The evaluation of occupational airways disease in the laboratory and workplace

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Occupational immunologic lung disease can be identified both in the individual patient under laboratory conditions and in a population of workers in industry. Occupational airways disorder is the most common occupational immunologic pulmonary process and is a disease of the airways caused by the inhalation of a substance or material that the worker manufactures or uses directly or that is incidentally present at the worksite. There are several occupational airways disorders, including industrial bronchitis, occupational asthma, and reactive airways disease syndrome, the latter two of which will be discussed more thoroughly. Occupational asthma can be appropriately identified when the following are present: (1) typical symptoms, i.e., wheeze, cough, shortness of breath, and/or chest tightness; (2) specific identification of the offending agent; (3) documentation that the agent can cause asthma; (4) wheezes on physical examination; (5) pulmonary function changes; (6) immunologic abnormalities; (7) airway hyperreactivity; and (8) positive bronchial challenge with specific material. The diagnosis of occupational airways disorder requires a comprehensive approach, including clinical history, physiologic measurements, immunologic testing, and identification of airway hyperreactivity. By this approach both individual subjects and working populations can be studied. (J ALLERGY CLIN IMMUNOL 70:56, 1982.)

The accurate evaluation of an individual or a population of individuals in a workplace is critical for detecting OILD. This article will focus specifically on OAD, one type of OILD. Discussions will include evaluation of worker populations utilizing epidemiologic techniques. The examination of working populations for OAD requires a multidisciplinary approach with professionals knowledgeable in immunology, epidemiology/biostatistics, industrial hygiene, toxicology, and clinical chest medicine. The methods used to study a population of workers are similar to those required for an individual patient. Thus taking an accurate history, performing pulmonary function tests, accomplishing an immunologic evaluation, and determining the status of airway reactivity provide critical information.

OADs include occupational asthma, "industrial bronchitis," and an entity not previously well described, RADS. This article will emphasize occupational asthma and RADS, both of which can occur as a result of an occupational exposure to uncontrolled high concentrations of a material in the workplace. This emphasis on relating high-concentration exposures to pathogenesis of disease is important for preventive medicine reasons, pointing out the need for limiting or avoiding this type of unacceptable work environment.

A major physiologic change identified in a majority of persons who have occupational asthma or RADS is airways hyperreactivity. The mechanism to explain this physiologic phenomenon is not known, but information suggests that nonimmunologic mechanisms may be important in some cases. In any event, the prevention of OAD requires a multidisciplinary approach directed at controlling exposures to the offending agent, effective worker surveillance program for detecting early disease, and, when necessary, proper and prompt medical treatment of affected workers.

Definition and prevalence

OAD is a disorder of the airways caused by the inhalation of a substance or material that a worker manufactures or uses directly, or that is incidentally present at the worksite. This definition encompasses a

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Abbreviations used

OILD:	Occupational immunologic lung disease
RADS:	Reactive airway disease syndrome
OAD:	Occupational airways disorder
RAST:	Radioallergosorbent test
FEV_1:	Forced expiratory volume in one second
FVC:	Forced vital capacity
PVC:	Polyvinylchloride

variety of disorders of airways (i.e., occupational asthma, industrial bronchitis, and RADS) regardless of their etiology and includes processes that occur as a result of both immunologic and nonimmunologic mechanisms. An important characteristic of OAD is generalized obstruction of the airways. This is usually intermittent and reversible in nature, but irreversible damage can occur. Often there is evidence of nonspecific airways hyperreactivity. In occupational asthma the airway hyperreactivity often occurs in the presence of late-occurring asthmatic responses.

The prevalence of OAD is not known. In the United States there are approximately 9 million persons with bronchial asthma; the percentage with occupationally related disease, however, is not well estimated. One conservative estimate is 2% of all asthmatic subjects in the United States have asthma on the basis of their occupation.[1] In some parts of Japan, the prevalence of occupational asthma may be as high as 15%.[1]

The type of occupation or process may influence prevalence rates. For example, about 5% of isocyanate workers develop asthma, whereas 10% to 45% of individuals working with proteolytic enzymes are affected.[2, 3] There are reports of 2% to 40% of grain dust–exposed individuals being affected with asthma, and in some cases 70% to 100% of individuals working in certain specific occupations become affected.[1, 2] The specific type of job may be important. For instance, with cotton dust exposure, the carding process may be associated with a 25% prevalence of byssinosis, while jobs with lower dust exposure report lower prevalence rates.[4] Another factor influencing the prevalence rate of OAD is geographic area. Byssinosis is more prevalent in the southern part of the United States; asthma from wood dust (i.e., red cedar) is seen in the western United States. In the Great Lakes area, problems with grain dust and flour occur; chemicals are indigenous to many areas, particularly the industrial eastern and midwest sections. Economic factors may influence disease prevalence. In Japan there was a reported association between the number of reported cases of red cedar asthma and quantity of western red cedar imported.[5] As imports of the wood increased, more cases and wider geographic distribution of disease were noted.

Causes of occupational asthma

Substances causing occupational asthma[1, 2, 6–56] can be divided into animal, vegetable, or chemical agents, as shown below:

Animal
- Animal hair, epidermal squamae, insects, molds, dander, bacterial and protein dusts
  - Animal handlers
  - Entomologists
  - Antibiotic workers
  - Detergent enzyme manufacturers

Vegetable
- Woods, cotton, flax, hemp, grain, flour, maiko, mold, castor and green coffee beans, garlic
  - Cotton mill workers
  - Wood workers
  - Bakers
  - Grain elevator operators

Chemicals
- ("Micromolecular" chemicals) chloromine, ethylenediamine, formaldehyde, chromium, platinum, gum arabic, anhydrides, isocyanates
  - Chemical workers
  - Platinum refiners
  - Epoxy resin workers
  - Polyurethane foam manufacturer

Asthma among animal handlers is an example of an animal agent causing disease. A number of different animals and antigens have been incriminated,[10–13] including small animals such as rats, mice, guinea pigs, and rabbits; moderate size animals such as cats and dogs; and larger animals such as cows, horses, or sheep. There are reports of disease with more exotic animals such as cheetah and chinchilla. Sources and types of antigen include dander, hair, urine or serum protein, saliva, foods (spores, additives such as antibiotics), and bedding.[10–13]

Vegetable causes of asthma are numerous and may affect spice factory workers, bakers, or woodworkers. A variety of allergenic material has been incriminated. An unusual case involved a worker employed in a plant manufacturing saponin, a product used for putting foam in root beer.[27] The raw product of the process was Quillaja bark imported from South America. During the process, raw Quillaja bark dust was generated and caused asthma in a sensitized worker. The diagnosis was confirmed by bronchial challenge with Quillaja bark; the worker's serum contained high levels of specific IgE antibodies.

