ray may be normal, or rounded nodules, less than 10 mm in diameter, may be present, predominantly in the upper lobes. These findings characterize the simple form of coal workers' pneumoconiosis. In spite of the presence of roentgenographic and pathologic abnormalities, only subtle abnormalities of small airways function are demonstrable in simple coal workers' pneumoconiosis (Morgan 1984a).

In certain chronic occupational lung diseases, parenchymal lung injury may be accompanied by evidence of restriction alone; in others, variable combinations of restriction and obstruction may occur. Relevant examples of these two types of processes are asbestosis (Seaton 1984a) and the complicated forms of coal workers' pneumoconiosis and silicosis (Morgan 1984a; Seaton 1984b).

Although asbestos exposure is associated with fibrosis of the respiratory bronchioles, the injury often progresses and involves the alveolar interstitium with the development of parenchymal fibrosis (Seaton 1984a). The clinical consequences of this parenchymal injury are cough and dyspnea. Other changes found in asbestosis include crackles, clubbing, and basilar, irregular, linear opacities on chest x ray. Pulmonary function testing shows only a restrictive pattern with reduced FVC, normal FEV/FVC%, and decreased TLC.

In contrast, the complicated forms of silicosis and coal workers' pneumoconiosis may be accompanied by obstruction in addition to restriction. In both disorders, large masses of dust and fibrosis replace the normal lung parenchyma and reduce FVC and TLC. Obstruction may also be present, presumably because of increased airways resistance and parenchymal abnormalities. Dyspnea is generally a prominent symptom.

Thus, for some occupational agents, the associated lung injury at specific anatomic loci resembles that from cigarette smoking. Large airway irritation, regardless of the exposure, is accompanied by abnormalities of the mucous glands and mucus hypersecretion. Small airways may be affected by occupational agents, and a pattern of injury distinct from that found in cigarette smokers has been described (Churg et al. 1985). However, the parenchymal abnormalities of advanced pneumoconiosis can be readily distinguished from emphysema associated with cigarette smoking.

Methods for Evaluating the Effects of Occupational Exposures on the Lungs

Workers exposed to occupational agents that cause chronic lung disease may be examined for diagnostic reasons, for surveillance, or for research. Regardless of the purpose of the evaluation, the same assessment techniques are generally used: history of respiratory symptoms, physical examination of the chest and extremities,

spirometry and other physiological tests, and chest x ray (American Thoracic Society 1982b; Boehlecke 1984; Townsend and Belk 1984). These techniques and their sensitivity to the effects of cigarette smoking are described below.

History of Respiratory Symptoms

Symptoms of lung disease are nonspecific; the most prevalent are cough, phlegm production, wheezing, and breathlessness or dyspnea (Gandevia 1981). Although a physician may take a conventional history to evaluate these symptoms, standardized questionnaires are generally used for surveillance and research purposes.

In the 1950s, the British Medical Research Council developed a standardized respiratory symptoms questionnaire for studies of the epidemiology of chronic bronchitis and chronic obstructive lung disease (Samet 1978; Florey and Leeder 1982). In 1968, this questionnaire was adopted for use in the United States by a committee of the American Thoracic Society (1969). Three years later, the National Heart and Lung Institute made available a version that had been modified to improve its suitability for the United States (US DHEW 1971). In 1978, the American Thoracic Society published a further revised respiratory symptoms questionnaire (Ferris 1978). The Medical Research Council questionnaire or one of these modified versions has been used in most studies of chronic lung disease in the workplace. All include a series of questions related to cough, phlegm, wheezing, and dyspnea.

The Medical Research Council questionnaire was originally developed for investigating the etiology of chronic bronchitis and airflow obstruction (Fletcher et al. 1959; Samet 1978). The questionnaire was designed, in part, to test one of the prevailing hypotheses about airflow obstruction: that mucus hypersecretion predisposed repeated lower respiratory tract infections and consequent airflow obstruction (Fletcher et al. 1959, 1976). Accordingly, the cough and phlegm questions were worded to be sensitive to the earliest phases of mucus hypersecretion, a condition largely attributable to cigarette smoking (US DHHS 1984). The questions may be less satisfactory for cough and sputum associated with other exposures, particularly if those other exposures produce a pattern of symptoms different from those due to cigarette smoking, such as nocturnal cough or episodic cough. Further, their sensitivity to cigarette-associated mucus hypersecretion may hinder separation of an occupational exposure's effect on the occurrence of cough and phlegm from that of cigarette smoking. The dyspnea and wheeze questions probably do not share this sensitivity.

