Clinical Evaluation, Management, and Prevention of Work-Related Asthma

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Work-related asthma (WRA) is asthma that is attributable to, or is made worse by, environmental exposures in the workplace. WRA has become the most prevalent occupational lung disease in developed countries, is more common than is generally recognized, and can be severe and disabling. Identification of workplace exposures causing and/or aggravating the asthma, and appropriate control or cessation of these exposures can often lead to reduction or even complete elimination of symptoms and disability. This depends on timely recognition and diagnosis of WRA. In this review, the diagnostic evaluation has been organized in a stepwise fashion to make it more practical for primary care physicians as well as physicians specializing in occupational diseases and asthma. WRA merits more widespread attention among clinicians, labor and management health and safety specialists, researchers, health care organizations, public health policy makers, industrial hygienists, and others interested in disease prevention. Am. J. Ind. Med. 37:121–141, 2000. *© 2000 Wiley-Liss, Inc.*

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INTRODUCTION

Asthma has been characterized as a chronic inflammatory disorder of the airways, with recurrent episodes of wheezing, breathlessness, chest tightness, and cough. These episodes are usually associated with airflow obstruction that is often reversible, either spontaneously or with treatment. There is an associated increase in bronchial responsiveness to a variety of stimuli [NAEPP, 1997]. A patient with asthma and chronic inflammation may have a fixed component of airflow obstruction, and a patient with Chronic Obstructive Pulmonary Disease (COPD) may have a reversible component, leading to some overlap between the diagnoses of asthma and COPD.

Work-related asthma (WRA) is asthma that is attributable to, or is made worse by, environmental exposures in the workplace. Over 250 agents have been associated with WRA in published reports. There is general agreement that WRA has become the most prevalent occupational lung disease in developed countries, although estimates of actual prevalence and incidence are quite variable. In the U.S., as in other industrialized countries, asthma of occupational etiology causes a largely unrecognized burden of preventable disease and disability. Both under diagnosis and over diagnosis can carry high economic and noneconomic costs.

Making the diagnosis of WRA can be difficult, particularly in differentiating between occupational and other environmental causative factors. Other than the fact that something in the workplace either makes asthma worse or actually caused it de novo, WRA looks and acts similar to other forms of asthma, and the medical component of the

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TABLE I. Four Key Questions When Work-related Asthma is Considered

1. Does this patient have asthma?
2. Is the asthma work-related?
3. What are the causative and/or triggering substances or work environments?
4. What workplace modifications would make it safe for the patient to continue working or return to work, and/or would protect coworkers?

treatment is the same. Of importance, however, is the fact that WRA, along with its associated costs, is preventable for many patients and their coworkers. In some cases that are diagnosed early, WRA may be partially or completely reversible if exposures are identified and adequately controlled or stopped.

An approach to diagnosis, management and prevention of WRA can be guided by the four questions listed in Table I. This approach emphasizes prevention of disability, and incorporates primary as well as secondary prevention. The diagnostic evaluation has been organized in stepwise fashion to make it practical for primary care physicians as well as physicians specializing in care of occupational diseases and asthma. Specific diagnostic subcategories are discussed further in the appropriate context.

This review summarizes the approaches to WRA which are being implemented by the New York State Department of Health Occupational Health Clinic Network. Several recent publications discuss these and related issues in detail [e.g., Bernstein et al., 1993; Rosenstock and Cullen, 1994; Chan-Yeung, 1995; Balmes, 1991; Chan-Yeung and Malo, 1997; Brooks, 1998]. Diagnosis and treatment of asthma in general are well reviewed elsewhere [e.g., NAEPP, 1997; Boushey, 1997], and are beyond the scope of this review.

BACKGROUND

Magnitude of the Problem

Asthma is a major public health problem in the United States. The estimated number of persons of all ages with self-reported asthma during 1993 was 13.7 million [Mannino et al., 1998]. Medical care utilization for asthma that year included 10.4 million office visits, 1.9 million Emergency Room visits, and 466,000 hospitalizations per year. Persons 15 years of age and older accounted for 70% of the persons with asthma, 70% of the medical care utilization for asthma, and 96% of the 5,400 annual asthma deaths. In the United States, residence in inner cities and in the northeastern states, low income, and African-American and Latino race/ethnicity are characteristics associated with disproportionately elevated, and recently increasing, asthma hospitalization, prevalence, and mortality rates, both in adults and children [Carr et al., 1992; Weiss et al., 1993; Mannino et al., 1998]. Asthma is the primary diagnosis in approximately 1% of all ambulatory care visits in the U.S. [Balmes, 1996]. Environmental factors are clearly involved in both the recent increase in asthma prevalence, and the large disparities among different populations. The identification, characterization, and control of environmental exposures in the work-place, home and community, as well as other modifiable risk factors, are topics of much current research.

Estimates of the proportion of prevalent adult asthma cases in the general population that is related to the work environment have varied from 2% to 33% [Brooks, 1998; Ng et al., 1994]. The wide range of these estimates reflects differences among studies in definitions, methodologies, populations, and other factors. Past population estimates of incidence of occupational asthma (OA) based on surveillance reporting by physicians have also varied widely, from 14 per million employed adults per year in the U.S. to 140 per million employed adults per year in Finland [Meredith and Nordman, 1996]. Ascertainment of cases was more complete and diagnostic methods were generally more rigorous in Finland. Surveillance studies based on physician reports have generally suffered from incomplete case ascertainment. Using capture-recapture methods to assess WRA incidence in Michigan resulted in a range of estimates from 58 per million per year to 204 per million per year, substantially higher than the estimate of 27 per million per year derived from cases reported to the statewide surveillance system [Henneberger et al., 1999]. The authors commented that these indirect estimates were probably still underestimates of the incidence of WRA because of under-recognition of WRA by physicians. A recent study of adult members of a health maintenance organization in Massachusetts directly estimated the incidence and reported that 21% of cases of new onset of asthma or reactivation of prior asthma that had become asymptomatic were definitely or probably attributable to occupational exposures [Milton et al., 1998]. In this cohort study, the estimated incidence of asthma attributable to occupational exposure, 710 per million persons per year, was far higher than incidence estimates from surveillance studies which have depended on recognition, diagnosis, and reporting of cases by community physicians. Other published evidence also consistently suggests that WRA is under-diagnosed and/or under-reported and is a public health problem of greater magnitude than generally recognized.

Definitions and Classification of Asthma in the Workplace

Work-related asthma (WRA)

WRA is physician-diagnosed asthma that is attributable to, or is made worse by, environmental exposures in the

TABLE II. ACCP Medical Case Definition of Occupational Asthma

Occupational Asthma requires A, B, C, and D2 or D3 or D4 or D5
Likely Occupational Asthma requires A, B, C, and D1

A. Physician diagnosis of asthma.
B. Onset of asthma after entering the workplace.
C. Association between symptoms of asthma and work.
D. One or more of the following criteria:
 1. Workplace exposure to agent known to give rise to OA,
 2. Work-related changes in FEV_1 or PEF,
 3. Work-related changes in bronchial responsiveness (e.g., serial Methacholine Challenge Testing),
 4. Positive response to specific inhalation challenge tests (Available only in a small number of research facilities in North America),
 5. Onset of asthma with a clear association with a symptomatic exposure to an inhaled irritant agent in the workplace.

ACCP criteria for diagnosis of reactive airway dysfunction syndrome (RADS) (should meet all eight)

1. Documented absence of preceding respiratory complaints.
2. Onset of symptoms after a single exposure incident or accident.
3. Exposure to a gas, smoke, fume, or vapor with irritant properties present in very high concentration.
4. Onset of symptoms within 24 h after exposure with persistence of symptoms for at least three months.
5. Symptoms simulated asthma: cough, wheeze, dyspnea.
6. Presence of airflow obstruction on pulmonary function tests (initial testing should be done shortly after exposure).
7. Presence of nonspecific bronchial hyper-responsiveness.
8. Other pulmonary diseases ruled out.

ACCP, American College of Chest Physicians; FEV1, Forced Expiratory Volume in 1 second; OA, Occupational Asthma; PEF, Peak Expiratory Flow; RADS, Reactive Airways Dysfunction Syndrome; WAA, Work Aggravated Asthma.

workplace. WRA includes two categories: occupational asthma (OA) and work-aggravated asthma (WAA) [Bernstein et al., 1993; Chan-Yeung, 1995]. Either diagnosis, or both, can be made in a given patient.

Occupational asthma (OA)

OA has been defined in several ways, appropriate for different purposes and in different circumstances. Definitions found valuable for research purposes or for worker screening or surveillance may not be entirely satisfactory for clinical or compensation purposes. National Institute for Occupational Safety and Health (NIOSH) developed a surveillance case definition of OA [Matte et al., 1990] requiring a physician diagnosis of asthma, association between symptoms of asthma and work, and at least one of the following four findings: (1) workplace exposure to an agent or process previously associated with occupational asthma; or (2) significant work-related changes in forced expiratory volume in one second (FEV_1) or peak expiratory flow (PEF); or (3) significant work-related changes in airways responsiveness as measured by nonspecific inhalation challenge; or (4) positive response to inhalation provocation testing with an agent to which the patient is exposed at work. A panel of clinical researchers has proposed a different definition of OA as ''... a disease characterized by variable airflow limitation and/or airway hyper-responsiveness due to causes and conditions attributable to a particular occupational environment and not to stimuli encountered outside the workplace.'' [Bernstein et al., 1993].

