Guidelines for the Epidemiologic Assessment of Occupational Asthma

Report of the Subcommittee on the Epidemiologic Assessment of Occupational Asthma, Occupational Lung Disease Committee

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Physician reporting of cases of communicable disease has played an important role in detection and control of disease outbreaks.[1] A similar expectation exists for physician reporting of occupational diseases, including occupational asthma. The diagnosis of a single case of occupational asthma may be a sentinel event that reveals the need to search for other cases, as well as remediable underlying causes.[2] As stated by Rutstein et al.,[3] such an occurrence may: "(1) provide the impetus for epidemiologic or industrial hygiene studies, or (2) serve as a warning signal that materials substitution, engineering control, personal protection, or medical care may be required." Also, other purposes may be served by consequent epidemiologic and industrial hygiene studies. An epidemiologic survey may be needed to convince responsible parties that a health problem exists that is in some measure attributable to workplace exposures. An epidemiologic survey will be needed to quantitate the magnitude of a work-related health problem, whether the magnitude is expressed as disease prevalence, incidence, or some other measure. An epidemiologic study may identify personal risk factors that explain why certain persons have manifested a disease as a consequence of their occupational exposure(s). Resultant recommendations for control of exposures in the workplace may facilitate management of the index case and affected co-workers, and help prevent the occurrence of additional cases.

INITIAL INVESTIGATION

The epidemiologic study most suited to the initial investigation of suspected occupational asthma is that described by Miettinen[4] as the "census-sample" study. Here, the investigator first conducts a survey (or "census," in Miettinen's terminology) to determine a study population's disease experience or to identify the presence of some characteristic suggestive of the disease in question. The investigator then conducts a detailed survey or examination of persons identified as cases and of a sample of the underlying population to obtain further information on the personal and environmental correlates of the disease. If potential cases are identified by a characteristic suggestive but not diagnostic of the disease, results of appropriate diagnostic tests should reduce false-positive classification of potential cases that do not truly have the disease.

For example, in a study of occuaptional asthma, an initial survey might be conducted of all workers by questionnaire, to classify each respondent with respect to symptoms suggestive of asthma (i.e., episodic wheezing, chest tightness, or shortness of breath). A second survey would be conducted on all potential cases and a sample of the underlying population to ascertain additional information. This information might include physiologic tests that determine whether underlying symptoms are attributable to asthma and tests that examine the temporal relationship of symptoms to precipitating circumstances at work. Other occupational correlates may be used, such as tests that measure sensitization to general environmental antigens and measure potential workplace allergens. Although not specifically identified as such, this approach has been used in many published studies, although in some studies the second survey of a sample from the underlying population may appear to have been omitted.[5-7]

The "census-sample" approach appeals to common sense. The initial survey is used not to provide definitive diagnoses, but only to identify workers with symptoms that warrant further evaluation.[7] Best use is made of researchers' time and resources because they are not spent evaluating in detail a preponderance

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of subjects without symptoms to identify those with occupational asthma.[8]

In general, the "architecture" of such an initial investigation is cross-sectional.[9] For each participant, membership in the population and disease status are determined at approximately the same time. Yet membership in a working population is dynamic. New members enter through hiring and old members leave for a variety of reasons, including possible acquisition of a disease that prevents their continued employment. Therefore a major pitfall of such cross-sectional studies must be recognized Cross-sectional studies measure the prevalence of disease at one point in time. When prevalence of disease is low, it approximately equals incidence of disease multiplied by the mean duration of disease within the population.[10] A disease with a high incidence may have a low prevalence if persons in whom the disease develops leave the population as soon as the disease develops or if the mean duration of the disease within the population is short. Consequently, a population of currently employed workers is likely to reflect survivorship bias. Persons who are not ill as a consequence of exposures in their workplace are more likely to continue employment than are those who have become ill. Furthermore, if either incidence or severity of illness depends on some personal characteristic, then that personal characteristic may be over- or under-represented in the surviving, employed population. For instance, in a cross-sectional study in which occupational asthma appears to have predominantly developed in nonatopic persons, one cannot exclude the possibility that earlier or more severe disease may have developed in atopic persons than in nonatopic persons. These atopic persons may have self-selected themselves out of membership from the worker population that remains for study.[10, 11] Since prevalence is thus determined in part by the probability of survival once disease has developed, cross-sectional studies yield associations that reflect not only the causes of the disease but also the determinants of survival within the study population.[10]