In population surveys, cigarette smoking is the major determinant of the prevalence of cough and phlegm (US DHHS 1984). This association has been confirmed in occupational groups as well as in

population samples (Gandevia 1981; US DHHS 1984; Petersen and Castellan 1984). Wheezing is also associated with cigarette smoking (Mueller et al. 1971; Samet et al. 1982; Schenker et al. 1982). Dyspnea has multiple determinants that interact in a complex fashion; cigarette smoking and smoking-related impairment of lung function contribute to the occurrence of dyspnea (Wasserman and Whipp 1975; Cotes 1979; Killian and Jones 1984).

Chest X Ray

The pneumoconioses are associated with characteristic radiographic abnormalities, although the chest film may be normal in the presence of biopsy-proven disease (Epler, McLoud et al. 1978). A conventional clinical interpretation is usually sufficient for establishing the presence of pneumoconiosis. Preferably, however, the chest x ray should be coded according to the classification established by the International Labour Office (ILO) (1980). This system, originally published in 1950, categorizes the types of abnormalities on the chest x ray by shape and size, and provides a grading (the profusion) for describing the density of small opacities. The opacities classified as small are grouped as rounded or irregular. If the opacities are less than 1 cm in diameter, they are called small; if equal to or greater than 1 cm, they are called large.

The effects of cigarette smoking on chest x-ray findings have been examined, using both conventional interpretations and readings in the ILO system. Human autopsy evidence and animal exposure studies show that cigarette smoking leads to abnormalities in the airways and parenchyma that might produce radiographic abnormalities (US DHEW 1979b; Weiss 1984). However, these changes are subtle in comparison with the pathological findings in the pneumoconioses. Cigarette smoking is associated with modest amounts of interstitial fibrosis in the lungs, in addition to airways abnormalities and emphysema (US DHEW 1979b; Weiss 1984). For example, Auerbach and colleagues (1974) examined lung sections from 1,443 men and 388 women deceased between 1963 and 1970, and found more fibrosis in smokers than in nonsmokers and a dose–response relationship between the degree of fibrosis and the amount smoked. The small airways of cigarette smokers, even at young ages, display inflammation with edema of the bronchiolar walls, smooth muscle hypertrophy, and goblet cell metaplasia (US DHHS 1984). These changes may underlie, at least in part, the pattern of increased lung markings in smokers described anecdotally by clinicians, but are unlikely to be confused with the more extensive fibrosis found in moderate or advanced pneumoconiotic lung disease.

Comparisons of chest x-ray findings generally show a higher frequency of abnormalities, interpreted as representing interstitial fibrosis, in smokers than in nonsmokers. These investigations have

been based on chest films from both the general population and specific occupational groups. Weiss (1967, 1969) reviewed chest films from two samples of adults—participants in a tuberculosis screening program and hospital employees. In both groups, he identified a pattern of increased lung markings, termed diffuse pulmonary fibrosis, more often in smokers, and showed that the prevalence of this finding increased with the amount and duration of smoking. These studies have been criticized because the films were 70 mm photofluorograms taken for screening purposes and not full sized (Kilburn 1981). Further, the films were not read directly according to the ILO classification. In another study that did not use the ILO system, Carilli and colleagues (1973) showed that radiologists could generally distinguish smoking women from nonsmoking women by the presence of linear and nodular fibrotic changes in the smokers. Epstein and colleagues (1984) read the chest x rays of 200 hospitalized patients according to the ILO classification. Twenty-two patients with at least category 1/0 profusion and no documented dust exposure or other explanation for nodular densities were identified, 10 of whom had not smoked cigarettes. Because this study included only hospitalized people, the results may not be generalizable to working populations.