A consensus panel of the American College of Chest Physicians (ACCP) has combined and operationalized these two definitions as a medical case definition which is summarized in Table II [Chan-Yeung, 1995]. The clinical utility of this case definition is substantially limited by the lack of availability in clinical settings of specific bronchial challenge testing or workplace challenge testing[1] and, in some areas, of quantitative testing for nonspecific bronchial responsiveness (NSBR). The consensus panel classifies OA into two subcategories: OA with latency and OA without

[1] Specific bronchial challenge testing using sub-irritant exposure levels of sensitizing agent(s) suspected to have caused the asthma has been labeled the ''gold standard'' for diagnosis of sensitizer-induced OA. Workplace challenge testing involves frequent, serial (e.g., hourly) pulmonary function testing in the workplace during a typical workday. They are not discussed in this review because at this time they are unavailable as diagnostic testing options for physicians in clinical practice in the U.S. Excellent discussions can be found in other references [e.g., Bernstein, 1993; Chan-Yeung, 1995b].

latency (mainly Reactive Airways Dysfunction Syndrome or RADS, which is discussed below). Latency is defined as the time (generally months to years) between initial exposure to the asthma inducing agent and development of symptoms. A history of childhood onset asthma in remission does not exclude OA.

In the United States, where Specific Bronchial Challenge Testing is not available in clinical settings, OA has recently been defined more broadly to include Occupationally Induced Asthma and Occupationally Aggravated Asthma [Balmes, 1991; Wagner and Wegman, 1998; Gassert, et al., 1998; Kuschner, et al., 1998]. This definition emphasizes the importance of prevention of morbidity and disability from asthma that is exacerbated by environmental exposures in the workplace. Wagner and Wegman, in formalizing this broader definition of OA, have included three categories [Wagner and Wegman, 1998]:

(1) Immunologically mediated asthma resulting from exposure to sensitizers in the workplace;
(2) Asthma resulting from exposure to irritants in the workplace; and
(3) Pre-existing asthma exacerbated by workplace environmental exposures.

Since medical or preventive management may differ among the three categories proposed, it is useful, when diagnostically feasible, to distinguish among them. Whether the term WRA, or OA (broadly defined), is preferred, the important points are that asthma exacerbated by workplace environmental factors is a clinical entity with public health and economic importance, and that it is often preventable.

Reactive airways dysfunction syndrome (RADS)

RADS is new onset asthma which begins within hours following a single exposure to inhaled irritants at very high concentrations, and continues to be symptomatic for three months or longer [Brooks et al., 1985; Alberts and DoPico, 1996]. When it is caused by an exposure in the workplace, RADS is considered to be a form of OA without latency. The ACCP consensus medical case definition for RADS is presented in Table II. The more inclusive term Irritant Induced Asthma, which includes RADS, has been proposed and may become the preferred term. Evidence is beginning to emerge that RADS can be seen as one end of a spectrum of irritant effects on the airways. Repeated exposures to lower levels of inhaled irritants may in some cases cause new onset of asthma or abnormal non-specific bronchial responsiveness (NSBR) [Chan-Yeung, et al., 1994b], or can cause individuals with previously undiagnosed and asymptomatic or subclinical asthma or atopy to progress to frank asthma [Brooks, 1998]. If these concepts gain more general acceptance, the category ''Irritant Induced Asthma'' could include cases which would otherwise be diagnosable as RADS, but do not meet all of ACCP RADS criteria 2,3,4, and 6 (Table II).

Work-aggravated asthma (WAA)

WAA is diagnosed in individuals with symptomatic asthma that is significantly worsened by workplace environmental exposures. This includes people with preexisting asthma, as well as with new onset asthma, as long as the asthma is clearly aggravated by environmental exposures in the workplace. Aggravation in the workplace can manifest as an increase in frequency or severity of asthma symptoms, an increase in medication required to control symptoms, or clinical improvement when workplace exposures are reduced or eliminated. Individuals with asthma induced by occupational exposures may also be diagnosed with WAA.

Workplace Exposures Associated with WRA

Over 250 agents or conditions found in the workplace (i.e., specific substances, occupations or industrial processes) have been reported to be associated with the onset of asthma, based on epidemiologic and/or clinical evidence. Published lists of these agents and references can be useful in the clinical setting, with the caveat that the lists are continuously evolving [e.g., Chan-Yeung and Malo, 1994; Malo and Chan-Yeung, 1997; Brooks, 1998]. In WRA, airflow obstruction can be caused by mechanisms involving immunologic response to sensitizing agents, direct irritant effects, or other nonimmunologic processes. Some agents (e.g., organophosphate insecticides) may cause bronchoconstriction by direct pharmacologic action. Most of the agents that appear in the referenced lists are thought to induce a sensitization response. A single exposure to a very high concentration of a respiratory irritant can cause new onset of asthma, i.e., RADS. In addition, a broad range of nonallergenic respiratory irritants which may be present in the workplace can, with repeated, lower levels of exposure, trigger or worsen symptoms in workers with existing asthma, and may possibly cause new onset of asthma symptoms.

Sensitizing agents that can cause OA are currently classified as high molecular weight (5,000 Daltons (Da) or greater) or low molecular weight (less than 5,000 Da); a few examples are shown in Table III. High molecular weight sensitizing agents primarily include proteins that act as allergens by an IgE-dependent mechanism. Low molecular weight sensitizing agents include highly reactive chemicals like isocyanates, and may act as haptens, combining with body proteins, or may act by IgE independent mechanisms. Current understanding of inflammatory mechanisms acting

TABLE III. Some Examples of Agents That Can Cause Occupational Asthma[a]

Classification	Sub-groups	Examples of substances and sources	Examples of jobs and industries
High molecular weight sensitizers	Animal-derived substances	Laboratory animals, crab/seafood, egg protein, grain mites, insects	Laboratory workers, seafood processing, egg production, silk workers
	Plant-derived substances	Flour and grain dusts, powdered natural rubber latex gloves, biologic enzymes, castor bean dust, vegetable gums	Bakers, health care workers, detergent making, pharmaceutical manufacturing, food processing
Low molecular weight sensitizers	Plasticizers, paints, 2-part adhesives, foams	Diisocyanates, acid anhydrides, aliphatic amines, methyl methacrylate and cyanoacrylate	Auto spray painting, varnishing, woodworking, dentistry and adhesive manufacturing
	Metals, fluxes	Platinum salts, cobalt, colophony	Platinum refineries, hard metal grinding, electronic (soldering)
	Wood dusts	Cedar (Plicatic acid), Oak	Sawmill work, carpentry
	Pharmaceuticals/Drugs	Psyllium, cephalosporins	Pharmaceutical manufacturing and packaging
Other chemicals		Chloramine T, polyvinyl chloride fumes, reactive dyes, formaldehyde	Janitorial work, meat packing, pest control, textile and dye manufacturing, embalming

[a]See Malo and Chan-Yeung [1997] for more complete list, with references.

in OA has been recently reviewed [Reibman and Brooks, 1998].

In clinical practice settings, a large variety of different agents are associated with WRA, generally with only small numbers of cases related to any one particular agent. In over 600 patients with WRA seen by 18 member clinics of the Association of Occupational and Environmental Clinics, and 8 additional clinics in the New York State Occupational Health Clinic Network, over 170 different agents and categories of agents have been reported [Hunting et al., 1995; personal communication with M. London, 1997]. A few of the more commonly identified sensitizing agents are included in Table III. Common irritants include chlorine, ammonia, hydrogen chloride, formaldehyde, oxides of nitrogen, ozone, sulfur dioxide, diesel fumes, fire smoke, and acid mists, and others [Guidotti, 1998]. Lists of agents implicated in new onset, irritant-induced asthma, have been published [Malo and Chang-Yeung, 1997; Brooks, 1998]. The range of irritants and physical agents that can aggravate existing asthma is quite broad. Symptom precipitants reported frequently by the 26 clinics nationally have included dusts, solvents, paints, molds and fungi, environmental tobacco smoke, welding fumes, cold air, and exercise.

In epidemiologic studies of workers in high risk occupations, workplace exposures are the most important determinants of the new onset of OA. Risk of developing OA with latency tends to increase with duration and estimated intensity of exposure, and peaks of exposure intensity may be important. Other factors, such as characteristics of the sensitizing agent (e.g., high or low molecular weight), may also affect risk of OA. In studies of agents that act through IgE dependent mechanisms, atopy is an important and smoking a somewhat less consistent risk factor for asthma occurrence. In studies of agents acting through IgE-independent mechanisms, neither atopy nor smoking appear to be an important determinant of asthma onset [Chan-Yeung and Malo, 1995].

Clinical Presentations of WRA

The symptoms of WRA are the same as those of other forms of asthma: recurrent episodes of cough (productive or nonproductive), wheeze, chest tightness, and shortness of breath. Patients sometimes present with cough variant or nocturnal asthma. WRA can be severe and disabling, and three deaths have been reported in the medical literature from sensitizer-induced OA previously documented by specific bronchial challenge testing [Fabbri et al., 1988; Ehrlich, 1994; Carino et al., 1997]. In all three fatal cases, asthma symptoms leading to death developed and worsened rapidly, following unprotected workplace exposures to isocyanates (two cases) or flour (one case), after medical recommendations to permanently cease exposure had been given but not followed.

Several features of the clinical history suggest occupational etiology or aggravation. Symptoms may frequently worsen at work or at night after work, improve on days off, and recur on return to work. Symptoms may worsen progressively toward the end of the work week. The patient may note specific activities or agents in the workplace that predictably trigger symptoms. Work-related eye irritation or rhinitis may be associated with asthmatic symptoms. These typical symptom patterns may be present only in the initial stages of WRA. Partial or complete resolution on weekends or vacations is common early in the course of WRA, but with repeated exposures, the time required for recovery may increase to one or two weeks, or recovery may be incomplete.