THE QUESTIONNAIRE IN THE ASSESSMENT OF OCCUPATIONAL ASTHMA

Following the paradigm outlined, questionnaires in surveys of occupational asthma serve the same function as the medical history in the clinical evaluation of occupational asthma. They attempt to separate subjects or workers into groups for further evaluation on the basis of the likelihood that asthma is actually present.[12] Questionnaires are limited to collecting the same type of information that is gathered during a medical history. As such, one should not expect a questionnaire to surpass the performance of the clinician in "diagnosing" occupational asthma by medical history.[13] The questionnaire is also used to collect data on relevant covariates, such as smoking, use of medications, and atopic history. It may also serve to evaluate work-related variation of asthma-like symptoms using the respondent's own assessment of severity, which may correlate with changes in pulmonary function.[14]

Like any good screening test, questionnaires are safe and acceptable to subjects. For use in an epidemiologic survey, they should also have other features. They should be both valid and reliable. That is, the questions should actually measure what they were intended to measure and repeatedly elicit the same answers. To increase its validity and reliability, the questionnaire should be "standardized." Procedures should be specified to define and control its content, order, and administration. Otherwise, poorly worded questions, inadequately trained personnel, and disregard for protocol will conspire unpredictably to introduce error into the measurement process. Unfortunately, no standardized questionnaire on occupational asthma is presently available. The two most widely used standardized respiratory questionnaires, the British Medical Research Council (MRC) questionnaire and the American Thoracic Society Adult Questionnaire (ATS-DLD), each contain a few questions that elicit either symptoms or a history of asthma.[15, 16] Neither asks questions regarding the temporal relationship of symptoms after potentially provocative exposures or stimuli. Since there is no previously standardized questionnaire for occupational asthma, examples abound in which investigators have modified existing asthma questionnaires, particularly to assess work-relatedness of reported symptoms. It is important to recognize that modification of previous standardized questionnaires unpredictably affects their reliability and validity.[17, 18] Yet where available questionnaires are inadequate to elicit information required to identify temporal work-relatedness of symptoms, no other reasonable option exists.

Validity. Several difficulties arise in assessing the validity of questionnaires for asthma or occupational asthma from published studies. Most of these stem from the absence of an objective "gold standard" for asthma. The confusion surrounding this issue is illustrated in the interpretation of data in two published surveys that compared questionnaire responses to bronchial hyperresponsiveness. In one survey, the authors used increased airways reactivity as the standard and concluded that "Questionnaire information is not adequate for discriminating between those with and without increased airway reactivity in population screening."[19] In the second survey, symptoms were

TABLE I. Sensitivity and specificity of symptoms, as well as symptom-based definitions of asthma, for positive MTC

Symptom/definition	Sensitivity	Specificity
Wheeze, regardless of other symptoms	67/229 = 29%	991/1163 = 85%
Breathlessness, regardless of other symptoms	82/229 = 30%	964/1163 = 82%
Wheeze and breathlessness	39/229 = 17%	1107/1163 = 95%
Wheeze or breathlessness	110/229 = 48%	848/1163 = 73%
Any respiratory symptom	149/229 = 65%	680/1163 = 58%
Asthma diagnosis		
Brooks[25]	49/229 = 20%	1067/1163 = 92%
Cookson[26]	43/229 = 19%	1020/1163 = 88%
Any reported	28/229 = 12%	1131/1163 = 97%
Physician diagnosed	23/229 = 10%	1148/1163 = 99%

Adapted from Enarson DA, et al. Am Rev Respir Dis 1987;136:65.

used as the standard, leading the authors to state that "bronchial hyperresponsiveness in epidemiologic surveys is limited at present in identifying subjects with asthma."[20]

This lack of a uniformly accepted gold standard precludes measurement of the true sensitivity and specificity of any test for asthma. However, "sensitivity" and "specificity" are still commonly used in reporting comparisons between two imperfect tests, in which one is used as a proxy for the standard. A limited number of studies have specificed independent—albeit imperfect—operational standards for evaluating their questionnaires.

High sensitivity and specificity are both desirable in any test, but in many instances, high sensitivity compromises specificity and vice versa. Given the screening function that questionnaires serve in epidemiologic studies, high sensitivity should take priority in the design of questionnaires on occupational asthma. Unfortunately, limitations in study design or in the data reported often prevent a direct assessment of the sensitivity and specificity of respiratory symptoms as elicited by questionnaire. These limitations include a failure to apply the standard to a sample of those screening negative by the questionnaire and the use of an additional questionnaire to refine the initial screen.[1, 21, 22] Other studies are found in which the standard has incorporated to an unknown extent the results of the test to which it is being compared.[23] Finally, because working populations tend to differ from community populations in the distribution of relevant covariates and other diseases, evaluations of questionnaires in community populations may not predict their performance in worker groups.