The results of investigations involving occupational groups do not show strong effects of cigarette smoking on the profusion of small opacities. Glover and colleagues (1980) read the chest films of slate workers and a nonexposed control group according to the 1971 ILO classification. In the controls, small irregular opacities were not seen in nonsmokers, but were present in 2 percent of current and former smokers. Investigators from the National Institute for Occupational Safety and Health interpreted chest x rays of 1,422 blue-collar workers whose present and past employment should not have involved exposure to respiratory hazards (Castellan et al. 1984). Only three workers had at least category 1/0 profusion, two with small rounded opacities and one with small irregular opacities. Sixty-one percent of the subjects were current or former smokers. However, the mean age of subjects in this study was only 33.9 years, substantially lower than the age at which pneumoconiosis or significant cigarette-related airflow obstruction would generally be manifest if exposure began at about age 20. In a much smaller study of similar design, Cordier and colleagues (1984) identified small opacities in only 1 person in a control group of 48 office workers, 31 percent of whom smoked.

Studies of workers exposed to hazardous agents show that cigarette smoking may modify the pattern of radiographic abnormality. In coal workers, small rounded opacities predominate in the simple phase of coal workers' pneumoconiosis, but irregular opacities may also be present (Amandus et al. 1976; Cockcroft et al. 1982,

1983). The irregular opacities are associated with cigarette smoking and with reductions of FEV_1, FVC, and diffusing capacity (Cockcroft et al. 1982). In autopsy specimens obtained from coal workers in the United Kingdom, Ruckley and colleagues (1984) demonstrated that emphysema was present in 90 percent of the lungs with small irregular opacities, but in only 60 percent with small rounded opacities alone. Dick and colleagues (1983) examined the radiographs of a stratified random sample of miners from 10 British coal mines and concluded that smoking did not influence the prevalence of rounded opacities. Smokers had a greater prevalence of irregular opacities, but after adjusting for the effects of differences in age and dust exposure, these results were not statistically significant.

Studies of other occupationally exposed groups also demonstrate that cigarette smoking may affect the pattern and extent of radiographic abnormality. In granite workers, Theriault and colleagues (1974) found that rounded opacities were related to an estimate of lifetime dust exposure, whereas small irregular opacities were more strongly related to smoking. In workers exposed to manmade vitreous fibers, the prevalence of small opacities was determined not only by estimated exposure but also by smoking habits (Weill et al. 1983). Using multiple logistic regression, Peters and colleagues (1984) showed that cigarette smoking, but not particulate exposure, predicted the occurrence of linear opacities in silicon carbide workers. In asbestos workers, the predominance of evidence indicates that cigarette smoking acts independently and additively with asbestos to create radiographic abnormalities (Weiss 1984).

The findings of these studies of occupationally exposed and nonexposed individuals indicate that cigarette smoking may affect chest x-ray readings. Cigarette smoking alone is occasionally associated with definite abnormalities classified in the ILO system. Smoking may also affect the radiographic pattern and independently increase the prevalence of abnormality. In addition, the threshold for detection of an abnormality on chest x ray may be exceeded more frequently or at an earlier age in workers who smoke than in workers who do not smoke.

Physiological Assessment

An evaluation of workers for diagnosis and surveillance may include auscultation of the chest, for breath sound quality and intensity and for the presence of adventitious sounds including crackles, and examination of the fingernails for evidence of clubbing. Crackles, also referred to as rales or crepitations, are discontinuous, interrupted sounds thought to arise from the sudden opening of small airways or from the bubbling of air through secretions in larger airways (Loudon and Murphy 1984). Fine crackles may be

heard in people with diffuse interstitial fibrosis. For example, Epler, Carrington, and colleagues (1978) reported that fine crackles were present in 60 and 65 percent of subjects with biopsy-proven and clinically diagnosed asbestosis, respectively. Some definitions of asbestosis incorporate the presence of crackles as a diagnostic criterion (Murphy et al. 1978). Because crackles may be heard in asbestosis and other occupational lung diseases, auscultation has been advocated as a surveillance technique for monitoring workers exposed to asbestos and other agents (Loudon and Murphy 1984; Murphy et al. 1984).