Chemical causes of occupational asthma may be due to "micromolecular" chemicals and are likely to be an increasing problem in the future as their use

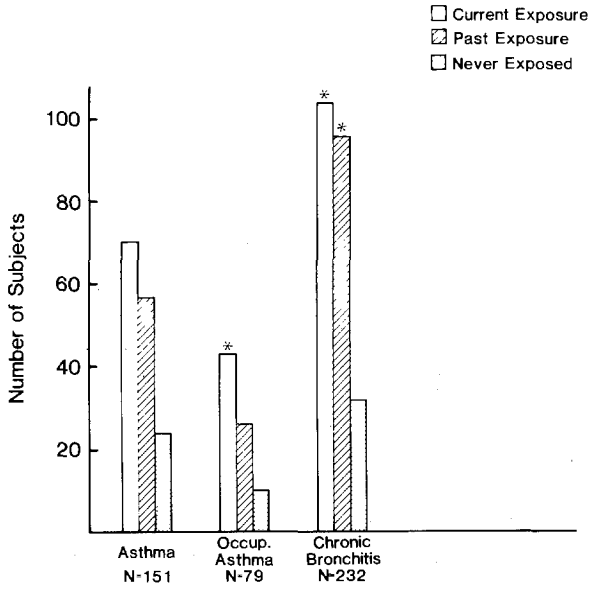

FIG. 1. Number of subjects in three isocyanate exposure groups manifesting disease as defined by results of questionnaire. A statistically significantly higher prevalence of occupational asthma was noted in currently exposed workers (asterisks, $p < 0.01$); both current and past workers had higher prevalence of chronic bronchitis.

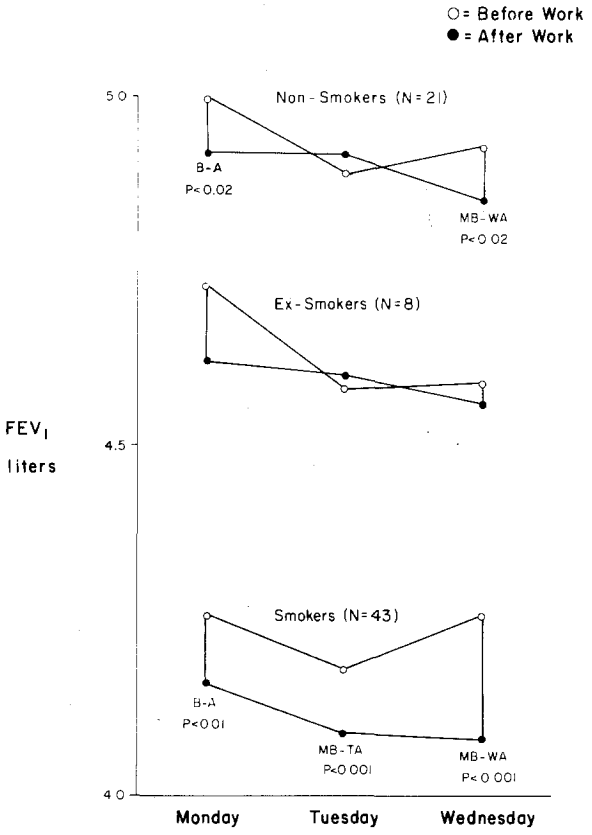

FIG. 2. Spirometric tests measured in western red cedar workers over a 3 day period with tests taken before and after a work shift. Smokers had a greater magnitude of change than nonsmokers. *B,* Before; *A,* after; *M,* Monday; *T,* Tuesday; *W,* Wednesday.

increases. Recently a great deal of interest has been generated in trimellitic anhydride.[52–54]

Epidemiologic approach to occupational asthma

To make the diagnosis of occupational asthma in an individual patient, the physician utilizes a relatively established routine, recognizing the presence of the following: (1) typical history (i.e., asthma, work), (2) specific identification of the offending agent, (3) documentation that the agent can cause asthma (i.e., cases in the literature), (4) wheezes on physical examination, (5) pulmonary function changes, (6) immunologic evidence (RAST, skin test), (7) airway hyperreactivity, (8) positive bronchial challenge test to confirm. The physician may conclude that occupational asthma is present when an individual provides a history of asthmatic symptoms that typically shows a relationship with work. The symptoms will improve or disappear on weekends and return on resuming work. Asthma attacks often occur only at night, since late-occurring asthmatic responses are common in occupational asthma. The worker states that the asthma symptoms were not present prior to starting employment but developed after working for a while, usually within the first few years. It is imperative that the physician obtain specific identification of the alleged offending agent; without this specific agent identification, the diagnosis of occupational asthma is suspect. Furthermore, it is very helpful to have documentation that the agent has previously been reported to cause asthma of occupational origin. This can be accomplished by literature search, government agencies, and other information sources. Important information is obtained when one can show that the agent in question has previously been documented to cause disease.

The physical examination may be negative but is helpful when one hears wheezes on auscultation of the chest. Pulmonary function tests may show a significant (i.e., 10% or more) postwork fall in spirometric values. It is not uncommon for pulmonary function tests to be "normal" at the time of examination, particularly if the individual has been off work for a while. Immunologic alterations help support a diagnosis of occupationally related asthma. Skin tests or RAST for specific IgE antibodies provides useful collaborative information; additionally, immunologic studies such as testing for cellular immunity can be useful.[51] Most cases of asthma are associated with hyperreactivity of the airways, usually documented

by bronchial challenges or by pharmacologic agents.[57] Finally, when a bronchial challenge to the specific material is performed and is positive, the diagnosis is confirmed. When the physician has positive information for all of these clinical components, there is no difficulty in making a diagnosis of occupational asthma.