In studies that compare symptoms elicited by questionnaire to more objective, independent correlates of asthma, investigators generally have chosen tests of nonspecific bronchial hyperresponsiveness (NSBH), such as methacholine inhalation challenge (MIC), as the standard against which the sensitivity and specificity of questionnaire items are assessed. Because NSBH is believed to be sensitive but not specific for identifying asthma, use of NSBH as a standard can result in underestimating the sensitivity of the questionnaire for the disease, as opposed to its sensitivity for NSBH as a surrogate for the disease.[24] Furthermore, the choice of criteria for a positive test of NSBH and the choice of questionnaire responses used to define occupational asthma will both influence apparent questionnaire performance.

Studies can be found in which questionnaire responses correlate well with bronchial hyperresponsiveness. However, the preponderance of the limited published evidence suggests that questionnaires function more poorly than an advocate for the "census-sample" study of occupational asthma would hope. Dales et al.,[19] using a French translation of the ATS-DLD questionnaire, studied 200 Canadian insulation workers. The sensitivity and specificity of "wheeze," "wheeze with dyspnea," and a "history of asthma," were assessed against methacholine challenge. A non-stringent criterion for a positive test was a PC_{15} (provocative concentration causing a 15% decline in FEV_1) of less than 16 mg/ml. The sensitivity of "wheeze" for a positive methacholine challenge was 26%, "wheeze with dyspnea" was 10%, and of a "history of asthma" was 7%. The specificities were 87%, 93%, and 97%, respectively. The sensitivity of "cough" and of "cough with sputum" was greater than that of "wheeze" (45% and 33%, respectively), with correspondingly lesser specificity. This latter observation suggested that the positive methacholine tests

identified bronchial hyperresponsiveness associated with chronic bronchitis.

Enarson et al.[20] reported a comparison of ATS-DLD questionnaire responses, modified to include additional questions on attacks of chest tightness, with MIC in 1392 workers, most of whom had been exposed to dusts or chemicals suspected of causing asthma. They reported the sensitivity and specificity of MIC (criterion for positive test of $PC_{20} < 8$ mg/ml) for identifying reported asthma or asthma-like symptoms. As shown in Table I, Enarson et al. provide the information necessary to examine the sensitivity and specificity of symptoms, as well as various symptom-based definitions of asthma (i.e., those of Brooks[25] and Cookson[26]) against positive MIC as the (imperfect) standard.

One could not become any more "sensitive" from a questionnaire than to query "Any respiratory symptom," yet the sensitivity of "Any respiratory symptom" for bronchial hyperresponsiveness was only 65%.

Burney and Chinn[27] report that the International Union Against Tuberculosis is developing an asthma questionnaire with questions drawn from the MRC, ATS-DLD, and other unspecified questionnaires. Reported to have "excellent repeatability," the sensitivity and specificity of "an attack of asthma in the past 12 months" against positive ($PD_{20} < 8$ μmol) histamine challenge are 50% and 90%, respectively. The sensitivity and specificity of "wheezing or whistling in your chest at any time in the past 12 months" were 86% and 72%, respectively.

To diagnose occupational asthma, Smith et al.[6] and London et al.[28] developed a questionnaire defining occupational asthma as wheezing or whistling respiration, episodes of shortness of breath, or episodes of chest tightness experienced within the preceding month. The symptoms had to occur after specific activities or exposures at work. On days away from work and on vacation, symptoms had to occur less frequently or not at all. Bronchial responsiveness was assessed in 25 workers who had been occupationally exposed to airborne egg protein, by serial peak expiratory flow rate (PEFR) determination, and by an independent "blind" clinical evaluation by a physician. Agreement between various questionnaire symptoms of wheezing, shortness of breath, or chest tightness temporally related to work and "dual physician/PEFR agreement" for the diagnosis of occupational asthma ranged from a Kappa of 0.738 to 1.0 (perfect agreement). The symptoms that best correlated with "dual physician/PEFR agreement" were identified a posteriori, and less clear-cut results would be expected in subsequent studies in which hypotheses are stated a priori. Furthermore, the workers were exposed to egg protein, a high molecular weight allergen, and the performance of the questionnaire might be expected to differ with other agents.