Few studies have addressed the effects of cigarette smoking on auscultatory findings, however. Epler, Carrington, and colleagues (1978) reported the results of a conventional clinical auscultation of patients with various interstitial disorders or with chronic obstructive lung disease, which is largely attributable to cigarette smoking. Fine crackles, characteristic of asbestosis, were heard in only 10 to 12 percent of the latter group, though coarse crackles were more common in those with chronic bronchitis. Two studies of asbestos workers suggest that cigarette smoking may independently increase the frequency of crackles. To quantify the separate effects of asbestos exposure and cigarette smoking on the prevalence of bilateral fine crackles, Samet and colleagues (1979) analyzed data from 409 survey subjects, using multiple logistic regression. Statistically significant effects of both smoking and asbestos exposure were found. In the other study (Murphy et al. 1984), a technician examined each subject with a standardized approach and a summary crackles score was calculated. Multivariate analysis suggested that cigarette smoking was associated with the lower abnormality levels of this score. The consistent findings of these two investigations seem plausible in view of the effects of cigarette smoking on the small airways, the site where fine crackles are presumed to originate (Loudon and Murphy 1984). In 590 employed men not exposed to respiratory hazards, crackles were heard predominantly in the older smokers (Gandevia 1981). This finding further supports a relationship between cigarette smoking and the presence of crackles.

Clubbing refers to a change in the configuration of the nail beds, which can be best quantitated by the hyponychial angle (Regan et al. 1967). It has many causes and is a nonspecific manifestation of advanced chronic respiratory diseases, lung cancer, and other disorders (Shneerson 1981). Because clubbing may be occasionally found with COLD, its presence may be related to cigarette smoking as well as to occupational lung disease. Samet and colleagues (1979) found that cigarette smoking and occupational exposure to asbestos were independent determinants of the prevalence of clubbing in four different populations of asbestos workers.

Findings on clinical examination, like respiratory symptoms, are nonspecific, and a conventional physical examination alone is an insensitive method for diagnosing chronic occupational lung diseases. However, the presence of fine crackles, in the setting of an appropriate exposure, should alert the clinician to the possibility of pneumoconiosis, even if the chest x ray is unremarkable. Clubbing, when attributable to a chronic pulmonary process, is generally a marker for more advanced disease. Diseases associated with cigarette smoking may be accompanied by crackles or clubbing.

Evaluation of pulmonary function in occupationally exposed individuals, whether for diagnostic or research purposes, should include spirometry, which measures FVC, FEV_1, and maximal expiratory flow rates (Ferris 1978; American Thoracic Society 1982b). The effects of smoking on spirometric parameters are discussed elsewhere in this chapter. The diffusing capacity for carbon monoxide may also be measured; it is a sensitive test that may detect early abnormalities in chronic occupational lung diseases (Weinberger et al. 1980). As with FVC, FEV_1, and other spirometric measures, cigarette smoking habits must be considered in interpreting the level of diffusing capacity, which is reduced by smoking-related lung disease (particularly emphysema) as well as by occupational lung disease (Make et al. 1982; Miller et al. 1983). FVC can be reduced either by restrictive lung diseases, such as asbestosis, or by COLD; therefore, TLC should be measured with a physiological or radiological method in order to establish the presence of a restrictive disorder. In evaluating subjects for occupational asthma, nonspecific bronchial reactivity may be assessed with pharmacologic agents, such as methacholine, or with cold air inhalation (Brooks 1982). Some studies indicate that nonspecific bronchial reactivity is increased in cigarette smokers (Kabiraj et al. 1982; Gerrard et al. 1980), though others do not (Kennedy et al. 1984; Wanner et al. 1985).

Exercise testing is one of the methods used to assess the degree of impairment resulting from a chronic occupational lung disease (American Thoracic Society 1982a). Exercise testing has been used to characterize the pathophysiology of chronic occupational lung diseases, but is rarely used for establishing clinical diagnoses or for epidemiological studies (Wiedemann et al. 1984) and is not discussed further in this chapter. Cigarette smoking can impair exercise performance through a variety of mechanisms (Cotes 1979).