Several characteristic temporal patterns of symptoms have been reported for sensitizer induced OA, based on data from specific bronchial challenge testing with sensitizing agents. *Early* asthmatic reactions typically occur shortly (less than one hour) after challenge. *Late* asthmatic reactions begin 4–6 h after challenge, and can last 24–48 h. Combinations of these patterns occur as *dual* or *biphasic* asthmatic reactions with spontaneous resolution of symptoms separating an early and late reaction, or as continuous asthmatic reactions with no resolution of symptoms between phases. For the small number of agents that have been studied, IgE-mediated reactions tend to be early or biphasic and IgE-independent reactions tend to be late or atypical [Chan-Yeung, 1995]. Actual exposures in the workplace, which often persist longer than a brief challenge in the laboratory, may produce atypical temporal patterns of bronchoconstriction and symptoms that differ from these classic patterns. Temporal patterns can be deceptive in some patients with late reactions who may paradoxically experience the onset of symptoms at home after leaving the workplace. Predictable onset of symptoms in evenings after work, with less severe or frequent symptoms in evenings of days off can be an important clue suggesting WRA. Some individuals with a history of childhood asthma or with concurrent asthma may develop OA as a result of workplace exposures [Chan-Yeung, 1995]. Sensitizer induced OA may have a highly variable latency period. It can be as short as several weeks, and is often less than two years, but in approximately 20% of cases is 10 years or longer.

RADS is caused by inhalation exposure to a high concentration of an irritant gas, fume, vapor, or dust resulting in significant acute airway injury. When caused by an exposure in the workplace, RADS is a form of OA without latency. Onset of chest symptoms occurs within 24 h of the inhalation injury. Asthmatic symptoms continue to occur for at least three months, accompanied by persistent or intermittent airflow obstruction and increased NSBR. The work-related temporal pattern of symptoms commonly seen in new onset sensitizer-induced asthma may be absent in RADS, especially if the injury was caused by a one-time accidental exposure without the ongoing workplace inhalation exposures to irritants.

WAA appears to be common, and may cause a substantial and preventable burden of disability, but little has been published on pathophysiology, diagnosis, management, or prognosis. The important characteristic of WAA is that exposures in the workplace cause worsening of asthma. Worsening of asthma may be obvious, as when asthmatic symptoms are triggered by specific exposures recognized by the patient, and begin minutes to several hours after exposure occurs. Work-aggravation of asthma may be less obvious with late or dual asthmatic reactions which occur many hours after the exposure. Increased frequency or severity of asthmatic symptoms may only be apparent when it is noted that increased medication is required to control symptoms, or that the symptoms only clearly improve when the relevant workplace exposures are reduced or eliminated.

The effect on prognosis of continuing exposure to the asthma-precipitating agent has been well studied in patients with sensitizer-induced OA [Bernstein et al., 1993]. Among patients whose exposures are terminated, a substantial proportion continue to have symptomatic asthma even years after cessation of exposure. Longer duration of symptoms prior to cessation of exposure has been associated with higher likelihood of permanent asthma, impairment, and disability. Observations that prognosis is better with shorter duration of exposure suggest that early diagnosis, when accompanied by identification and appropriate control of causative exposures and conditions, can improve the long term prognosis. In Ontario, where ongoing medical screening for isocyanate workers is mandated, the better prognosis of patients with OA induced by isocyanates (compared with patients with OA induced by other sensitizers) has been attributed to earlier recognition, diagnosis, and exposure cessation [Tarlo et al., 1997]. In general, the high likelihood of chronicity of OA supports placing a high priority on primary prevention of sensitization.

DIAGNOSIS: A STEPPED APPROACH

Diagnosis of WRA involves establishing both the diagnosis of asthma and the relation between asthma and workplace exposures. The diagnostic process for WRA involves initial suspicion of possible WRA, preliminary evaluation, and confirmatory evaluation [Chan-Yeung, 1995]. Once WRA has been suspected, the diagnostic evaluation has been divided into four steps, summarized in Table IV. The first two steps constitute the *preliminary evaluation* (clinical evaluation for asthma and thorough occupational and environmental history) and, if possible, are performed in the primary care setting. Referral of a patient with suspected WRA to an occupational medicine or pulmonary specialist for the detailed occupational and environmental history is a reasonable alternative if the primary care provider is not able to perform this step. The *confirmatory evaluation* includes immunologic assessment and prospective clinical monitoring at and away from work. For a few occupational sensitizers, specific serologic tests are commercially available and can be quite helpful to the

TABLE IV. Steps and Diagnostic Tools for Clinical Evaluation of Patients with Suspected Work-Related Asthma

Preliminary evaluation

Step 1: Clinical Evaluation for Asthma

- Thorough medical history and review of medical records
- Directed physical examination
- Pulmonary function testing
- Quantitative testing for nonspecific bronchial responsiveness
- Other laboratory testing

Step 2: Occupational and Environmental History

- Employment history
- History of temporal pattern of symptoms with respect to work
- History of occupational and environmental exposures and symptom triggers
- Objective verification of exposures, if possible

Confirmatory evaluation

Step 3: Immunologic assessment

- Serologic tests
- Skin prick testing

Step 4: Prospective clinical monitoring at and away from work

- Step 4a: Clinical monitoring during routine work schedule (including evenings and weekends)
- Step 4b: Clinical monitoring during diagnostic trial of avoidance of exposures
    - Serial chest auscultations
    - Serial spirometries
    - Prospective patient diary
        - Serial peak expiratory flow measurements
        - Workday vs. day off
        - Asthma Symptoms
        - Relief Bronchodilator use
        - Exposures

This is intended as a general guide to facilitate practical and efficient diagnostic evaluation. It is strongly recommended that physicians who diagnose and manage WRA refer to current clinical literature as well.
WRA, Work-Related Asthma; Rast, Radioallergosorbent Test; ELISA, Enzyme Linked Immunosorbent Assay; PEF, Peak Expiratory Flow; NSBR, Nonspecific Bronchial Responsiveness.

primary care provider. Subspecialty expertise may need to be considered in the performance and interpretation of non-FDA approved immunologic tests and/or workplace clinical monitoring. In locations where either specific bronchial challenge testing or workplace challenge testing is available to practicing clinicians, one or both of these may be performed as a fifth step. This is, however, not the case in the United States, so these tests have not been included as part of the stepwise diagnostic procedure. The diagnostic evaluation may be terminated after any of the four steps if the evidence for WRA is sufficient to support the necessary management, prevention, and public health decisions, or if the remaining steps are not feasible (e.g., patient is no longer working).

Differential diagnosis of WRA includes asthma that is not work-related; chronic obstructive pulmonary disease; airway symptoms or chronic bronchitis due to inhaled irritants without airflow obstruction or increased NSBR; hypersensitivity pneumonitis; inhalation fevers due to metals, polymers or organic dusts; laryngeal or vocal cord dysfunction; congestive heart failure with wheezing; airway obstruction due to tumor, foreign body, or stricture; recurrent gastroesophageal reflux with aspiration; and carcinoid syndrome. Some of these can be easily ruled out in the preliminary evaluation.

Early and accurate diagnosis of WRA, accompanied by appropriate modification or cessation of exposures, can bring substantial benefits, by improving the long term prognosis for significant improvement, or even cure, of the patient. This can potentially reduce or eliminate the substantial costs of medical care and disability due to chronic asthma. Recognition of one index case in a workplace may provide an opportunity to prevent new onset asthma in coworkers. If the work-relatedness is not recognized, the clinician forfeits the opportunities for effective treatment of the individual, and for prevention of asthma in coworkers. Conversely, a diagnosis of WRA may obligate a complete change of occupation, or substantial interventions in the workplace in order to prevent or limit ongoing disability. Thus, accuracy in distinguishing asthma that is not work-related from WRA is important. Underdiagnosis and over-diagnosis of WRA can both lead to avoidable, substantial costs to patients, their families, employers, health care insurance organizations, and society.

In spite of the importance of accurate and timely diagnosis of WRA, the diagnostic process is not always straightforward. Thorough clinical evaluation of WRA can be time consuming and difficult, and sometimes is not feasible. It may require multiple spirometries, immunologic testing, prospective clinical evaluation during routine work schedule, or a diagnostic trial of control or avoidance of the exposure(s) suspected of causing or aggravating asthma symptoms. Some components of the clinical evaluation are not readily available to many physicians (e.g., serial quantitative testing for NSBR). Other components may simply not be achievable, (e.g., clinical evaluation at work if the patient is no longer working; adequate serial PEF measurements). Often, only a few of these tests will be necessary or achievable for a given patient, although diagnostic certainty is likely to increase with the thoroughness of the clinical evaluation. For each individual patient, decisions on the extent of medical evaluation will need to balance costs of the evaluation with the clinical, social, financial, and public health consequences of incorrectly diagnosing or ruling out WRA.

In consideration of these difficulties, a stepped approach to the diagnosis of WRA is outlined in Table IV and the flow chart in Figure 1, and details are discussed below. This is intended as a general guide to facilitate accurate, practical, and efficient diagnostic evaluation, recognizing that some of the suggested procedures may not be available, and a different order may be more expeditious in some cases. After each step, for each patient, the physician will need to determine if the evaluation can or should proceed to the next step, or whether the information at hand is sufficient to support the necessary decisions. If facilities and resources are available, the time and cost of continuing the clinical evaluation may be justified by the importance of making an accurate determination of the relationship of asthma to work. As shown in Figure 1, evaluation may need to be an iterative process, returning to an earlier step for reassessment after completing a later step. For example, if the patient diary described in Step 4 suggests particular agents not previously considered, Steps 2 and/or 3 may be repeated to gather more information on workplace exposures or immunologic sensitization.