Reliability. There are problems in demonstrating that questions are repeatable when one is studying a dynamic disease process such as asthma.[29] This is particularly true when one of the widely accepted diagnostic tests for asthma—namely, bronchial hyperresponsiveness—fluctuates in response to exposure status. Perhaps because of this fact, there are few data on the reliability of questionnaires for asthma and none for occupational asthma. Limited information available on the reliability of the MRC questionnaire demonstrates that its repeatability varies from 62% to 91% when used by trained personnel, and some investigators may regard this as less than optimal.[29]

PHYSIOLOGIC ASSESSMENT OF OCCUPATIONAL ASTHMA

Objective ventilatory function tests are necessary to document variable and reversible airflow obstruction, which is generally recognized as a fundamental clinical feature of asthma.[30-32] Although originally used to validate questionnaire responses, the results of ventilatory function testing are frequently used as response variables in and of themselves. Results from a single test have quite limited sensitivity and specificity for asthma. Between asthmatic attacks, persons may have normal ventilatory functions, either because they have completely recovered or because of the relatively wide range of "normal" values, which result from large intersubject variability in measured ventilatory function. Even if the tested individual does demonstrate an obstructive ventilatory impairment, this isolated test result may be indistinguishable from nonasthmatic chronic obstructive pulmonary disease, which is highly prevalent in the general population.[33] Maximal specificity for asthma should result when the objective tests of ventilatory function are applied, using individuals as their own controls, to demonstrate significant variability in airway function. Maximal specificity for occupational asthma is achieved when significant reduction in function is documented to be temporally related to workplace exposure.

A nebulized bronchodilator can be used with patients in epidemiologic studies to assess reversible airways disease.[34] The information gained will be of limited usefulness however, because negative test results may occur in individuals with asthma if they do not have airway obstruction at the time of the test, and positive tests cannot be considered specific for airway disease caused by workplace exposure.[35]

Two methods for measuring variation in airway ob-

struction have been most commonly used in epidemiologic studies of occupational asthma: standard spirometry performed before and after a work shift, and ambulatory monitoring of peak expiratory flow rates over a period of weeks.

Spirometry "shift" studies. In a modification of the "stop-resume work test" traditionally used to assess work-related allergy, acute work-related decrements in ventilatory function were first documented in an epidemiologic study by measuring spirometry just before and after a Monday work shift among cotton workers.[36] Since then, spirometric measurement of forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), and their ratio have become the most commonly used and standardized tests of lung function, both in the clinical laboratory and in epidemiologic field studies. Standard spirometry is easily performed in only a few minutes and is very reproducible. The required instrumentation is relatively inexpensive and portable.[37] Much of the utility of the FEV_1 and FVC derive from understanding sources of variability and controlling those that might confound or obscure test results.

Variability of spirometry measurements results from measurement error and from true biologic variation.[12] Measurement error can be effectively minimized by consistently following generally accepted recommendations for standardization of spirometry instrumentation and procedures.[38] Thus, proper spirometry testing should include quality equipment, frequent calibration, leak checks, and BTPS correction factors to minimize measurement errors. At least three acceptable maximal expirations should be recorded for each subject, and these should be properly measured using standard methods. Quality assurance programs built into automated spirometers are no substitute for visual inspection of all spirograms for acceptability.[39] Spirometer temperatures should be carefully controlled at field study test sites to avoid the variable effect of spirometer temperature on BTPS-corrected FEV_1 results.[40, 41]

In addition to measurement errors attributable to instrumentation or technique, true diurnal variation in airflow may serve to obscure the airway effect of an exposure in the workplace.[42] Even with optimal spirometry testing, some amount of variability exists in repeated measures on the same individual in the absence of airway insult. Over short intervals of laboratory testing in relatively healthy subjects, mean intrasubject coefficients of variation for FVC and FEV_1 have generally been found to be on the order of 3% or less,[43] with only slightly greater values found under field testing conditions.[44] There is good evidence, however, that these parameters are not so reproducible among subjects with chronic "fixed" obstruction in which coefficients of variation for FEV_1 and FVC have been on the order of 10%.[45, 46] Understanding this residual variability is critical to an appropriate interpretation of spirometry results from "shift" studies. Therefore, arbitrary exclusion of spirometry data that do not meet recommended reproducibility standards may bias results.[47] This is particularly true in short-term longitudinal studies used to assess the acute ventilatory effects of exposures in the workplace over the period of one work shift (so-called "shift" studies).

The Occupational Safety and Health Administration (OSHA) currently requires "shift" testing of cotton workers to identify those who experience an FEV_1 decrement of 5% or more,[48] commonly referred to as cotton dust "reactors." However, this degree of FEV_1 change is best used as a sensitive screening tool and needs repeat testing for confirmation.[37] In fact, 14% of a large population of unexposed workers had FEV_1 reductions at least this large over the course of their workshift.[49] A more common criterion categorizing FEV_1 shift-related declines of at least 10% over a workshift is largely empirically based, but may be justifiable for relatively healthy workers on the basis of intrasubject coefficients of variation for FEV_1 discussed earlier.[25] Furthermore, using the traditional statistical approach of defining an "abnormal" range as the lowest 5% of a gaussian distribution of "normal" values,[26] the 10% criterion fits well with "shift" study results from a large population of unexposed workers.[49]