Quantification of Effects of Smoking and Occupation in Populations

Concepts of Interaction

Interaction has been defined as "the interdependent operation of two or more causes to produce an effect" (Last 1983, p. 51). Epidemiologists may also apply the term "effect modification" to variation in the magnitude of an exposure's effect as the level of another exposure changes (Last 1983). Synergism refers to an increased effect of the exposures when both are present, and antagonism refers to a reduced effect (Last 1983). Statistical modeling techniques are generally used to test for the presence and direction of interaction. The most widely applied statistical techniques measure interaction on either an additive or a multiplicative scale (Rothman et al. 1980; Kleinbaum et al. 1982). Ideally, the choice of a model should be based on a specific biological formulation of disease pathogenesis; most often, however, the underlying biological mechanisms are not well established and largely statistical considerations govern the selection of an analytical model.

The results of such models must be interpreted not only statistically but also in biological and public health contexts (Rothman et al. 1980). Rothman and colleagues (1980) argued that biological models should be explicitly described; in their view, the labeling of mechanisms as synergistic or independent does not advance the understanding of disease etiology. They broadly described two categories of mechanisms: those with the multiple etiological factors acting interchangeably at the same step and those with the factors acting at different steps. The corresponding statistical models are the additive and the multiplicative, respectively. These authors and others (Blot and Day 1979; Saracci 1980; Kleinbaum et al. 1982) have concluded that, from the public health viewpoint, departure from additivity represents interaction.

Both advancing the understanding of disease etiology and the need for protecting public health provide a compelling rationale for assessing interaction between cigarette smoking and workplace exposures. Cigarette smoking may interact with a particular exposure through diverse mechanisms that range from behavioral to molecular levels (Table 4). The 1979 Report of the Surgeon General (US DHEW 1979b) partially addressed different forms of interaction between smoking and occupational exposures; other plausible hypotheses concerning interaction between cigarette smoking and occupational agents can also be postulated. The interactions listed in Table 4 are intended to be illustrative and not exhaustive.

Some consequences of cigarette smoking might lead to a reduction of the dose of an inhaled agent. In comparison with nonsmokers, current and former smokers have higher rates of absenteeism from

TABLE 4.—Some potential interactions between cigarette smoking and occupational exposures in the pathogenesis of chronic occupational lung diseases

Source of interaction	Potential consequence
Increased absenteeism by smokers from work	Reduced inhaled dose in smokers
Selection of more fit nonsmokers into aerobically demanding jobs	Reduced inhaled dose in smokers
Contaminated cigarettes act as a vector	Increased exposure of smokers
Workplace chemicals are metabolized to toxic or more toxic agents by cigarettes	Increased exposure of smokers
Increased tracheobronchial deposition of particulates in smokers and people with chronic bronchitis	Differing regional lung doses in smokers and nonsmokers
Reduced mucociliary transport in smokers	Increased dose in smokers
Reduced alveolar clearance of particulates in smokers	Increased dose in smokers
Increased numbers of polymorphonuclear leukocytes and other inflammatory cells in lungs of smokers	Increased lung injury in smokers

work (US DHEW 1979b). Because cigarette smoking and cigarette-related cardiorespiratory diseases are associated with reduced aerobic capacity, nonsmokers may tend to perform the more strenuous tasks in the workplace. The higher ventilatory requirements of such jobs might increase the amount of dust or other agents inhaled; smokers would be spared to the extent that they are selected for more sedentary jobs. The excess mucus production of chronic bronchitis might protect against soluble agents through the increased absorptive capacity of the mucus.