A central diagnostic question is whether the patient can be evaluated while working in the job associated with asthma symptoms. If it is both feasible and safe, prospective monitoring at work and away from work of asthma symptom patterns, medication use, and physiologic measurements is the diagnostic approach of choice. If this is medically inadvisable, is not feasible, or places the worker at the risk of job loss, the level of diagnostic certainty may be limited to that achievable in the first two or three steps. In evaluation of work aggravated asthma, objective verification of worsening of asthma at work should be attempted, if at all possible.

Initial Suspicion of WRA

The possibility of WRA should always be considered if new onset or substantial worsening of symptoms suggestive of asthma occurs in a working adult, whether or not asthma has been previously diagnosed. Recognition and diagnosis of WRA depend critically on initial suspicion of possible WRA by primary care providers, as well as by subspecialist and emergency physicians, nurses, other clinicians, or workers themselves.

Three clues to possible WRA should be elicited and, if present, any one of these should motivate further evaluation for WRA. The first clue is a work-related temporal pattern of symptoms suggestive of asthma. Second, the patient may identify specific agents, processes or conditions at work that trigger asthma symptoms. Third is inhalation exposure to any of several broad categories of airborne agents in the workplace in which asthmatic symptoms began, distinctly worsened, or had a work-related temporal pattern. Broad exposure categories include: dusts; irritating gases, fumes, vapors or smoke; or airborne presence of known sensitizing agents such as those in Table III or one of the published lists. If any one of these three clues is present, the individual should undergo the preliminary evaluation as outlined in the next section.

Preliminary Evaluation

Preliminary evaluation consists of the clinical evaluation for asthma (Step 1) and an occupational and environmental history (Step 2). Once the suspicion of WRA has been raised, the diagnosis of asthma should first be confirmed or excluded. If possible, reasonable objective evidence supporting the asthma diagnosis should be obtained before investing a great deal of effort in evaluating the relation of asthma to work.

Step 1. Clinical Evaluation for Asthma

Diagnosis of asthma is reviewed in other sources [NAEPP, 1997; Boushey, 1997] and will not be discussed in detail in this review. Components of the diagnostic process particularly pertinent to evaluation of WRA are highlighted

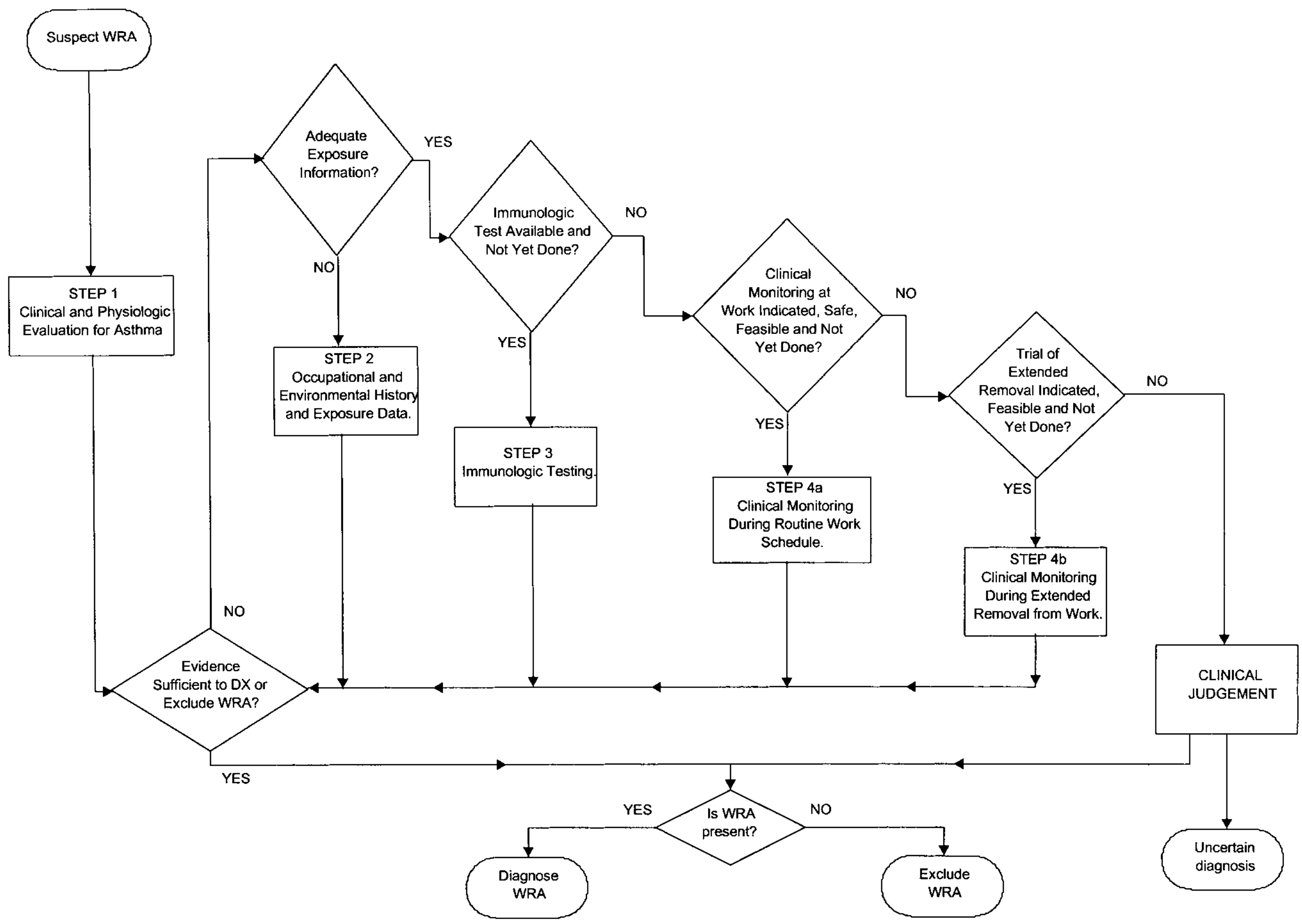

FIGURE 1. Flow chart for the clinical evaluation of patients with suspected work-related asthma. WRA, Work-Related Asthma; DX, Diagnosis.

below, including medical history, physical examination, evaluations of airway physiology and other laboratory studies.

Medical history

The medical history of patients with possible WRA should emphasize respiratory, skin and cardiovascular systems, allergies, smoking, and current medications. Thorough review of medical records for diagnostic evidence related to asthma can often be quite helpful and should be done if possible. Respiratory history should emphasize details of asthma. In particular, it is important to document upper and lower respiratory symptoms, symptom triggers (i.e., specific aggravating factors both at work and outside work), date of first onset of symptoms, date and supporting evidence of prior asthma diagnosis, any prior objective evidence of reversible airflow obstruction (e.g., spirometry, PEF, wheezing on physical examination), and indicators of severity of asthma. Past history of other respiratory disorders, especially respiratory infections, bronchitis, or emphysema, should be noted. A recent chest radiograph and complete blood count with differential should be reviewed. Results of allergy testing, as well as personal history of allergic rhinitis, sinusitis, urticaria, atopic dermatitis, food allergies, past anaphylaxis, and family history of asthma or allergies are relevant. Gastroesophageal reflux can aggravate symptoms of asthma, particularly at night. Ingestion of aspirin, other nonsteroidal anti-inflammatory drugs, beta blockers, and sulfites in food can precipitate symptoms. Angiotensin converting enzyme (ACE) inhibitors can cause cough which may be confused with asthma.

Assessment of severity of asthma is important to guide both treatment and diagnostic procedures. Severity should preferably be classified according to the standard 4-step classification of asthma severity: mild intermittent, mild persistent, moderate persistent, severe persistent. Classification of severity is based on FEV_1, PEF, limitation of physical activity, as well as frequencies of symptoms, exacerbations, use of bronchodilator inhaler, and nocturnal symptoms [NAEPP, 1997].

Physical examination

Physical examination is sometimes helpful, particularly when repeated on several different occasions. Wheezing during normal breathing is a more reliable sign of airflow obstruction than wheezing on forced exhalation. In a patient with a history consistent with asthma, a physical finding of wheezing combined with a recent exam without wheeze is supportive of the diagnosis of asthma. It should be noted that a variety of conditions other than asthma can be associated with wheezing and the finding of wheezing by itself is not highly specific for asthma. Prolonged expiratory phase and overinflation of the thorax are also supportive signs. Other physical findings relevant to asthma (e.g., nasal polyps); upper respiratory or mucosal inflammation or allergy (e.g., rhinitis, sinus tenderness, or conjunctivitis); skin allergy (hives, atopic dermatitis, or eczema); as well as potential clues to diagnostically relevant exposures (e.g., caustic burns or tobacco stains on skin) should be noted. Crackles, third heart sound, jugular venous distension, stridor, fever, or clubbing may suggest alternative diagnoses. Since variability of airway obstruction is a hallmark of asthma, many patients with asthma (especially mild intermittent asthma) may have no abnormal findings at the time of the scheduled physical examination.