A recent publication states that "there is no general agreement on what decrement of function over a workshift is necessary to make a diagnosis of occupational asthma."[50] Any chosen criteria for determining the "significance" of a decline are unlikely to be optimal for all purposes in all situations, and a theoretic discussion of a rational means for selection of a criterion to identify occupational asthma has been published.[51] In another vein, it is possible that with further evaluation of how best to express the difference between two FEV_1 tests on the same individual, use of absolute change rather than percentage change will prove superior, particularly for epidemiologic studies in which subjects are not as closely studied as they may be in the clinical setting.[52]

Although useful, the "shift" study approach has major limitations. Shift testing for epidemiologic studies is often done on only one day. Thus, particularly for industrial processes that are intermittent in nature, a representative exposure may not occur on the day of testing. Beyond that potential pitfall, many workers with occupational asthma may have a relatively fixed impairment of airway function from repeated expo-

sures at work and may not experience an acute ventilatory decrement during a "shift" study test.[53] Alternatively, "shift" study tests will lack sensitivity in workers with the "later" pattern of asthmatic response, in whom acute response may follow the affected worker's after-shift test session.[54] Thus the lack of a response on a "shift study" does not necessarily exclude the presence of occupational asthma.[55] Given these special characteristics of occupational asthma and the difficulty of arranging standard spirometry testing for workers at odd hours of the day, epidemiologic investigators are increasingly turning to a less-standardized but more suitable method for documenting work-related variability in ventilatory function.

Ambulatory monitoring of peak flow. Just as ambulatory monitoring of maximal expiratory peak flow has earned a niche in the clinical management of persons diagnosed as having asthma, it has demonstrated effectiveness in identifying workers with occupational asthma for epidemiologic studies. Over the past decade, portable peak expiratory flow meters have become widely marketed. Although the performance standards of these inexpensive meters may not meet standards of accuracy and reproducibility recommended for spirometers, they can still yield meaningful objective data when the same meter is used over an extended period of time.[56] This method also allows for several days of observations away from the workplace, as well as several days during exposures at work.[57]

One recommended schedule for recording ambulatory peak flows requires subjects to record peak flow at 2-hour intervals during waking hours over a prolonged period of time. It has been suggested that this monitoring be maintained for as long as 1 week of work, followed by 10 days off, then by 2 weeks of work.[58] However, shorter periods of observation at less frequent intervals have been used effectively in the epidemiologic investigation of occupational asthma.[6] Long periods of serial self-monitoring offer many data points that can be used to judge the validity of the recorded flow rates, but also require the investigator to instill a high degree of motivation in the study participants.[53] The interpretation of the peak flow patterns is not well established,[55] although a criterion in the range of 20% to 25% appears reasonably justified for establishing significance of daily variability of peak flow measurements.[59] Arbitrarily chosen criteria for judging consistency of daily and weekly work-related patterns of peak flow variability have been suggested.[60]

One major criticism of self-recorded peak flow monitoring is that a subject may intentionally bias the test by variable effort or may falsify records.[55] Although suggestions for identifying these problems by careful inspection of records have been offered, it may be necessary to obtain other confirmatory objective data in situations in which this remains a serious consideration.[53] This might include standard spirometry at intervals selected on the basis of a pattern of peak flow established in the self-recorded record of ambulatory monitoring. Alternatively, it might include less frequent serial monitoring of nonspecific airway reactivity.

Bronchial provocation tests. Bronchodilator testing, nonspecific bronchial challenge testing, and specific bronchial challenge testing all have a place in the evaluation of occupational asthma, but none—not even specific challange studies—is 100% predictive of the presence of occupational asthma. Challenge tests are discussed elsewhere (see Report of Subcomittee on Bronchoprovocation), but issues of relevance to the epidemiologic evaluation of occupational asthma will be mentioned here.

Inhalation challenge testing with methacholine or histamine can be used to characterize airway hyperreactivity among groups of workers at risk for occupational asthma. Standard protocols can be modified to reduce the time required for administration.[62] Challenge testing for bronchial hyperresponsiveness at a single point in time is not 100% specific for asthma or occupational asthma because nonasthmatic conditions may be associated with increased airway reactivity.[63] Also, there are a few reports that suggest these types of studies lack sensitivity in occupational asthma.[64-66] Another drawback of nonspecific challenge testing is that, no matter how carefully this testing is done, bronchoconstrictive symptoms may be induced in susceptible individuals. Also, potential study participant concerns that methacholine is an "artificial" stimulus may reduce participation rates, leading some investigators to propose cold air challenge as a "natural" stimulus more palatable to participants.[67]