The study of occupational asthma in populations of workers, however, is more difficult, but the same type of information and approach is necessary, as shown in the following outline:

I. Symptoms
   A. Symptoms consistent with occupational asthma
   B. Symptoms only of chronic cough (diagnosis of "chronic bronchitis")
   C. No symptoms
II. Pulmonary functions
   A. Generalized airway obstruction (i.e. $FEV_1/FVC < 70\%$)
   B. Prework and postwork change in test values (i.e., 10% fall in FEV_1)
   C. More rapid yearly decline
   D. Normal pulmonary functions
III. Immunologic
   A. Presence of specific IgE (RAST, skin test)
   B. Other immunologic abnormalities (i.e., positive migration inhibition factor, IgG, etc.)
   C. Atopy
   D. No immunologic abnormalities
IV. Airway reactivity
   A. Hyperreactive airways
   B. Normal airway reactivity

Clinical history. Respiratory questionnaires have been incorporated for epidemiologic studies. Most questionnaires are designed for "chronic bronchitis," with less attention being paid for defining "asthma." In our own studies, responses from administered questionnaires were used to define "occupational asthma" and included: (1) presence of typical asthma symptoms, i.e., wheeze, cough, shortness of breath, and chest tightness; (2) absence of these asthma symptoms before beginning employment and development of symptoms after starting employment; (3) a documented relationship between development of symptoms at work and improvement with vacations or weekends off; and (4) symptoms occurring only at night.

Reliance only on historical information for identifying occupational asthma poses problems, since a variety of clinical presentations of asthma can occur. Workers may present with typical symptoms of occupational asthma as defined by a questionnaire (outlined previously); individuals may note only chronic cough, which may inadvertently be diagnosed as "chronic bronchitis"; finally, many individuals with occupational asthma have no clinical complaints at all.

An example of how a questionnaire can be used to identify disease is demonstrated by a recently conducted study on workers exposed to isocyanates.[58] The clinical criteria obtained from questionnaires and used to define "asthma", "occupational asthma," and "chronic bronchitis" are shown below:

Asthma

(Yes response to at least four of five)

(1) Regularly noticed wheezing, cough, phlegm, shortness of breath or chest tightness
(2) Usually have a cough
(3) Chest sounds wheezy or whistling (cold *or* apart from cold *or* most days or nights)
(4) Attack of wheezing with shortness of breath
(5) Shortness of breath upon hurrying on level or up slight hill

Occupational asthma

(1) Diagnosis of asthma
(2) Symptoms not present before employment started
(3) Yes response to at least two of three:
   a. Symptoms improve or cease on weekends off
   b. Symptoms improve or cease on vacations
   c. Symptoms worsen on returning to work

Bronchitis

(1) Cough and/or phlegm for most days
(2) For 3 consecutive months or more
(3) For 2 years or more.

The study population consisted of workers located in two plants, one where isocyanates were utilized and the other, a few miles away, where isocyanates were not used. Detailed industrial hygiene measurements of isocyanates were repeatedly less than 10 parts per billion. The study population of 639 workers was carefully matched for several variables and divided into three isocyanate exposure groups: 279 currently exposed, 237 with past exposure, and 123 never exposed.

Fig. 1 indicates there was a statistically significant higher prevalence of clinical occupational asthma in currently exposed workers and for both current and past isocyanate-exposed persons for "chronic bronchitis." A variety of other types of information was obtained from the questionnaire. Individuals with previous isocyanate exposure reported twice as many respiratory illnesses resulting in 3 or more days away from work. There were 59% of all isocyanate-exposed workers who reported past job transfers; 16.2% gave histories of being transferred out of an isocyanate work area because of respiratory problems believed to be due to their job. Information was obtained on exposure to accidental isocyanate spills, a situation where very high concentrations of isocyanates occur. A significant relationship was noted between past exposure to more than 10 isocyanate spills and the presence of clinical "asthma," "occupational asthma," and "chronic bronchitis." No relationships with disease

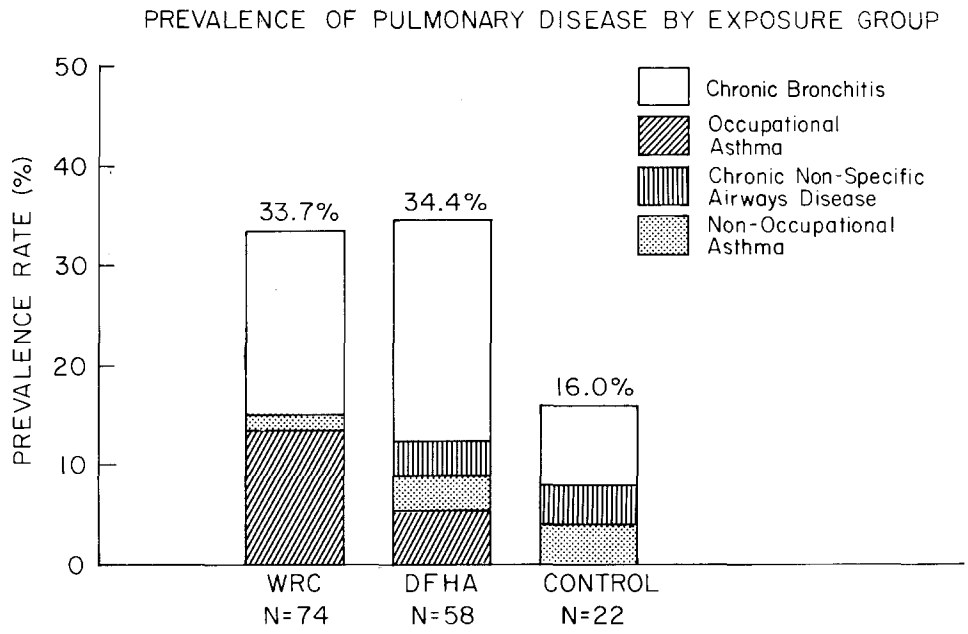

FIG. 3. Prevalence of various pulmonary diseases by exposure groups. Exposures are for western red cedar *(WRC),* Douglas fir-hemlock-alder *(DFHA),* and control.

were noted for workers exposed to less than 10 spills.

Thus questionnaire data can be used to provide criteria for diagnosing clinical syndromes such as asthma, occupational asthma, or chronic bronchitis. Furthermore, when industrial hygiene data are lacking, some exposure information can be obtained from the questionnaire.

Pulmonary function testing. There may be one of several patterns of pulmonary function test change in individuals with occupational asthma. Findings might include generalized airway obstruction, i.e., $FEV_1/FVC < 70\%$; significant fall in postwork pulmonary function, i.e., $>10\%$ fall in FEV_1; observations of a more rapid decline in yearly tests in exposed workers; and frequently, normal test results.