Initial evaluation of airway physiology

If physiologic testing supporting the diagnosis of asthma has already been performed elsewhere, these results should be reviewed. In particular, quality and reproducibility of spirometry and degree of bronchodilator response should be noted. Baseline spirometry at the beginning of the evaluation for WRA should be performed, before and after bronchodilator. If possible, it may be useful to perform spirometry at a time when the patient is experiencing asthmatic symptoms. Airway obstruction is considered reversible and supports the diagnosis of asthma if it is accompanied by an increase of 12% or more in FEV_1 after bronchodilator, with at least 200 mL/s absolute increase [ATS, 1991, 1995]. Diurnal variability of PEF of 20% or more also supports the diagnosis of asthma [NAEPP, 1997]. Distinction between asthma and COPD may need to be made, considering the overall clinical presentation. If spirometry reveals significant airflow limitation that does not improve after inhaled bronchodilator, re-evaluation after more prolonged trial of therapy, including corticosteroids, should be considered [ATS, 1993; NAEPP, 1997]. Individuals who have experienced an identifiable episode of exposure to a respiratory irritant at very high concentration, with acute symptoms, should be evaluated as soon as possible after the event for presence of airflow obstruction and, if appropriate, NSBR.

For patients in whom the existence of reversible airway obstruction or hyper-responsive airways remains in question, quantitative bronchoprovocation testing by an experienced pulmonary function laboratory using methacholine or histamine should be considered. Quantitative testing for NSBR in this situation can be useful for three reasons. First, it can identify patients with early stage WRA who may have the greatest potential for complete resolution of symptoms or prevention of chronicity and disability, but who would be missed if testing is stapped after a normal spirometry. Second, if spirometry and NSBR are normal during or within two weeks of stopping regular work in the workplace environment associated with the symptoms, WRA can generally be ruled out without further testing. Third, if abnormal, a quantitative measurement of NSBR (e.g., PC_{20}) may be useful in monitoring the patient for improvement after diagnostic trial of avoidance of the suspected causal exposure, and in long-term follow-up.

Other laboratory studies

In some cases, there may be a role for other laboratory studies. The chest radiograph is often normal in asthma. Findings of overinflation of the lungs or bronchial wall thickening, with clinical correlation, suggest asthma, and other findings may suggest other diagnoses. Blood eosinophilia, positive skin prick or serologic testing to common home and community antigens, and elevated serum total IgE may, if present, provide evidence of allergy and support the diagnosis of asthma. Sputum examination is not part of the routine evaluation of asthma or WRA, but in occasional cases, may be helpful in differentiating asthma with copious sputum production from chronic bronchitis, if it reveals eosinophil predominance, Charcot-Leyden crystals or Curschmann's spirals. Unless asthma can be ruled out based on the initial evaluation, diagnostic evaluation should proceed to the next step: occupational and environmental history.

Step 2. Occupational and Environmental History

The occupational and environmental history should include employment history, assessment of temporal patterns of symptoms, and a detailed exposure history, with objective verification if possible. Taking a detailed occupational and environmental history may be quite time consuming. Adequate patient encounter time should be allotted for this important step, which frequently takes an hour or longer. This often is an iterative process, which may require reassessment of temporal patterns after identification of workplace activities or exposures suspected to be related to symptoms, or reassessment of relevant workplace activities and exposures after exploration of temporal symptom patterns. Employment history, temporal pattern of symptoms, and a detailed history of exposures and symptom triggers should be included.

Employment history

Employment history should include current work status, as well as details of current and relevant past employment with dates, job titles, industry, and job tasks. At a minimum, this should be completed for current job and jobs held at time of first onset, recurrence, or significant worsening of symptoms. In some cases, a chronological employment history including all jobs held since beginning of asthma symptoms may be helpful.

Temporal pattern of symptoms

After clarifying the asthmatic symptoms the patient is experiencing, it is important to assess any temporal pattern that may exist between the occurrence of these symptoms and workdays, days off, and specific activities or exposures in the workplace that are suspected to be related to the symptoms. A five-item questionnaire has been reported to be highly sensitive, although not specific, for OA when a "yes" response is given to one or more of the questions [Matte et al., 1990; Klees et al., 1990; Balmes, 1991]. The five questions are:

- Did symptoms of asthma develop after a worker started a new job or after new materials were introduced on a job? (a substantial period of time may elapse between initial exposure and development of symptoms)
- Do symptoms develop within minutes of specific activities or exposure at work?
- Do delayed symptoms occur several hours after exposures or during the evenings of workdays?
- Do symptoms occur less frequently or not at all on days away from work and on vacations?
- Do symptoms occur more frequently on returning to work?

While symptoms typically show a work-related pattern in WRA of recent onset, this pattern may become less distinct or disappear over time, even in well-documented cases of sensitizer-induced OA. Thus, it is important to explore temporal pattern of symptoms not only for current job, but also for past jobs, especially the job held when asthma symptoms first began or significantly worsened.

Exposures and symptom triggers

It is helpful to begin the exposure history in an open ended way by reviewing exposure to, or work with, broad categories of airborne agents or sources of bioaerosols: dusts; chemicals; animals; and irritating gases, fumes, vapors or smoke. Positive responses should then be investigated in more detail. For example, details of exposure to specific organic dusts of animal, plant, microbial or pharmaceutical origin should be elicited. Products containing proteolytic enzymes should be identified, if possible. Visible mold or fungal growth due to excessive moisture or water leaks is a clue to possible airborne allergens. Animals that generate bioaerosols that may induce asthma include cats, rodents, and other animals that may be found in laboratories or other workplaces, as well as insects. Specific chemicals of interest are numerous. Some important examples of agents reported to cause OA are given in Table III, and more complete lists can be found in standard references (e.g., Malo and Chan-Yeung, 1997; Brooks, 1998]. It is useful to try to distinguish irritants from likely sensitizing agents, although there is overlap for some chemicals.

Symptom triggers can provide important clues to relevant exposures. The patient is often able to identify specific activities or exposures that trigger typical asthma symptoms. Identification of triggers of rhinitis and ocular symptoms may also be helpful in recognition of triggers of asthma symptoms. Asking the patient to sketch the work area and describe step-by-step the activities and exposures involved in the most recent symptomatic workday can be a useful exercise. Materials used by coworkers, or those released in high concentration from a spill or other source, may be relevant. In addition to identifying symptom triggers in the current workplace, it is important to determine exposures and triggers at the time of first onset, recurrence, or significant worsening of asthma symptoms.

The patient may be able to identify specific product names, work processes, or generic categories of agents that have triggered symptoms, but usually will not know the constituents of brand-name products. Efforts should be made to identify and document in as much detail as possible the specific exposures in the workplace that are causing or aggravating the asthma. Identification of relevant workplace exposures is best done with the cooperation of both the employer and the patient. Patient confidentiality is key, however, even if the physician and/or industrial hygienist work for the employer. The physician and industrial hygienist must be sensitive to the possible risk of job loss, and, when appropriate, should discuss this with the patient before communicating with the employer.

Qualitative exposure identification can be time consuming and difficult, and is perhaps most efficiently approached by starting with the products or processes that the patient has identified as symptom triggers. Further information can often be obtained from the patient or employer on the exact product name, and name, address and phone number of the manufacturer of the product. Product labels and Material Safety Data Sheets (MSDSs) may provide useful information on toxic constituents of specific products, particularly those with known irritant properties. One caveat is that these tend to include only recognized toxic ingredients present in more than trace quantities. In the case of asthma induced or triggered by a sensitizing agent, however, the sensitizing agent may not be listed at all if it is not generally regarded as a toxic chemical (e.g., many allergens), or constitutes only a very small proportion of the product composition. Specific agents used in commercial products, as well as some of their important chemical and physical properties and health effects can be identified through a variety of sources, including textbooks, CD-ROM and online databases, and Poison Control Centers. If these sources do not provide adequate information, it may be necessary to call the manufacturer and request a complete list of product constituents as a matter of urgent medical necessity. The physician may be required to provide written assurance of confidentiality if some ingredients are ‘‘trade secrets’’.

The process of exposure assessment can often benefit from the specialized expertise of an industrial hygienist. An industrial hygienist experienced with allergens as well as chemical toxicants can sometimes provide qualitative information critical to diagnosis, on likely causal or triggering exposures and exposure pathways. In addition to gathering and interpreting information from the sources above, in some cases, the industrial hygienist may be able to arrange a walkthrough inspection of the workplace. Identities of specific exposures, probable and improbable exposure pathways, availability and utilization of preventive measures, and potential for remediation of hazardous exposure conditions may only become clear through first hand evaluation of the workplace.

Measurement of air concentrations of specific chemicals is not usually necessary in the evaluation of WRA, but may be useful in certain limited circumstances. For example, when an industrial hygiene intervention is conducted to lower exposures, serial measurements of air concentrations of specific irritant chemicals may provide useful information to complement ongoing clinical monitoring of selected individual patients. The role in diagnostic evaluation and routine management is less clear, however. If the patient is sensitized to a specific agent, even extremely low or unmeasurable air concentrations can cause asthmatic reactions of unpredictable severity. Even in cases of irritant-aggravated asthma, average air levels of irritants do not reliably correlate with aggravation of symptoms, and air level standards were not designed to protect asthmatic individuals from triggering of symptoms by irritants. Peak concentrations of irritants, which may be important predictors of symptoms, vary considerably over short time intervals and are difficult to capture accurately. Thus, measurement of air levels of suspected causal agents is useful only in very limited circumstances, and is not expected to play any role in the majority of clinical evaluations for WRA. As dose–response relationships are highly variable, qualitative exposure assessment is more frequently useful than quantitative exposure assessment.

Suspected exposures should be compared with a comprehensive list of agents associated with WRA [Brooks, 1998; Malo and Chang-Yeung, 1997]. The strength of evidence supporting causal relation for agents on published lists varies greatly by agent, from individual case reports to large epidemiologic studies or clinical studies utilizing specific bronchial challenge testing. Induction and aggravation of asthma by agents not previously described, or not on the lists, undoubtedly occurs as well. For these reasons, online literature searches and critical appraisal of the primary literature may be extremely useful for some suspected exposures. Detailed identification and objective verification of specific workplace exposures should be considered in all cases, although inability to do so is not uncommon and should not preclude diagnosis of WRA if other evidence is adequate.

