneumonitis, but rather associated with the production of high levels of IgG antibodies (precipitins) and a cellular hypersensitivity reaction. The resulting lung damage is associated with pulmonary fibrosis, a restrictive pulmonary pattern, and a decreased DLCO (diffusion). Clinical symptoms may vary; symptoms typically include shortness of breath, however, wheezing is not present.

Three clinical patterns have emerged in the development of hypersensitivity pneumonitis, which are very different from that seen in OA:

The acute form: presents as fever, chills, chest tightness, dyspnea without wheezing, and non-productive cough 4 to 8 hours after exposure. The acute form resolves within 24 hours following avoidance of the allergen.

The subacute form presents as a productive cough, malaise, myalgia, dyspnea, and nodular infiltrates on chest x-ray. Any form of hypersensitivity pneumonitis can lead to severe, irreversible pulmonary fibrosis with irreversible change; thus, it is important to recognize this disease early in its development so that significant irreversible lung damage can be prevented.

The chronic form results from prolonged low-level exposure. Patients have mild coughing, dyspnea, fatigue, pulmonary fibrosis, and weight loss.

Table 3:
Causes of hypersensitivity related to specific occupations

Disease	Exposure	Agent
Farmer's lung	Moldy hay	Saccharopolyspora rectivirgula (Micropolyspora faeni)
Bagassosis	Moldy sugar cane fiber	Thermoactinomyces sacchari
Grain handler's lung	Moldy grain	S. rectivirgula, T. vulgaris
Humidifier/air conditioner lung	Contaminated forced-air systems, heated water reservoirs	S. rectivirgula, T. vulgaris
Bird breeder's lung	Pigeons, parakeets, fowl, rodents	Avian or animal protein
Cheese worker's lung	Cheese mold	Penicillium casei
Malt worker's lung	Moldy malt	Aspergillus clavatus
Paprika splitter's lung	Paprika dust	Mucor stolonifer
Wheat weevil	Infested wheat	Sitophilus granarius
Mollusk shell hypersensitivity	Shell dust	Sea snail shells
Chemical worker's lung	Manufacture of plastics, polyurethane foam, rubber	Trimellitic anhydride, dimethylene diisocyanate

2. PNEUMOCONIOSIS is a restrictive, occupational lung disease caused by the inhalation of **mineral dust**. It results in a pulmonary function study that reveals a chronic restrictive lung pattern, and x-rays reveal pulmonary fibrosis.

Type of pneumoconiosis	Responsible agent
Anthracosis	carbon dust
Coalworker's pneumoconiosis (also known as "black lung")	coal dust
Asbestosis	asbestos dust
Silicosis (also known as "grinder's disease")	silica dust
Bauxite fibrosis	bauxite dust
Berylliosis	beryllium dust
Siderosis	iron dust
Byssinosis	cotton dust

J. TREATMENT

The management of OA consists of limiting the worker's exposure to the offending agent to amounts that will not induce disease. A number of approaches can be taken. For example, the worker can be moved to another location within the workplace where little or no offending agent is present. Other techniques include using effective equipment to remove dust and vapor exposure and improving

workplace ventilation so that frequent air exchange limits agent accumulation. Evaluation of the workplace should be conducted by a trained industrial hygienist who can measure the degree of agent exposure. It is important to remember that levels of exposure below the legal limits are based on toxicity studies and, therefore, the presence of even tiny amounts of sensitizing agents may still cause immunologic reactions. Face masks of the filtering type are not especially efficient or well-tolerated. In contrast, a compressor with a HEPA filter creating a positive air flow through a mask or head piece can markedly diminish inhalation of airborne dust and therefore may be helpful when working with HMW agents.

Ideally, the work environment should be designed to limit the concentration of potential sensitizers to safe levels. Since this may be impractical in many manufacturing processes, even in a carefully monitored facility, recommended thresholds may be exceeded. Therefore, total avoidance of the workplace may be the only alternative for some sufferers of OA and may entail retraining and reassigning the employee(s) to another job free of potential exposure to the suspected agent.

Pharmacologic management of OA is rarely helpful in the presence of continued exposure on a chronic basis. Asthma resulting from contact with occupational exposures responds to therapeutic agents such as β-adrenergic agonists, cromolyn sodium, and steroids. As exposure continues, sensitivity may increase, rendering medication less effective.

Immunotherapy has been used with various occupational allergens causing asthma, including treatment of laboratory animal workers, bakers, and oyster gatherers, with reported success.

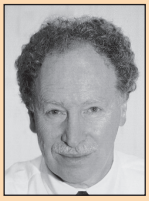
K. PREVENTION

The most important principle of OA management is prevention, rather than treatment. Educating exposed workers and managers in high-risk industries is crucial so that affected workers can be recognized early. Right-to-know legislation should increase awareness of occupational asthma.

At this time, there are no pre-employment screening criteria that have been shown to be accurate in predicting the eventual appearance of OA. There is conflicting evidence as to whether HLA studies are useful in predicting isocyanate asthma or anhydride asthma. It has been reported that atopy is a predisposing factor for a worker to develop IgE-mediated disease. Further, as many as 25-50% of the work force may have allergy, but it is impractical to avoid hiring such a large portion of the potential work force when only a small number of these individuals may develop OA.

L. PROGNOSIS

Many workers with occupational asthma do not completely recover, even though they have been removed from exposure to a sensitizing agent for years. An unfavorable prognosis has been reported to be associated with a persistent, high level of specific IgE to the suspected agent, long duration of symptoms (>1 to 2 years), abnormal pulmonary function test results, and a high degree of airway hyperreactivity. The obvious conclusion based on these observations is that early diagnosis and removal from exposure are requisites for the goal of complete recovery. In workers who remain exposed to offending agents after being diagnosed with OA, further deterioration of lung function and increased airway hyperreactivity are likely. It should be understood that life-threatening attacks and even deaths have been reported with continued exposure after diagnosis of OA.



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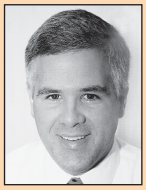

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