Any method for objectively monitoring an acute airways response to exposure in the workplace can be considered unsuitable for use in individuals who have histories of work-related asthmatic episodes so severe that it would be unsafe to return the individual to work. In these situations, carefully performed specific challenge done under vigilant clinical monitoring can be considered. However—particularly for epidemiologic studies—specific challenge testing has significant limitations and should not be used routinely.[68] It is much less standardized than nonspecific challenge testing and is usually restricted to hospital settings, primarily because, in contrast to the immediate and

short time course of responses to nonspecific challenges, responses can be delayed, prolonged, and difficult to reverse with bronchodilators.[56, 69] False-negative tests may result from inappropriate selection of the form of challenge agent, whereas false-positive data may result from challenge with unrealistically high doses that cause irritative bronchoconstriction. If considered only from an ethical perspective, use of specific challenges should remain largely restricted to the clinical evaluation of individual cases because exposures involve administration of potential sensitizers.

ENVIRONMENTAL ASSESSMENT

The environmental assessment serves a number of distinct purposes. It may be conducted to respond to specific complaints, to evaluate worker exposures to specific agents, to determine compliance with specific recognized workplace exposure standards, and to evaluate the effectiveness of engineering controls.[70]

Furthermore, the environmental assessment should assist in the design of environmental exposure control technologies. Occupational exposures can be controlled by application of engineering controls, proper design of work practices, and use of personal protective equipment. These measures may be applied at or near the source of exposure, at the actual point of exposure to worker(s), or within the general workplace environment. Engineering measures applied at the source of the hazardous exposure, including materials substitution, process/equipment modification, isolation or automation, and local exhaust ventilation, are generally preferred and provide the most effective means of control. Controls that may be applied to hazards that have escaped into the workplace environment include dilution ventilation, dust suppression, and housekeeping. Controls that may be applied to individual workers include the use of remote control rooms, isolation booths, fresh-air showers, work practices, and personal protective equipment. In general, a combination of all three types of control measures is required to provide worker protection. Process and workplace monitoring devices, personal exposure monitoring, and medical monitoring are important mechanisms for providing feedback concerning the effectiveness of the controls in use. Ongoing monitoring and maintenance of controls to ensure proper use and operating conditions, and the education and commitment of both workers and management to occupational health, are also important elements of an effective control program.[71]

The environmental assessment should be conducted by an experienced industrial hygienist. However, the physician should be knowledgeable of potential workplace hazards, and should be prepared to assist in identifying pertinent physical or chemical exposures that must be evaluated. In general, the environmental evaluation will require that the investigative team become familiar with all processes. Chemical and physical agents must be inventoried, job activities and work practices reviewed, sources of air contaminants and physical agents identified, and existing control measures studied (i.e., process enclosures and shielding, local and general exhaust ventilation, and imposition of barriers through the use of personal protective equipment).[72, 73] If personal protective equipment is used, then a program of training and maintenance in the use of equipment should be in place, and use of personal protective equipment, when necesssary, should be mandated by management and not optional on the part of the employee.

In regard to the conduct of the environmental survey, it is the industrial hygienist who must determine how, when, where, how long, and how many environmental samples should be obtained. It is particularly important to know if the device(s) and/or method(s) are specific for the contaminant(s) to be measured and what other substances interfere with the procedure(s). Issues of reliability and validity arise just as in the epidemiologic study. More than 200 chemical and physical agents have been implicated as causes of occupational asthma.[55] It is therefore neither practical nor feasible to recommend in this general discussion specific sampling strategies for all such workplace contaminants known to be associated with occupational asthma. It is appropriate to state that sampling should be conducted in accordance with accepted standard methodologies where available, and that the samples be analyzed in accordance with accepted standard analytic procedures.

Immunochemical assessment. It should be recognized that new, useful techniques evolve that do not gain immediate understanding or acceptance. Immunochemical assessment of exposures to biological substances in the workplace, such as animal- and plant-derived proteins, comprise a set of such procedures and will be briefly reviewed.

The application of immunochemical techniques for the detection and quantification of aeroallergens in the workplace holds promise as an effective means to enhance the environmental assessment. The basic concerns that need to be considered in using this methodology include sample collection, extraction, and analysis. In general, the collection and extraction methodologies are similar to what would be done for a variety of types of materials, but, because allergens can provoke a reaction at concentrations at which dust levels are low, some added precautions are necessary.

Air samples should be collected using an appropriate filtration media and, because allergens may be present at very low concentrations, it may be necessary to use either high-volume samplers or sample for an extended period of time to ensure that an adequate amount of sample is collected. Filters should be extracted in an appropriate solvent and by a method that ensures quantitative recovery of the allergen. Because it is often advisable to use a large volume of solvent, it may be necessary to concentrate the extract by lyophilization or ultrafiltration to obtain detectable concentrations of the allergen in the extract.