Other environmental history should include review of exposures in the home or community that could trigger asthma (e.g., house dust hygiene; cats, cockroaches and other animals; cleaning chemicals; seasonal allergens; hobby exposures; tobacco smoke; water damage or excessive moisture with visible mold or fungal growth). Existence of one or more asthma triggers outside the workplace appears to be common in WRA, and this does not exclude the diagnosis of OA or WAA. Significant exposure to triggers outside the workplace can obscure a work-related environmental component of asthma.

At this point in the diagnostic process, the only evidence available to determine work-relatedness of asthma is the clinical history. While the diagnostic accuracy of the clinical history for WRA is not known, the accuracy of the clinical history in diagnosing and ruling out sensitizer-induced OA has been reported [Malo et al., 1991]. The study group was composed of patients referred by primary care or chest physicians or the Workers' Compensation Board for evaluation of possible occupational asthma. An open-ended clinical history elicited by experienced specialists in occupational asthma was compared with a ‘‘gold standard’’ diagnosis based on objective assessment, including serial peak flow measurements and/or serial nonspecific bronchial challenge testing, and/or specific bronchial challenge testing with specific sensitizing agents present in the workplaces of the patients. Subjects with RADS were excluded, and subjects with symptoms triggered only by nonspecific or irritant substances were included and classified as not having OA. In this series of referred patients, prevalence of OA by objective assessment was 46%, specificity of the clinical history was 55% and sensitivity was 87%, yielding a predictive value positive of 63% and a predictive value negative of 83%.

These results apply only to sensitizer-induced OA, not to irritant-aggravated or irritant-induced WRA. Even so, the authors' recommendation to seek objective information in addition to the clinical history whenever possible in making a diagnosis of OA seems a reasonable approach to diagnosis of WRA as well. The one caveat is that, in settings in which objective tests for WRA are often unavailable, and in which prevention of chronic asthma and disability are important priorities, clinicians will often be compelled to recommend reasonable interventions in the face of diagnostic uncertainty. The consequences of incorrectly diagnosing or excluding WRA provide substantial motivation to proceed to the confirmatory evaluation, Steps 3 and 4.

Confirmatory Evaluation

Once thorough medical and exposure histories are gathered, compatibility with the clinical presentation of WRA described in that section should be evaluated. Work-related temporal pattern of symptoms, workplace exposure to agents or conditions previously reported to induce or aggravate asthma, and patient report of symptom trigger(s) in the workplace are particularly important. If all three of these are absent, the diagnosis of WRA can be excluded at this point. If one or more is present, the patient generally can be placed into one of the three presumptive classes of WRA: OA with latency, OA without latency (including RADS), or WAA, and confirmatory evaluation should be done, if possible. Confirmatory evaluation can include immunologic assessment (Step 3) and/or prospective clinical monitoring at and away from work (Steps 4a and 4b). Specific bronchial challenge testing with suspected causal agent(s) cannot be considered part of the clinical evaluation of WRA in locations, such as the United States, in which it is not currently available as a clinical test.

If a specific sensitizing agent is suspected, and a standardized reagent is available for either skin testing or serologic antibody testing, immunologic assessment may be diagnostically helpful. In order to prospectively contrast asthma symptom patterns and physiologic measurements at work with those away from work, the patient can be evaluated clinically over a several week period while working in the job associated with symptoms. If the patient is not working in the relevant job, but return to work in that job is feasible, clinical evaluation away from work can be completed first, followed by a clinical evaluation during routine work schedule. If clinical evaluation at work in that job is not feasible, clinical decisions must be made based on evidence available from the first two or three steps. Until more definitive and practical diagnostic tests are widely available, confirming or excluding the diagnosis of WRA will sometimes be based primarily on clinical judgment. It is expected that in most but not all cases, the confidence with which WRA can be diagnosed or excluded will be adequate to support the important decisions that need to be made. After the confirmatory evaluation, the specific categories of OA with latency, OA without latency (including RADS), or WAA should be determined, if possible. Distinguishing among these diagnoses and identifying the specific causal or aggravating agent(s) can be helpful in guiding clinical and public health management.

Step 3. Immunologic Assessment

Immunologic assessment for workplace-relevant allergens can be very helpful in investigating work-relatedness, especially in cases where physiologic evaluation at work is no longer possible. If medical and occupational history suggest sensitizer-induced WRA (i.e., OA with latency) and suspected aeroallergens present in the workplace are identified, skin prick or serologic testing may be able to demonstrate or exclude IgE-mediated immunologic sensitization. The utility of immunologic evaluation is greatest for agents for which standardized in vitro tests or skin prick reagents are available, such as platinum salts, natural rubber latex, wheat, some molds, some laboratory animals, and detergent enzymes. For serologic tests, clinicians may want to utilize laboratories with which they have enough experience to judge reliability of the assays. Currently, the major limitation of immunologic evaluation is that standardized serologic or skin prick tests are available for only a small fraction of workplace-relevant antigens.

Evidence is beginning to emerge that, when appropriate immunologic tests are available, a positive result may be diagnostically helpful. Specifically, the combination of (1) clinical history suggestive of WRA, (2) documented asthma or airway hyper-responsiveness, and (3) immunologic evidence of sensitization may, for some sensitizing agents, be adequately predictive of confirmation of OA by specific bronchial challenge testing. In one study of *Psyllium*-exposed workers, all of six subjects who met all three of these conditions had OA confirmed on subsequent specific bronchial challenge testing [Malo et al., 1990]. In another study, of latex allergy, all of five subjects who met all three criteria had OA confirmed on specific bronchial challenge testing [Vandenplas et al., 1995]. Attempts by these and other research groups to replicate these observations with larger numbers and for other sensitizing agents will be important.

The diagnostic significance of negative immunologic testing is limited, since it is difficult to ensure that all likely causal antigens in the workplace have been included in the testing. A negative result on an immunologic test for a particular antigen can only be used to rule out sensitization to that specific antigen, and then only if the diagnostic sensitivity of the test is adequate and the pre-test probability of sensitization is not too high. This must be determined individually for each patient and allergen. Skin prick testing tends to be more sensitive than serologic tests. It is, however, less readily available and must be done by physicians experienced with the procedures, in a setting where possible adverse reactions can be managed appropriately.

Step 4. Prospective Clinical Monitoring At and Away from Work

If diagnostic evidence is inadequate after the first three steps, and the patient is currently working in the job associated with symptoms, or return to work at that job is feasible, efforts should be made to conduct a prospective clinical evaluation at and away from work. This step includes two parts. Step 4a is clinical monitoring of asthma during routine work schedule (including evenings and weekends off), and Step 4b is diagnostic trial of avoidance of suspected causal exposures. In some cases, if the patient has already stopped working and a diagnostic trial of return to work is both feasible and safe, Step 4b can be performed first, followed by Step 4a after return to work. Diagnostic tools for the serial clinical evaluations are the same for both steps and include chest auscultation, spirometry, and prospective patient diary including serial PEF measurements.

Step 4a. Clinical Monitoring During Routine Work Schedule

If the patient is currently working in the job associated with symptoms, clinical evaluation of asthma at work may be relatively straightforward. The first consideration, however, is safety of the patient. In some cases of severe asthma, with reasonable preliminary clinical evidence supporting association with work, the physician's judgment may be that immediate medical removal is indicated. In these cases, attempts should be made to negotiate with the employer and patient the possible return to work after symptoms are stabilized. Resignation from the job will likely jeopardize future rights to Workers' Compensation, and this issue should be discussed with the patient at the first visit.

Often the most reproducible, readily available physiologic test of changes in degree of airway obstruction is serial spirometry. To improve validity and precision, spirometry should be performed using methods and procedures recommended by the American Thoracic Society [ATS, 1995]. Unfortunately, single day cross-shift spirometry, performed before and after the workshift, is by itself neither adequately sensitive nor specific to diagnose sensitizer-induced OA. At times, however, it can contribute useful information on work-associated variability in airway obstruction in both OA and WAA. Diagnostic information may be improved by performing multiple pre- and post-shift spirometries, for example at the end of a weekend off (e.g., Monday, before and after work), and at the end of a workweek (e.g., Friday, before and after work). Timing of spirometries may be adjusted according to predictable symptom patterns or fluctuations in serial PEF measurements (see below), although mid-workday spirometries may be disruptive to the work schedule and difficult to arrange. Results should be interpreted considering symptoms, medication use and workplace exposures to potential symptom triggers. Diagnostic use of short-acting bronchodilator with these spirometries can be considered, as appropriate to the clinical situation.

An important diagnostic technique to investigate work-relatedness of asthma is serial measurement of PEF combined with a detailed patient diary. This facilitates prospective examination of temporal patterns of asthma and correlation with work. Using an inexpensive (about $20) portable meter, the patient measures PEF and records measurements at least 4 times a day [Chan-Yeung et al., 1995b; Gannon et al., 1998]. Measurements less than four times a day provide lower diagnostic accuracy. Scheduled measurements every 2 h do not provide substantially greater diagnostic accuracy, and patient compliance is more difficult. At each time, the patient also records asthma symptoms, use of relief bronchodilator medications, workday or day off, and any exposures or activities suspected to be related to asthma symptoms. For most patients, measurements should be made immediately after awakening, in the middle of the workshift, at the end of the workshift, and before sleep, plus additional times that symptoms begin or worsen. It is important that measurements be done on days off as well as workdays, at similar times each day, and that the first morning PEF be done immediately after awakening. If the patient experiences asthma symptoms at other times, additional measurements should be done, before use of short-acting relief bronchodilator medication.