Tobacco products might serve as vectors for the transformation of workplace chemicals into more harmful agents. For example, smokers are placed at increased risk for polymer fume fever through contamination of their cigarettes by fluorocarbons; toxic products are generated by the cigarette's heat and are inhaled by the smokers. Reduced pulmonary defenses in smokers might also increase the effects of occupational agents. The mucociliary apparatus of the airways removes particles and absorbed gases by physical transport (Wanner 1977; Lippmann et al. 1980). Both cilia and mucus are affected by tobacco smoke, and direct measurements of mucociliary

transport in animals and in humans confirm that long-term smoking impairs particle clearance (Wanner 1977; Lippmann et al. 1980; US DHHS 1984). Cohen and colleagues (1979) have demonstrated impaired alveolar clearance of particulates in smokers, as well. A plausible, though not established, consequence of reduced clearance is the increased pulmonary residence time of harmful agents and an increased dust burden in the lungs. Finally, alterations of lung cell populations and the presence of inflammation in smokers might amplify the effects of inhaled occupational agents. Inflammatory cells are thought to have a central role in lung injury caused by occupational agents (Campbell and Senior 1981; Bitterman et al. 1981). The lungs of smokers yield markedly increased numbers of macrophages and neutrophils in bronchoalveolar lavage fluid in comparison with the lungs of nonsmokers (US DHHS 1984). Thus, synergism between cigarette smoking and an occupational agent could reflect a greater release of enzymes and other toxic products from the large numbers of inflammatory cells that have been recruited into the lung by cigarette smoke.

Study Design

Several epidemiological study designs are used to assess the independent and interactive effects of smoking and occupational exposures in human populations. The cross-sectional study, or survey, is the most widely used approach, primarily because of its feasibility and low cost. Most surveys involve data collection from samples defined by employment status or union membership. In a cohort study, exposed and nonexposed people are followed over time and monitored for the development of disease. Large-scale cohort investigations of workers exposed to asbestos, silica, and coal dust have been carried out. The case–control design involves the identification of cases with the disease of interest and a control series of people without the disease who would be potentially selected as cases if they were to develop the disease. The exposure histories of the cases and controls are ascertained and compared. This design has been used infrequently for studying chronic occupational lung diseases.

As a minimum, when cigarette smoking and a single occupational agent are of interest, the study should provide estimates of their independent effects and of the combined effect. This minimum is suggested because the impairment observed in a particular population reflects the consequences not only of the occupational agent but also of all other damaging environmental exposures. Of these, cigarette smoking is by far the most important and the most readily assessed. Cross-sectional, case–control, and cohort designs meet this requirement if the cigarette smoking practices and exposure histories of the subjects can be accurately determined.

Assessment of Exposures

Cigarette Smoking

The American Thoracic Society (Ferris 1978) has recommended that a cigarette smoking questionnaire include smoking status (never, current, or previous), age started smoking, age stopped smoking (for former smokers), current and usual amount smoked, and depth of inhalation. Questions concerned with brand and extent of filter cigarette smoking are optional, but should be used when possible to address research questions related to types of cigarettes smoked. The recommended items provide several measures of exposure to cigarette smoke for data analysis: usual amount smoked, duration of smoking, and cumulative consumption. The items related to cigarette smoking status can be used to stratify a study population into current, former, and never smokers.

These simple measures of exposure to cigarette smoking strongly predict the risk of both age-specific overall mortality and COLD mortality (US DHEW 1979b; US DHHS 1984). In the major prospective cohort studies, dose–response relationships between amount smoked and age-specific mortality have been demonstrated; the findings have been similar for duration of smoking (US DHEW 1979b). Associations with self-reported depth of inhalation have been less consistent. Indices of pulmonary morbidity also vary with measures of cigarette smoke exposure (US DHHS 1984). The consistency of these findings for morbidity and mortality emphasizes the importance of collecting information on the parameters of cigarette smoking in epidemiological investigations.

Self-reported data may underestimate true cigarette consumption; however, the degree of bias has not been shown to vary with occupational status. For the United States and other countries, estimates of nationwide consumption based on survey data are generally lower than consumption figures calculated with information from manufacturers and government agencies (Todd 1978; Warner 1978). In the Multiple Risk Factor Intervention Trial (MRFIT), validation of smoking with serum thiocyanate measurements documented underreporting of smoking, which was greater in the group randomized to special intervention (Neaton et al. 1981; Ockene et al. 1982). This finding implies that bias in reported smoking may vary with the context in which the information is collected. Workers exposed to agents associated with lung disease might report their smoking habits differently from unexposed workers; both more and less accurate reporting by the exposed population can be postulated.