An example of how pulmonary function tests were utilized in an epidemiologic study of occupational asthma concerns a population exposed to western red cedar wood dust.[28] Spirometric measurements were made on six occasions, beginning immediately before work on Monday (after the weekend off, again immediately after work that day, and then before and after work for the next 2 days for a total of 3 consecutive days. Environmental air monitoring by personal air samples was performed by standard methods. Fig. 2 shows changes in spirometric values in workers exposed to red cedar dust according to smoking history. Current cigarette smokers showed more pronounced postwork declines in FEV_1 than nonsmokers or ex-smokers.

Results of pulmonary function tests can be combined with questionnaire data for better definition of disease, as shown in Fig. 3 for cedar workers. "Chronic bronchitis" was determined by response from questionnaire; occupational asthma was defined by the questionnaire criteria (as described previously) and by the recording of a decline in FEV_1 greater than 10% compared with the value taken on the Monday morning before work. A designation of "nonspecific airways disease" was made when abnormal pulmonary function value (FEV_1/FVC less than 70%) was present in the absence of clinical symptoms of asthma or bronchitis. Those workers with "nonoccupational asthma" were persons with asthma histories and who indicated there was no relationship with work. A higher prevalence of "occupational asthma" was noted in cedar workers compared with other groups. Both wood dust exposures, however, showed greater prevalence of chronic bronchitis symptoms.

Immunologic testing. Immunologic studies on populations may include administration of skin tests for various antigens, collection of blood for total or specific immunoglobulins (i.e., RAST), or performance of procedures for testing cellular immunity. Abnormal tests help substantiate a diagnosis. Identification of atopic persons may indicate sensitive individuals who may be more prone to develop disease. Generally, the majority of tested workers will have no immunologic abnormality noted.

An example of how immunologic tests were used in

an epidemiologic study involves the previously mentioned isocyanate study.[58] Blood was tested by RAST for *p*-tolyl isocyanate–specific IgE antibodies as well as for five common airborne allergens (ragweed, timothy, cat and dog dander, and box elder). The frequency of positive RAST results for common airborne allergens varied depending on the antigen, ranging from 19% for ragweed to 7.4% for box elder. "Atopy" was defined as the presence of two or more positive RAST determinations for common allergens. There were 114 of 639 individuals who fit this category. Tests on current isocyanate-exposed workers showed more atopic persons than the other groups, but no association between asthma or bronchitis symptoms and "atopy" was noted. In the 114 atopic workers, a positive RAST for ragweed was seen in 87%. Interestingly, the presence of "atopy" could be predicted in 97% of the 114 workers by noting RAST positive results just for ragweed and cat dander.

Rast binding for *p*-tolyl isocyanate was considered "abnormal" if the value was greater than 2 standard deviations outside the mean for the 639 tested individuals. The mean ± SD for the total group was 2.5% ± 0.82%, with a range of 0.15% to 9.97% binding; thus greater than 4.1% binding was considered abnormal (Fig. 4). With this criteria, 10 individuals with "positive" RAST results were noted. Two were currently exposed, six were previously exposed, and two were never exposed to isocyanates. Three had no previous exposure to isocyanate spills, while three were exposed to 10 or more spills. Levels of total IgE in the 10 were not elevated. "Asthma" symptoms occurred in four, with one designated "occupational asthma"; "bronchitis" was seen in six. Only one individual had an "abnormal" pulmonary function test. The study demonstrates that the RAST battery for common allergens is useful for determining atopic status, but RAST for *p*-tolyl isocyanate is not a good screening test for identifying affected workers; only about 1.5% of the exposed population had a positive test.

Airway reactivity. In individual patients the presence or absence of airway hyperreactivity is crucial for making the diagnosis of asthma. Testing involves aerosolizing pharmacologic agents such as methacholine, histamine, or carbachol.[57] Increasing inhaled concentrations of the agent are tested against pulmonary function, with dose-response effects noted. A 20% or greater fall in FEV_1 has been considered a positive test.[57]

The utilization of pharmacologic agents for population studies is more difficult for a variety of reasons. There is often reluctance of industry and labor to accept tests requiring the administration of a "drug,"

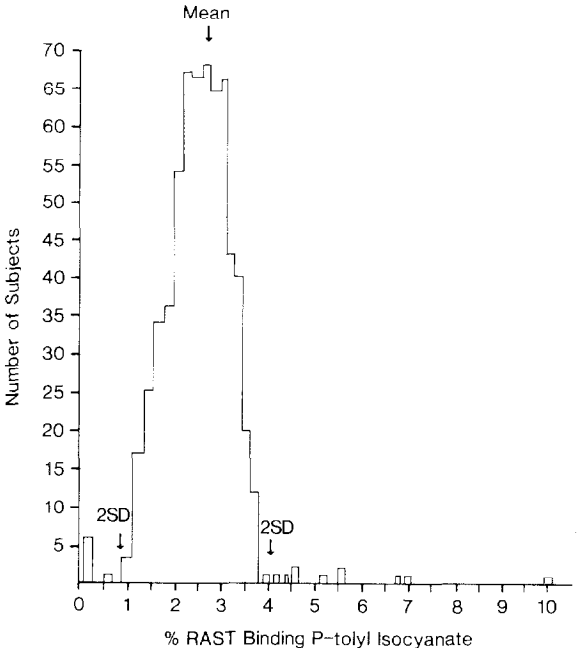

FIG. 4. RAST binding in 639 workers. An abnormal RAST was defined as a value 2 standard deviations greater than the mean.

especially when extremely sensitive workers might have significant responses. The pharmacologic bronchial challenges are generally time consuming, perhaps requiring 30 to 60 min to complete. This time factor makes it difficult to study large populations.

Recently we have used a cold-air challenge to assess airways reactivity.[59] The procedure is safe, fast, and acceptable. Recent studies confirm its sensitivity.[60] The protocol we developed completes the test within 10 min. Hyperventilation of −40° C air with added CO_2 is followed by serial spirometric measurements. We designated 38 individuals as being "normal" by questionnaire, pulmonary function tests, skin testing, and physical examination. Their change (mean ± SD) in FEV_1 was −2.38% ± 3.2%, with a range of +6.2% to −9.4%. We therefore concluded that for this study our "normal" value would represent a value 2 standard deviations greater than the mean; thus a −9% or greater fall in FEV_1 would constitute a "positive" cold-air challenge.