Patients need to be carefully instructed to use and read the peak flow meter accurately. At each time of day, measurements are repeated three times. If the best two readings differ by more than 20 L/min, one or two additional measurements should be made. The highest value at each recording time is used for interpretation [Leroyer, 1998]. The measurements should be made for at least 16 consecutive days, e.g., two workweeks and three weekends off, if the patient can safely tolerate continuing to work. Measurements should be made during a period when the worker is exposed to the suspected causal agents at work and is experiencing a work-related pattern of symptoms. The same PEF meter should be used through the entire period.

The prospective patient diary is important, not only for the PEF measurements, but also because the prospectively gathered information allows temporal correlation of PEF, symptoms and use of relief bronchodilator medications with attendance at work, specific work activities, and exposures to suspected symptom triggers. A sample PEF diary is provided in Figure 2. Sample diaries for PEF monitoring have also been published elsewhere [e.g., Chan-Yeung, 1995]. Compliance and accuracy of the PEF measurements and diary can be enhanced if the physician and patient together record the first measurements during the office visit, if spirometry and patient measurement of PEF are performed together once to ''calibrate'' patient measurements of PEF, and if the patient is asked to mail in the diary results weekly. It is recommended that the patient record the numbers in a table, rather than in graph format. It is helpful to review with the patient what is meant by each symptom, which medication is the short-acting bronchodilator to be recorded, and which workplace exposures and activities to note.

To facilitate interpretation, the diary results should be plotted graphically by the physician. DOS-based software to do this is available free of charge from NIOSH [Hankinson, 1997], and can include symptoms and medication use at each time of day. With moderate effort, a generic spreadsheet program can also be used. Certain patterns suggest WRA, but none are pathognomonic and interpretation by an experienced reader is often necessary. Details of interpretation of PEF records are discussed elsewhere [e.g., Chan-Yeung, 1995; Burge, 1993; Gannon and Burge, 1997].

Asthma medications tend to reduce the effect of work exposures on measures of airflow. However, it is generally not medically advisable to completely discontinue medications during airflow monitoring at work. Rather, the patient should be maintained on a constant minimal safe dosage of anti-inflammatory medications throughout the entire diagnostic process, with close monitoring of symptoms, airflow, and the use of short-acting bronchodilators as needed to control symptoms. All use of bronchodilator medication should be recorded in the diary. Gannon and Burge [1997] reported that use of asthma medication to control symptoms during clinical evaluation at work lowered the sensitivity of the PEF technique to 42% from the 77–87% when no asthma medications were used [Gannon and Burge, 1997].

Advantages of serial PEF testing are low cost and produce a reasonably good correlation with results of specific bronchial challenge testing. Disadvantages include the high degree of patient training and cooperation required, the inability to confirm definitively that data are accurate, lack of a standardized method of interpretation, and the need for some patients to take one or two consecutive weeks off work to show significant improvement. Effort and procedure can significantly influence PEF measurements, especially immediately after awakening [ATS, 1995]. Portable electronic recording peak flow meters and spirometers designed for patient self monitoring are becoming more available and, for some patients, can address some of the disadvantages of serial PEF.

Increased NSBR, generally measured by histamine or methacholine challenge, is considered a cardinal feature of WRA. If a diagnosis has not yet been established, and the patient has not yet had quantitative testing for NSBR, and has no medical contraindication, it should be done at this step, immediately after at least two weeks of workplace exposure. NSBR may vary significantly over time. In a patient with WRA, NSBR may decrease within several weeks after cessation of exposure, although some degree of abnormality in NSBR commonly persists for months or years after exposures are terminated. Conversely, in a nonasthmatic person, NSBR may be temporarily increased by a recent viral bronchitis. In individuals with RADS, NSBR is not expected to vary with exposure. Changes in NSBR should be interpreted with an understanding of the potential sources of variability. Serial quantitative bronchoprovocation testing for NSBR has been advocated by some authors, but enthusiasm for this is tempered by two difficulties. First, NSBR is not readily available in many clinical settings. Second, it is not clear how large a change in PC_{20} represents a significant change in NSBR (i.e., beyond expected laboratory variability). If quantitative testing for NSBR is available and variability is well characterized in the institution's pulmonary function laboratory, the time course and degree of NSBR may be useful in diagnosis and monitoring.

A diagnostic trial of return to work should be considered. If the patient is not currently working in the job associated with symptoms, and return to work in that job is feasible. This needs to be carefully negotiated with the patient and employer. The first phase of this is optimization of medical management away from that job. The patient may be working in another job or location, but the physician should be sure that there are no workplace exposures to agents (especially allergens) that may provoke symptoms. Use of anti-inflammatory medication should be kept as constant as possible, at the minimum dose that will safely and reliably control symptoms away from exposure. Once symptoms are adequately stabilized off work, the patient should measure PEFs and keep a complete diary, as described above, until adequate baseline monitoring has been done for two weeks. Once this is done, if no medical contraindications exist to monitored re-exposure to the suspected agents in the workplace, and if agreeable to both the patient and employer, then the diagnostic trial of return to work may be performed. Before return to work, pulmonary function testing and quantitative testing for NSBR are useful to establish a baseline for comparison with repeat tests done after return to work.

For a patient with presumptive diagnosis of WRA based on Steps 1 and 2, medical contraindications to diagnostic

PEAK FLOW DIARY

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<tr><td>Write actual time</td><td>PF 1</td><td>PF 2</td><td>PF 3</td><td>Symptoms</td><td>BD? (Time)</td><td colspan="2">Comments</td></tr>
<tr><td>Awake</td><td></td><td></td><td></td><td></td><td></td><td colspan="2"></td></tr>
<tr><td>Midshift</td><td></td><td></td><td></td><td></td><td></td><td colspan="2"></td></tr>
<tr><td>EndShift</td><td></td><td></td><td></td><td></td><td></td><td colspan="2"></td></tr>
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<tr><td>Other:</td><td></td><td></td><td></td><td></td><td></td><td colspan="2"></td></tr>
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FIGURE 2. PEF diary. BD, Bronchodilator (short-acting); PF, Peak Flow; Y, Yes; N, No.

trial of return to work include, but are not limited to, the following: history of very severe or life threatening asthma exacerbation requiring hospitalization, history of anaphylaxis in the workplace, current treatment with systemic corticosteroids, or Severe Persistent asthma (NAEPP Step 4) away from work exposures, with continual symptoms or FEV_1 60% of predicted or lower. Other patients (e.g., Moderate Persistent asthma, NAEPP Step 3) may also have frequent enough symptoms or exacerbations while on optimal medical management away from work exposures, that return to the job associated with symptoms would be either unsafe or diagnostically unrevealing.

Once serial PEF monitoring has been completed for at least two weeks during the routine work schedule, the patient diary and graphical PEF results, as well as results of serial spirometries and initial and repeat measures of NSBR, should be evaluated in conjunction with the medical record. In addition to the numerical data from physiologic evaluations, frequency of symptoms, frequency of use of short-acting bronchodilator, changes in dose and type of anti-inflammatory medication needed to control symptoms, patterns of work absences due to asthma symptoms, and frequency of utilization of medical services for symptomatic asthma can all be helpful in making a diagnosis. If a work-related pattern in some or all of these parameters is consistent and WRA can be diagnosed, evaluation may stop here.

If a work-related pattern of PEF values is suggested but not clear, monitoring can be extended and serial PEF measurements at work can be continued for several more weeks, if medically advisable. If evidence at hand is still inadequate to diagnose or exclude WRA, a diagnostic trial of avoidance of suspected causal or aggravating exposures in the workplace is indicated if it has not yet been done.

Step 4b. Diagnostic Trial of Avoidance of Exposures

A diagnostic trial of avoidance of suspected causal or aggravating exposures in the workplace is sometimes indicated. The failure to observe work-related changes in PEF while the patient is working in a routine schedule does not exclude the diagnosis of WRA, since many patients will require more than a two-day weekend to show significant improvement in PEF. One study recommended that a PEF record not be considered negative unless at least ten consecutive days off work were recorded [Burge, 1982]. The patient can be removed from work temporarily, or can be moved to a different job and location which will entail no exposure to agents which are suspected of provoking symptoms. Workplace exposure to even trace amounts of allergens suspected of causing or aggravating symptoms is to be avoided during this period. If doubt exists, complete temporary removal from work is indicated. The initial diagnostic trial consists of continuation of PEF measurements at least four times daily, for at least nine consecutive days away from work exposures (e.g., five weekdays away from exposure or off work, plus weekends before and after). Doses of anti-inflammatory and long-acting bronchodilator medications should be kept constant during the trial, and each use of short-acting bronchodilators should be recorded in the diary. If this record, compared with the serial PEF diary at work, is not sufficient for diagnosing WRA, measurements should be continued for a second consecutive week away from work. After maximal time away from exposures (but at least two weeks), spirometry should be repeated, with bronchodilator if obstruction is present. If spirometry is normal, quantitative bronchoprovocation testing for NSBR should be performed and compared to NSBR while at work.

The physician should carefully assess the potential risks, costs, and benefits to all parties of diagnostic trials of avoidance of exposure or return to work, and the plan should be discussed in detail with the patient as well as the primary care physician and employer. Such diagnostic trials can be extremely useful in confirming or excluding the diagnosis of WRA, although they may also be difficult and expensive. If such a diagnostic trial is conducted, it is best to maximize the diagnostic yield and efficiency by including, if possible, serial PEF, FEV_1, and NSBR tests in a comprehensive, carefully coordinated evaluation. Frequent physician visits for brief clinical assessments, counseling and review of the prospective patient diary can help to ensure complete and accurate results.