Several studies in the last few years have documented that aeroallergen levels can be determined using either RAST inhibition or ELISA type assays.[7, 74-81] The RAST inhibition assay requires a sufficient volume of serum from an allergic individual or, preferably, a serum pool from several individuals to serve as the source of IgE antibodies for the detection of the allergen. The use of sera from exposed workers ensures that appropriate antibody specificities are present. However, obtaining and fully characterizing an adequate volume of sera for repeated measurements can be a problem. The ELISA and ELISA inhibition assay often uses antigen-specific antisera obtained from preimmunized animals. Although adequate supply is not a problem, the sera should be tested by immunologic methods to ensure that there is adequate specificity for the antigen being measured. Both types of immunoassays are sensitive and specific and thus are useful in detecting low levels of a substance. Future development of monoclonal antibodies with specificity for epitopes on occupational antigens will probably enhance the sensitivity and permit standardization of immunochemical assays.[82]

Most of the studies reported to date have demonstrated that these immunochemical techniques can be used for assessing levels of exposure at the worksite, but limited information is available regarding the use of these techniques in evaluating environmental controls or sources of exposure. For example, the effect of air change rate and humidity on airborne allergen levels in a laboratory animal house was reported.[83] Reducing airflow increased allergen levels measured by RAST inhibition whereas increasing humidity reduced allergen level by 54% to 77%. Recent studies in NIOSH's Morgantown, West Virginia laboratory have shown that the distribution of rat allergens within a research facility can be quite complex. High levels of allergens were found in areas with large numbers of animals (e.g., holding rooms) or a high dust exposure level (e.g., cage dumping and clearing areas), but detectable levels of the allergens were also found in employee locker rooms and break rooms. These results suggest that allergens may be carried on clothing and that controlling ventilation may not be sufficient to control exposure.

The application of immunochemical assays for monitoring environmental controls of evaluating work practice changes has not been fully realized. The evaluation of environmental control and work practice changes can be accomplished in a quantitative and specific manner. The concentration of antigen associated with either sensitization or provocation may be estimated and exposure limits based on protecting hypersensitive individuals can be rationally evaluated.

RECOMMENDATIONS

The uncertain validity and feasibility of various approaches taken to diagnose asthma in epidemiologic studies have led to the recent generalization by one authority that "asthma has not yet been defined with concepts that can be translated into criteria and procedures for use by epidemiologists."[24] This statement should not be taken as reason not to undertake epidemiologic assessments of asthma, but rather as a challenge to the investigator to choose methods carefully, apply them appropriately, interpret results cautiously, and obtain knowledgeable peer review before finalizing conclusions.

I. The initial study design.
   A. The design of the initial epidemiologic study will no doubt be dictated by the purpose or question of paramount importance to the investigator(s). When the primary purpose of the epidemiologic study is to determine the prevalence of occupational asthma, and/or to identify environmental or occupational correlates, then the investigators may choose a "census-sample" approach. This approach makes best use of limited personnel and equipment resources.
   B. Potential cases of asthma should be identified by questionnaire responses suggestive of asthma (i.e., episodes of wheezing, shortness of breath and/or chest tightness).
   C. Follow-up in a second survey (or "census") of all potential cases, plus a sample (which could be a 100% sample) of the underlying population, should include tests to document physiologic correlates of asthma, determine work-relatedness of symptoms, and personal and environmental correlates.
   D. Control subjects should be selected to be representative of the population from which the cases were derived and to which inferences will be generalized. They

should not be selected merely because they have volunteered to participate in the study. Reasons for refusal to participate should be examined when possible.

E. Although personal characteristics such as atopy should be determined, the investigator must bear in mind that in a cross-sectional study, no conclusive inference can be drawn about personal characteristics and risk for developing disease.

F. Researchers should recognize that in an employee population, a disease with a high incidence may nonetheless have a low prevalence if mean duration of disease is short. The severely ill may no longer be present at the worksite. Therefore, efforts should be made to identify not just all current employees, but former employees as well. Attempts should be made to ascertain their reasons for leaving employment. Such followup of former workers may enable investigators to speculate whether prevalence measures derived from the initial study under- or over-represent the true magnitude of disease.

II. The questionnaire.

A. Experience does not currently warrant recommendation of a single "best" questionnaire for assessment of occupational asthma.

B. It is advisable to include questions from available, published questionnaires to ask about asthma symptoms because such questions have already been largely "debugged" in terms of ease of understanding and lack of ambiguity.

C. When choosing questions to assess work-relatedness of symptoms, it is best to allow for a variety of temporal patterns in relations to work (e.g., weeknight symptoms, Monday morning symptoms, etc.), especially if the suspect asthma-causing agent is a low molecular weight compound likely to cause late reactions.