Cold-air challenge tests were performed on 109 individuals exposed to platinum salt. Eighty-six workers had negative skin prick tests for platinum salts,[59] and of this group, 11.6% had "positive" cold-air challenge. In contrast, of the 23 individuals with positive skin prick tests for platinum salt, there were 10 or 43.5% with "positive" cold-air challenge tests. Between 60% and 70% of all positive cold air–chal-

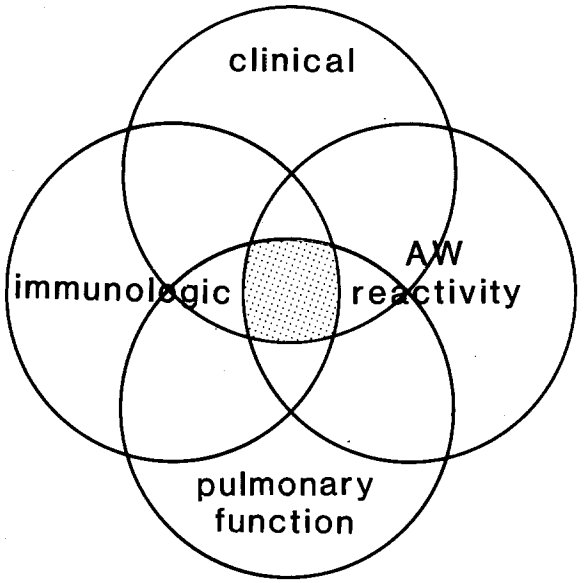

FIG. 5. Variety of presentations for occupational asthma, including clinical, immunologic, pulmonary function, and airway reactivity status.

lenged workers in each immunologic category reported lower respiratory tract symptoms.

Presentation of occupational asthma in population studies

Because of the variability in the presentation of asthma, there is difficulty in studying populations. A number of different responses can occur for clinical, immunologic, pulmonary function, or airway reactivity parameters. This variability in presentation is depicted in Fig. 5. When all tests or information are positive (a small percentage), the diagnosis of occupational asthma is not difficult. Unfortunately, usually only one aspect of the disease is apparent, and the diagnosis is not conclusive. Future studies will require better development of epidemiologic techniques for identifying asthma in populations. This needed research includes development of better questionnaires and rapid and sensitive immunologic screening tests. Development of simple noninvasive methods for identifying "hyperreactive" airways in populations is extremely important. The incorporation of more sensitive pulmonary function tests than FEV_1 is needed. The use of portable peak flow meters, which have been used in some studies, needs to be better tested in larger population studies.

Relationship between exposure and development of disease

The pathogenesis of occupational asthma may relate to intermittent high concentration exposure. Historical data were obtained on 332 individuals who reported previous exposure to isocyanate spills; this represented 65% of the isocyanate-exposed population.[58] Although workers reported isocyanate spills in the past, none was observed during the time of the study. Detailed industrial hygiene data at time of study showed low-level isocyanate exposure, generally less than 10 ppb. Employees were asked to estimate the number of spills they were exposed to in the past: 29% reported exposure to more than 20 spills, and 44% were exposed to more than 10 spills. Fig. 6 relates prevalence of asthma and bronchitis symptoms and abnormal pulmonary function tests to the number of isocyanate spills. There was a highly statistically significant relationship noted between exposure to more than 20 isocyanate spills and the presence of clinical asthma and chronic bronchitis. Individuals with no isocyanate spill exposures were more likely to be asymptomatic. No relationship with disease was noted in workers exposed to less than 10 spills. Furthermore, individuals exposed to more than 10 spills had significantly lower pulmonary function test results. Thus workers exposed to the most isocyanate spills showed the most abnormalities.

Another example of the association of high-dose exposure with greater disease prevalence is in workers exposed to western red cedar dust, as shown in Fig. 7. "Occupational asthma" was noted in 13.5% of workers, as determined by clinical and physiologic criteria described above. A relationship between the amount of cedar dust exposure and prevalence of "occupational asthma" was noted. Sawyers, packs, and splitters, those with the "dustiest" jobs, showed the highest prevalence rates. These data provide further evidence that high-dose exposure is an important factor in disease development. This observation has particular preventive medicine significance because reduction of uncontrolled high-level exposures can be instrumental in reducing disease.

Prognosis of occupational asthma

Individuals with occupational asthma follow a number of clinical courses. Initially, exposure to a material at work results in asthma as a result of a variety of potential mechanisms, which will not be discussed at this time. Subsequent removal of the worker from exposure usually results in prompt recovery of asthma. Sometimes, recovery is delayed for a few weeks. In a small percentage of cases, disease persists for months or years and is associated with essentially irreversible obstructive airways disease. This is particularly true for western red cedar asthma and isocyanate asthma.

We have noted that a major manifestation of individuals with persistent asthma is hyperreactive airways. Our previous studies have indicated a relationship between disease severity and degree of activity of

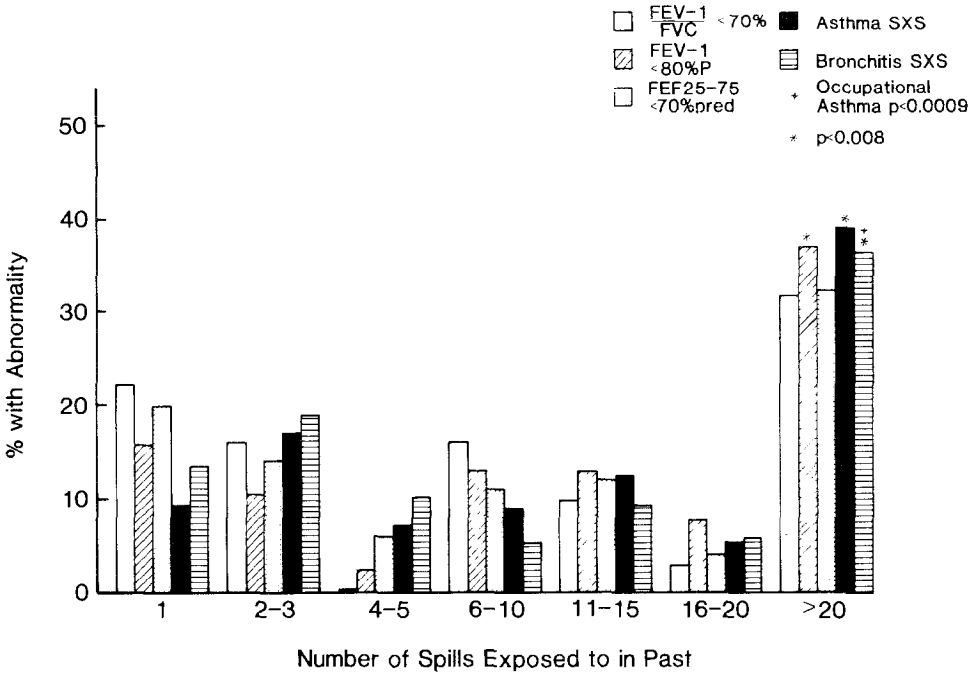

FIG. 6. Prevalence of various clinical diagnoses by questionnaire and abnormal pulmonary function tests in isocyanate workers. More abnormalities were noted in employees exposed to more than 20 spills in the past. *FEF 25-75,* Forced expiratory flow at 25% to 75% FVC. *SXS,* Symptoms.