After monitoring the patient for at least two weeks at and two weeks away from work, all the diagnostic evidences should be reviewed. Clinical judgment is generally required to decide if the evidence for WRA is adequate to justify one or more of the treatment, preventive and public health interventions discussed in the next section. If there is a sufficient degree of confidence, the appropriate remedial actions should be taken as soon as possible. If the diagnostic uncertainty remains excessive to support treatment or prevention decisions, in some locales and for some agents it may be possible to identify a research group that would agree to perform Specific Bronchial Challenge testing or Workplace Challenge testing.

MANAGEMENT: INDIVIDUAL AND PUBLIC HEALTH ASPECTS

Work-Related Asthma is preventable, treatable, and potentially curable. Management of WRA must address individual and public health aspects. The treating physician in a clinical setting must take responsibility for both.

Treatment of Individual Patients

Treatment of WRA for individual patients includes both medical treatment and preventive interventions. The medical component of treatment of WRA is similar to medical treatment of other forms of asthma, is well reviewed elsewhere [e.g., NAEPP, 1997; Fish and Peters, 1997], and will not be discussed here. The focus of this review is on preventive interventions and public health measures related to exposures in the workplace.

In individuals with new onset WRA, ongoing exposure to the asthma-provoking agent(s) can lead to progression from mild and intermittently symptomatic to more severe persistent asthma. Published evidence does not provide reassurance that medical management can prevent this progression, if exposure is not controlled or eliminated. Therefore, even if medical management alone is adequate to optimally control the symptoms, preventive intervention by control or cessation of exposure is an integral part of the treatment. Timely recognition, diagnosis and treatment are important in order to improve long term prognosis.

In individuals with OA induced by a known sensitizing agent(s), simply reducing (without eliminating) exposure to the sensitizer(s) does not usually result in complete resolution of symptoms. Severe asthmatic episodes or progressive worsening of the disease may be caused by exposures to very low concentrations of the sensitizing agent, and complete and permanent cessation of exposure is recommended [Chan-Yeung, 1995]. These individuals, even when completely asymptomatic outside the workplace, are generally considered to be permanently disabled for work with the specific agent(s) to which they are sensitized. They may have no ventilatory impairment at the time of pulmonary function testing. Their medical impairment consists of abnormal NSBR, or sensitization to specific agent(s) found in the workplace with potential for significant asthmatic response on re-exposure, or both. While individuals with sensitizer-induced OA are considered disabled with respect to work with the sensitizing agent, if they have little or no ongoing ventilatory impairment, they may have no disability with respect to other kinds of work.

Timely referral for vocational rehabilitation, including counseling as well as job retraining, may be a necessary component of treatment. If complete cessation of exposure would incur great hardship for the patient, he or she may request to continue working in the same job. However, the risk of progressive worsening of asthma is substantial if a symptomatic patient continues to be exposed to the sensitizing agent, even with reduction of exposure level and close medical monitoring and management. Based on currently available information, this cannot be recommended as a general approach. Vocational retraining supported by Workers' Compensation insurance should be available in many jurisdictions and may be the most viable alternative for workers whose trades would involve potential re-exposure to the offending substance in any workplace.

For asthma aggravated irritants, dose response may be more predictable and continuation at work with careful control of irritant exposure levels, accompanied by close medical monitoring, may be less risky and more likely to be effective than for sensitizer-induced OA. If the reduction in exposure is sufficient to keep the patient asymptomatic with only occasional use of medication, this may be adequate. The long term prognosis of irritant-induced and irritant-aggravated asthma have not been well studied, however, and the safety of controlling symptoms with regular medication while exposure is ongoing has not been tested. If the patient chooses to continue working under modified conditions, medical follow up should include frequent physician visits with continuation and regular reviews of the PEF diary, well planned access to emergency services, and serial spirometry and/or methacholine challenge testing, as appropriate. This will require a degree of clinical judgment on a case by case basis. For example, if symptoms improve when away from work, it would be difficult to justify the long term toxicity of repeated medical treatment with systemic corticosteroids in order to allow a patient with WRA to continue in the same employment.

Related to diagnosis and treatment of WRA are a variety of issues of impairment, disability, and Workers' Compensation. Disability due to WRA may have a particularly important impact on the patient's life because it directly affects his or her source of livelihood. These issues are very important, but are complicated and variable from state to state, and a detailed discussion is beyond the scope of this review. Interested readers are referred to several other sources [ATS, 1993; Barnhart and Balmes, 1996].

Public Health Management

Once a particular workplace is suspected to be high risk, evidenced either by occurrence of a sentinel case of WRA or inadequately controlled use of known asthma-causing agents, public health preventive methods can be very useful. The treating clinician has the responsibility to ensure that this public health process is carried out appropriately. Approaches and options available to practicing clinicians include:

- Medical evaluation of individual co-workers of the index case.
- Walk-through investigation of the workplace with a qualified industrial hygienist.
- Education of management and co-workers about relevant causes of WRA.
- Negotiation with employer for implementation of appropriate exposure control measures.

- Negotiation for an appropriate program of workplace surveillance for WRA.
- Notification of governmental evaluation and/or enforcement agencies.
- Referral to an academic Occupational Medicine clinic, if limitations of time or experience preclude the treating physician from these actions.

Early recognition, effective treatment, and prevention of disability in workers with existing WRA, and prevention of new onset asthma in coworkers are clear priorities. Some "problem" workplaces may have several individuals complaining of symptoms suggestive of asthma. One initial approach is to conduct a clinical evaluation of the few most symptomatic individuals first, and then assess the situation in the entire workplace. Identification of specific causal agent(s) and work conditions is important. Control or elimination of causal exposures and avoidance and proper management of spills or episodes of high level exposures can lead to effective primary prevention of sensitization and OA in coworkers of the sentinel case. If access to the workplace can be negotiated and resources are available to do a walk-through inspection, this can be very valuable. The usual exposure control hierarchy of substitution, engineering and administrative controls, and personal protective equipment should be implemented as appropriate. Notification and education of coworkers and managers of index cases about exposure to known asthma-causing agents and potential risk of WRA is important. Selective exclusion from high risk workplaces of asymptomatic workers who have a history of atopy or other potential susceptibility factors is not supported by the current literature, however, and would probably result in unnecessary removal of large numbers of workers to prevent relatively few cases of WRA.

In workplaces that have reason for concern about WRA, surveillance for workers with new onset of asthma-like symptoms or asthmatics with work-related symptom patterns should be considered. One approach is a cross-sectional workplace questionnaire survey, evaluating criteria A, B, C, D1 and D5 in the ACCP case definition of OA (see Table II). This approach can identify individuals for whom further clinical evaluation might be indicated and help identify possible causal agents or circumstances. In addition, evaluation of group results can help decide whether further workplace investigation or intervention is indicated and, if so, provide valuable guidance in targeting future prevention efforts in the most effective and efficient manner. A questionnaire survey is not adequate, however, to establish individual medical diagnoses, since predictive values positive of questionnaires for OA are not high enough. If a greater level of diagnostic certainty is needed, systematic medical surveillance of exposed groups or subgroups of coworkers should be considered. This may utilize diagnostic procedures appropriate to the situation, such as serial spirometries, quantitative testing for NSBR, and PEF recordings, as well as immunologic testing. In addition to one-time cross-sectional evaluations, ongoing surveillance and screening programs may be necessary in order to effectively address the problem.

Proactive employers will initiate or participate in some or all of the public health approaches discussed above, but in the event that adequate preventive action is not taken and the treating physician believes that workers continue to be at high risk, notification of government agencies may be helpful. NIOSH has the capability and authority to perform Health Hazard Evaluations (including both exposure and medical evaluations) of selected problem workplaces. Other government agencies, such as state and federal Occupational Safety and Health Administrations (OSHA) and state and local departments of health, can sometimes be helpful as well.

Physicians who diagnose and manage WRA should be aware of and comply with local reporting requirements. In some states, such as New York, WRA is a reportable condition, and should be reported to the NYS DOH. Surveillance for WRA is ongoing in Massachusetts, New Jersey, Michigan, and California through the NIOSH-sponsored Sentinel Event Notification System for Occupational Risks (SENSOR) program [Matte et al., 1990].

If the treating clinician does not have the resources to personally conduct these public health activities, he or she should take responsibility to otherwise facilitate their completion. The patient can be referred to an academic Occupational Medicine clinic experienced with WRA. The Association of Occupational and Environmental Clinics in Washington, DC [(202) 347-4976] has over 50 affiliated clinics nationally and can provide a referral. The NYS DOH has a network of 8 Occupational Medicine clinics around New York State. A Health Hazard Evaluation by NIOSH can be requested by calling (800) 35-NIOSH.

CONCLUSIONS

WRA has become the most prevalent occupational respiratory disease in several developed countries. It is more common than generally recognized, can be severe and disabling, and is amenable to primary, secondary, and tertiary prevention approaches. A stepped approach to diagnosis can often confirm or rule out WRA with adequate confidence, although better access to existing diagnostic methods and further research to develop more accurate diagnostic methods are both needed. Early recognition and effective preventive interventions may lead to complete remission in some patients, and for others can substantially reduce the severity of the disease, the risk of permanent disability, and the high social and financial costs associated with chronic asthma. For many reasons, WRA merits more widespread attention from clinicians, labor and management health and safety specialists, researchers, health care organizations, public health policy makers, industrial hygienists, and others interested in prevention of disease.

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