D. The experience reviewed with the MRC and ATS-DLD questionnaires suggests that a single symptom like wheezing may not have the desired sensitivity. It is therefore preferable to use more than one symptom in combination with work relatedness to screen workers for further evaluation.

E. In order to assess the validity of a questionnaire for occupational asthma, a standard must be chosen that is independent of the questionnaire itself and is applied to both those with a positive and negative questionnaire screen. Symptoms and physiologic changes should be described separately, so that the relationship between outcome variables may be examined as well as the relationship of each outcome with the independent variable(s). "Clinical" diagnoses translated into case definitions tend to incorporate, to an unknown and/or unrecognized extent, the results of the tests under consideration and should be avoided.

F. Investigators who are not using previously published questionnaires should publish any questions used in their analysis.

G. Various combinations of symptoms used as criteria for a positive "screen" on the questionnaire should be assessed.

III. Pulmonary function testing.

A. Whenever feasible in the epidemiologic assessment of occupational asthma, objective pulmonary function testing on more than one occasion should be used to document variable airways obstruction that is temporally related to workplace exposure.

B. Questionnaire responses that describe the temporal pattern of asthma symptoms should be considered in deciding whether a single "shift study" spirometry survey will be likely to succeed in documenting most work-related airway responses, or whether longer term serial monitoring of peak flow should be done. If necessary, consideration should be given to making observations during and after a week or longer away from work.

C. Current widely used criteria for documenting variable airways obstruction include a 10% or greater reduction in FEV_1 over a single work shift or a 20% or greater reduction in peak flow over the course of a single day. Other criteria may be used, but should be justified with supporting statements.

D. When spirometry is used, American Thoracic Society recommendations for standardization should be followed. The investigator should limit unintentional bias by equivalent pulmonary function testing of both study and control subjects.

E. Airways "hyperreactivity" can be documented with nonspecific bronchial challenge testing, but should not be strictly

equated with asthma. (See Report of Subcommittee on Bronchoprovocation for recommended methods.)

F. Inherent risks and expense restrict specific inhalation challenge testing to the laboratory and to select samples of worker populations surveyed for occupational asthma.

IV. Environmental monitoring.

The work environment should be investigated to determine the source and the concentrations of causative agents, which may include allergens. The application of immunochemical techniques can be of value in such investigations of occupational allergens, but these need to be part of a survey of industrial hygiene. Such information can be used to make recommendations about control technology or personal protective equipment.

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Guidelines for the Immunologic Evaluation of Occupational Lung Disease

Report of the Subcommittee on Immunologic Evaluation of Occupational Immunologic Lung Disease

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Whereas to control disease it is always important to determine the etiologic agent responsible for a given allergic respiratory disorder, there are additional reasons to identify the etiologic agent of those disorders caused by occupational allergens. In occupational allergic disorders the particular etiologic agent affects not only the treatment but also the worker's job placement and may even affect the worker's compensation.[1] The criteria for the diagnosis of occupational immunologic lung diseases (OILDs) are the same as those for the diagnosis of nonoccupational immunologic lung disease such as animal asthma.[2] First, the patient's symptoms must be compatible with those symptoms being caused by a given etiologic agent. Second, immunologic tests are necessary to demonstrate that the patient has an immunologic response to the presumptive etiologic agent. It is important to recognize that positive results of appropriate immunologic tests are a necessary but not a sufficient criterion for the diagnosis of OILD or of nonoccupational allergic disease such as cat asthma. In contrast to certain diagnoses that can be made with laboratory data alone, such as for diabetes or anemia, the diagnosis of allergic respiratory disease requires a correlation between clinical evaluation of the patient and confirmatory immunologic tests.

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SENSITIVITY, SPECIFICITY, AND POSITIVE PREDICTIVE VALUE

In general the value of a laboratory test in diagnosing a given condition in a given population is judged by the sensitivity, specificity, and positive predictive value of the test.[3] Even for in vitro and in vivo tests of common food and inhalant allergens, there are minimal data. There are, for all practical purposes, no such data for occupational allergens. In a number of studies of skin testing with commonly used inhalants, 10% to 20% of adults without symptoms had positive skin test results.[4-8] Thus the specificity of skin testing for allergic rhinitis or extrinsic asthma is approximately 80% to 90%. However, it should be noted that "asymptomatic" does not necessarily equate with no past or future allergic diseases. By diagnostic criteria the sensitivity of cutaneous testing with an appropriate antigen approaches 100% because all patients with cat asthma, for instance, must have evidence of IgE to cat allergens. There are no large, reported studies of the