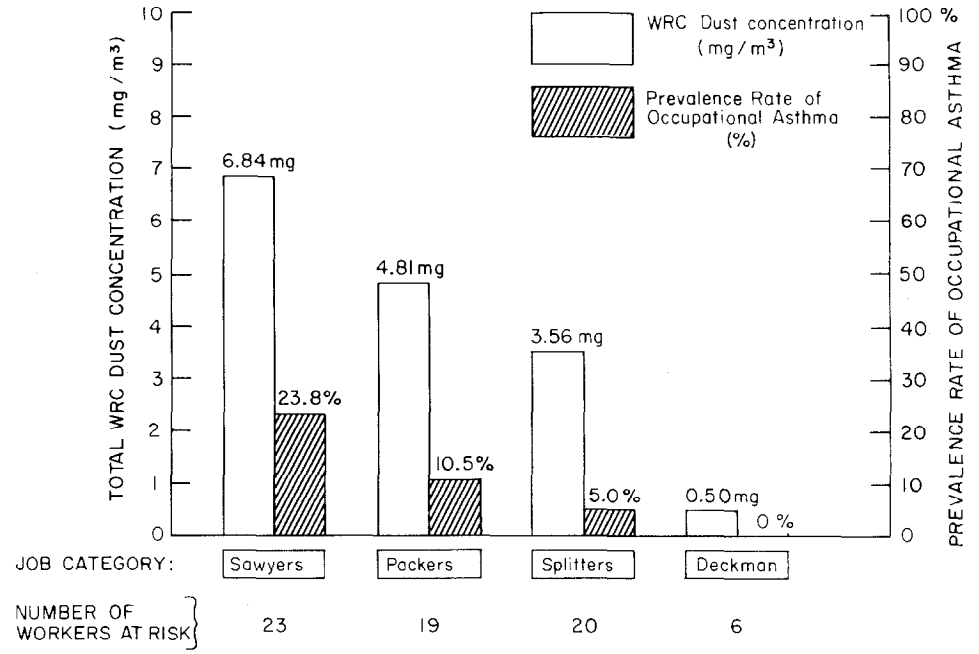

FIG. 7. Relationship between prevalence of occupational asthma and dust measurements in western red cedar *(WRC)* workers.

airways as measured by methacholine challenges.[61] Individuals with the most clinically severe asthma had airways most sensitive to methacholine, a finding confirmed by others.[62]

We know there are a variety of factors reported to affect the responsiveness of the airways, including recent allergen challenge, croup, acute viral respiratory infections, air pollutants (e.g., ozone and SO_2), vaccination (influenza, rubella), and occupational exposure to certain substances such as dimethyl ethanol-

amine, red cedar, and PVC pyrolysis products.[63] For instance, Boushey et al.[64] demonstrated increased airway reactivity in subjects who had inhaled PVC fumes.

The thermal decomposition products of PVC meat-wrapping film contains a number of irritants, such as hydrogen chloride and pyrolysis products of plasticizer, particularly di-2-ethylhexyladipate.[56] It is clear that environmental agents are capable of increasing airways reactivity.

Irritant exposures seem to cause symptoms of chronic cough and sputum. An entity termed "industrial bronchitis" has been reported from a variety of industrial substances (many being irritants), including coal, silica, asbestos, wood, flax and grain dusts, and welding fumes, and has been described to occur among foundry, rubber, coke-oven furnace, and chemical workers.[65] Because individuals with asthma can present only with chronic cough, it is not clear whether all cases reported as "industrial bronchitis" are truly bronchitis. Furthermore, there is evidence showing that agents affecting airways activity can result in cough.[63]

Reactive airways disease syndrome resulting from exposure to high concentrations of irritants

As noted previously, our data indicate an association between clinical disease severity and reactive airways.[61] Individuals with the most reactive airways, as determined clinically or pharmacologically, have the most severe asthma. Since a variety of environmental agents can adversely affect airway reactivity, it seems plausible that exposure to very high concentrations of an irritant may affect airways reactivity to the extent that it results in a clinical syndrome simulating asthma. We have described such a syndrome, which we call (for lack of a better name) RADS.[66] This is a disorder of the airways characterized by cough, dyspnea, and wheezing; it may be acute or chronic in nature. It is caused by the inhalation of high concentrations of irritating fumes, gases, or smokes. A characteristic of RADS is that it simulates asthma, with cough as a major symptom, but there is no specific etiologic factor to the entity. The onset of disease is frequently acute in nature, often beginning hours after exposure. In our study of 16 patients, about 75% developed symptoms within hours to a few days after exposure to very high levels of an irritant. In all cases the individual reported a specific incident where there was an unusually high exposure. After such an exposure, asthmalike symptoms occurred and often persisted for a number of years; in some patients symptoms resolved in a few weeks or months. A characteristic of this syndrome seems to be the development of irritable airways. Spirometric results were often abnormal, and methacholine challenge, when performed, was usually positive. A variety of occupations were reported for RADS patients, such as "barrel cleaner," arc welder, coating applier, and janitor. Although there were many reported causes of RADS, in all cases the exposure was characteristically to an irritant such as ammonia, welding fumes, propylene glycol fumes, printing mist, chlorine, chemical fumes, and fumigating solution.

The pathogenesis of RADS is unknown but seems to be nonimmunologic in nature and may be associated with direct injury to the bronchial epithelium.

Management of occupational asthma

The management of occupational asthma usually involves removal of the worker from exposure. Industrial hygiene measures can decrease environmental contaminant concentrations. Avoidance of spills and uncontrolled high-level exposure is mandatory. Sometimes specific manufacturing changes are helpful such as the substitution of one chemical for another. It is imperative that medical surveillance programs be provided, since subtle changes in workers' conditions might indicate early disease. Those individuals who become symptomatic with disease need prompt and vigorous treatment and removal from worksite exposures.

Conclusion

OADs are common problems in industry and may be caused by a variety of agents. The mechanisms of the airways disorder may be based on immunologic and/or nonimmunologic factors. A proper surveillance program of a working population for the presence of occupational asthma requires collection of information, including clinical (i.e., questionnaire), physiologic (i.e., pulmonary function tests), immunologic, and airways reactivity status. Epidemiologic techniques for identifying occupational asthma can be developed for the study of populations. Uncontrolled exposures at work may be responsible for initiating an airways disorder, perhaps with hyperreactive airways, i.e. RADS. Initiation of proper control measures for environmental agents, effective surveillance programs, and prompt treatment of disease will provide optimum protection for workers exposed to agents that might cause OADs.

REFERENCES

1. Brooks SM: Bronchial asthma of occupational origin. Scand J Work Environ Health 3:53, 1977.

2. Murphy RLH Jr: Industrial disease with asthma, *in* Weiss EB, and Segal MS, editors: Bronchial asthma: mechanisms and therapeutics. Boston, 1976, Little, Brown & Co., pp. 517-536.
3. National Institute for Occupational Safety and Health: Criteria for a recommended standard: occupational exposure to diisocyanates. U.S. Department H.E.W., P.H.S., C.D.C. (NIOSH) Publication No: 78-215, Sept. 1978.
4. Bernstein IL: Occupational asthma: current problems in the United States: *in* Allergology. International Congress Series No. 323, Amsterdam, 1973, Excerpta Medica, pp. 112.
5. Ishizaki T, Shida T, Miyamoto T, Matsumora Y, Mizuno K, Tomaru M: Occupational asthma from Western red cedar dust *(Thuja plicata)* in furniture factory workers. J Occup Med **15:**580, 1973.
6. Chan-Yeung M: Fate of occupational asthma. Am Rev Respir Dis **116:**1023, 1977.
7. Hansen K: Occupational and industrial asthma, *in* European Academy of Allergy, occupational allergy. Springfield, Ill., 1958, Charles C Thomas, Publisher, pp. 29-34.
8. Michel H: Occupational sensitization of the upper and lower air passages by organic types of dust, *in* European Academy of Allergy, occupational allergy. Springfield, Ill. 1958, Charles C Thomas, Publisher, pp. 35-47.
9. Freedman SO: Allergic and toxic mechanisms in occupational lung diseases. Mod Treatment **3:**838, 1966.
10. Pepys J, Davies RJ: Occupational asthma, *in* Middleton E Jr, Reed CE, Ellis EF, editors: Allergy: principles and practice. St. Louis, 1978, The C. V. Mosby Co., pp. 812-842.
11. Voorhorst R: The human dander allergen, *in* European Academy of Allergy, occupational allergy. Springfield, Ill., 1958, Charles C Thomas, Publisher, pp. 260-272.
12. Taylor AN, Longbottom JL, Pepys J: Respiratory allergy to urine proteins of rats and mice. Lancet **2:**847, 1977.
13. Ohman JL Jr, Lowell FC, Black KJ: Allergens of mammalian origin. II. Characterization of allergens extracted from rats, mouse, guinea pig, and rabbit pelts. J ALLERGY CLIN IMMUNOL **55:**16, 1975.
14. Flindt MLH: Pulmonary disease due to inhalation of derivatives of *Bacillus subtilis* containing proteolytic enzymes. Lancet **1:**1177, 1969.
15. Franz T, McMurrain KK, Brooks SM, Bernstein IL: Clinical, immunologic and physiologic observations in factory workers exposed to *B. subtilis* enzyme dust. J ALLERGY **42:**170, 1971.
16. Parkes WR: Occupational lung disorders, London, 1974, Butterworths, pp. 450-456.
17. Seaton A: Occupational asthma, *in* Morgan WK, Seaton A, editors: Occupational lung diseases. Philadelphia, 1975, W. B. Saunders Co., pp. 251-264.
18. Chan-Yeung M, Barton GM, MacLean L, Bryzybowski S: Occupational asthma and rhinitis due to western red cedar *(Thuja Plicata).* Am Rev Respir Dis **108:**1094, 1973.
19. Ordman D: Wood dust as an inhalant allergen: bronchial asthma caused by kejaat wood. S Afr Med J **23:**973, 1949.
20. Bouhuys A: Response to inhaled histamine in bronchial asthma and in byssinosis. Am Rev Respir Dis **95:**89, 1967.
21. Cooper WC, Perone VB, Scheel LD, Keenan RG: Occupational hazards from castor bean pumice: tests for toxicity. Ind Hyg J **25:**431, 1964.
22. Gronemeyer W, Fuch E: Coffee: an occupational allergen, *in* European Academy of Allergy, occupational allergy. Springfield, Ill., 1958, Charles C Thomas, Publisher, pp. 29-47.
23. Ordman D: Buckwheat allergy. S Afr J Med Sci **21:**737, 1947.
24. Pilat L, Popa V, Stanescu D, Teculescu D: Weavers' asthma. Acta Allergol **22:**39, 1967.
25. Williams N, Skoulas A, Merriman JE: Exposure to grain dust. II. A clinical study of the effects. J Occup Med **6:**359, 1964.
26. Chan-Yeung M, Abboud R: Occupational asthma due to California redwood dusts. Am Rev Respir Dis **2:**1027, 1976.
27. Raghuprasad AK, Brooks SM, Litwin A, Edwards JJ, Bernstein IL, Gallagher J: Quillaja bark (soapbark)-induced asthma. J ALLERGY CLIN IMMUNOL **65:**285, 1980.
28. Brooks SM, Edwards JJ, Apol A, Henderson F: An epidemiologic study of workers exposed to western red cedar and other wood dusts. Chest **80:**30, 1981.
29. do Pico GA, Redden W, Flaherty D et al: Respiratory abnormalities among grain handlers: a clinical, physiologic and immunologic study. Am Rev Respir Dis **115:**915, 1977.
30. Brooks SM, Vandervort R: Investigation of polyvinyl chloride film thermal decomposition products as an occupational illness of meat wrappers. II. Clinical studies. J Occup Med **19:**192, 1977.
31. Bruckner HC: Extrinsic asthma in a tungsten carbide worker. J Occup Med **9:**518, 1967.
32. Card WI: A case of asthma sensitivity to chromates. Lancet **229:**1348, 1935.
33. Freedman SO, Krupey J: Respiratory allergy caused by platinum salt. J ALLERGY **42:**233, 1968.
34. Celfend HH: Respiratory allergy due to chemical compounds encountered in the rubber, lacquer, shellac and beauty culture industries. J ALLERGY **34:**374, 1963.
35. Kammermeyer JK, Methews KP: Hypersensitivity to phenylglycine acid chloride. J ALLERGY CLIN IMMUNOL **52:**73, 1973.
36. Kern RA: Asthma and allergic rhinitis due to sensitization to phthalic anhydride: report of a case. J ALLERGY **10:**64, 1939.
37. Maccia CA, Bernstein IL, Emmett EA, Brooks SM: In vitro demonstration of specific IgE in phthalic anhydride hypersensitivity. Am Rev Respir Dis **113:**701, 1976.
38. Pepys J, Pickering CAC, Loudon WG: Asthma due to inhaled chemical agents: piperazene dihydrochloride. Clin Allergy **2:**189, 1972.
39. Schwarting HH: Occupational allergy in printers, *in* European Academy of Allergy, occupational allergy. Springfield, Ill. 1968, Charles C Thomas, Publisher, pp. 278-289.
40. Butcher BT, Jones RN, O'Neil CE, Weill H, Salvaggio J: Longitudinal study of workers employed in the manufacture of toluene diisocyanate. Am Rev Respir Dis **116:**411, 1969.
41. Pepys J, Pickering CAC, Bredin ABX, Terry DJ: Asthma due to inhaled chemical agents—toluene diisocyanate. Clin Allergy **2:**225, 1972.
42. McKay RT, Brooks SM, Johnson C: Isocyanate-induced abnormalities of beta adrenergic receptor function. Chest **80** (Suppl.):61, 1981.
43. Smith AB, Brooks SM, Blanchard J, Bernstein IL, Gallagher J: Absence of airway hyperreactivity to methacholine in a worker sensitized to toluene diisocyanate (TDI). J Occup Med **22:**327, 1980.
44. Pepys J, Parish WE, Cromwell O, Hughes EG: Passive transfer in man and the monkey of type I allergy due to heat labile and heat stable antibody to complex salts of platinum. Clin Allergy **9:**99, 1979.
45. Feinberg AR, Feinberg SM, Benaim-Pinto C: Asthma and rhinitis from insect allergens. J ALLERGY **27:**437, 1956.
46. Dosman JA, Cotton DJ, Graham BL, Robert Ky et al: Chronic bronchitis and decreased forced expiratory flow rates in lifetime, nonsmoking grain workers. Am Rev Respir Dis **121:**11, 1980.
47. Jones RN, Diem JE, Glindmeyer H et al: Mill effect and dose-response relationships in byssinosis. Br J Ind Med **36:**305, 1979.
48. Ganelin RS, Cueto C, Mail GA: Exposure to parathion—effect

on general population and asthmatics. JAMA **188:**108, 1964.
49. Johnson TG, Cagort AG, Marvin HN, Pringle RB, Sheldon JM: Bronchial asthma, urticaria, and allergic rhinitis from tannic acid. J ALLERGY **22:**494, 1951.
50. Brooks SM, McKay RT et al: Epidemiologic study of workers exposed to isocyanate. NIOSH Health Hazard Evaluation Report. HHE-78-39, 1980.
51. Gallagher JS, Tse T, Brooks SM, Bernstein IL: Heterogeneous patterns of immunoreactivity in TDI asthma. J Occup Med **23:**610, 1981.
52. Patterson R, Addington W, Bonner AS, Byron GE et al: Antihapten antibodies in workers exposed to trimellitic anhydride fumes: a potential immunopathogenetic mechanism for trimellitic anhydride pulmonary disease-anemia syndrome. Am Rev Respir Dis **120:**1259, 1979.
53. Zeiss CR, Patterson R et al: Trimellitic anhydride–induced airway syndromes: clinical and immunologic studies. J ALLERGY CLIN IMMUNOL **60:**96, 1977.
54. Patterson E, Zeiss CR, Roberts M et al: Human antihapten antibodies in trimellitic anhydride inhalation reactions. J Clin Invest **62:**971, 1978.
55. Cromwell O, Pepys J, Parish WE, Hughes EG: Specific IgE antibodies to platinum salts in sensitized workers. Clin Allergy **9:**109, 1969.
56. Vandevort R, Brooks SM: Polyvinyl chloride film thermal decomposition products as an occupational illness. I. Environmental exposures and toxicology. J Occup Med **19:**189, 1979.
57. Guidelines for bronchial inhalation challenges with pharmacological and antigenic agents. American Thoracic Society News, Spring, 1980, Vol. 6.
58. McKay RT, Brooks SM: Toluene diisocyanate (TDI): biochemical and physiological studies. Am Rev Respir Dis **123:** 132, 1981.
59. Gallagher JS, Baker D, Gann PH, Jarabek A, Brooks SM, Bernstein IL: A cross-sectional investigation of workers exposed to platinum salts. J ALLERGY CLIN IMMUNOL **69:**134, 1982. (Abst.)
60. O'Byrne PM, Ryan G, Morris M, McCormack D, Jones NL, Morse JLC, Hargreave F: Asthma induced by cold air and its relation to nonspecific bronchial responsiveness to methacholine. Am Rev Respir Dis **125:**281, 1982.
61. Brooks SM, Raghuprasad P, Bernstein IL, Mieczkowski L: Clinical severity of asthma and airway responsiveness. Rev Respir Dis **121:**117, 1980.
62. Hargreave FE, Ryan G, Thomson NC, O'Byrne PM, Latimer MD, Juniper EF, Dolovick J: Bronchial Responsiveness to histamine or methacholine in asthma: measurement of clinical significance. J ALLERGY CLIN IMMUNOL **68:**347, 1981.
63. Boushey HA, Holtzman MJ, Sheller JR, Nadel JA: State of the art. Bronchial hyperreactivity. Am Rev Respir Dis **121:**389, 1980.
64. Boushey HA, Empey DW, Laitinen LA: Meat wrapper's asthma: effects of fumes of polyvinyl chloride on airways function. Physiologist **18:**148, 1975.
65. Higgins ITT: Epidemiology of chronic respiratory disease: a litrature review. Environmental Health Effects Research Series, Publication No. EPA-650/1-74-007, August 1974.
66. Brooks SM: Reactive airways disease syndrome. Am Rev Respir Dis **123:**133, 1981.