Occupational Exposures

For clinical and research purposes, exposure to occupational agents should be documented and both duration and concentration estimated, when possible. The techniques used to establish exposure, duration, and concentration are diverse, and are not considered in detail here. Comprehensive reviews and books about them have been published (Hammad et al. 1981; Dodgson 1984; Cralley and Cralley 1979). The methods include self-report, use of industry, occupation, or job title as a surrogate for exposure, area sampling, personal dosimetry, and biological markers.

Data Analysis

In an epidemiological investigation of a population at risk for chronic occupational lung disease, information concerning workplace exposures and cigarette smoking is collected and appropriate health outcome measures, such as the chest radiograph and spirometry, are assessed. Data analysis is directed at characterizing associations between risk factors and disease and at the modifiers of these associations; in studies of chronic occupational lung disease, cigarette smoking and exposure to the occupational agent are the primary risk factors to be considered. Data analysis with epidemiological methods can provide estimates of the independent effects of smoking and the occupational agent and test for interaction between them (Kleinbaum et al. 1982). These techniques, some quite complex, are not described here, but approaches for assessing interaction are considered.

Analysis of data related to a chronic occupational lung disease, regardless of the study design, must address the potential confounding and effect modification, or interaction, resulting from cigarette smoking. Confounding refers to the bias introduced when the effects of one factor are not separated from those of another. In studies of chronic occupational lung diseases, confounding may occur when estimates of exposure to the occupational agent are associated with cigarette smoking. For example, in a study of asbestos workers, confounding would be present if the more heavily exposed individuals were also heavy smokers. Comparisons of blue-collar workers with white-collar employees may be confounded because the former are more often smokers.

Confounding can be controlled at the design phase or at analysis by either stratified or multivariate techniques (Kleinbaum et al. 1982). Options in study design include restriction of participants to smokers or to nonsmokers alone and matching of occupationally exposed and nonexposed subjects for smoking habits. At analysis, whether stratified or multivariate, biologically appropriate and valid measures of cigarette smoking are needed. More simplistic variables,

such as categorical indicators designating never and ever smokers, may not be satisfactory, and their use may only partially control confounding. In particular, measures of cumulative consumption seem most appropriate for the lung function changes of COLD (Burrows et al. 1977; US DHHS 1984). However, errors in the measurement of smoking may reintroduce confounding and apparent effect modification (Kleinbaum et al. 1982).

Simple generalizations cannot be offered concerning the potential magnitude of bias that uncontrolled confounding by cigarette smoking can produce. The bias will depend on the strength of the association between the occupational exposure and cigarette smoking and on the magnitude of smoking's effects in the population. However, because there is a high prevalence of smoking in the workforce and smoking has a strong association with lung function impairment, it should not be dismissed as a confounder merely because some particular level of effect is found for an occupational exposure. Further, the attainment of statistical significance for the effect of an occupational exposure does not exclude confounding.

Either stratified or multivariate statistical techniques can be used to test for interaction. In the first approach, variation in the effects of one factor (e.g., an occupational agent) is examined across strata defined by the second factor (e.g., cigarette smoking). More often, multivariate regression models, either linear or logistic, are used to test for interaction (Kleinbaum et al. 1982). In linear regression models, the dependent variable is a continuous measure, such as FEV_1; in the logistic model, the dependent variable is the occurrence or nonoccurrence of a discrete outcome, such as the presence of crackles. In both types of models, the independent variables may include terms for the individual exposures and cross-product terms to test for interaction. The regression coefficients estimate the effects of the exposures on the dependent variables. For example, models developed for an asbestos-exposed study population might include a variable for cumulative asbestos exposure, a variable for cumulative cigarette consumption, and a variable created by multiplying the two. Statistically, the null hypothesis of no interaction is tested by the cross-product term. Failure to reject this null hypothesis indicates that the data are consistent with the two factors acting independently. However, interpretation of such analyses must consider the scale on which interaction is measured; linear models assess departure from additivity, whereas logistic models test departure from a multiplicative interaction (Kleinbaum et al. 1982). The coefficient for the cross-product term specifies the direction and magnitude of the effect of interaction, at various levels of the two interacting factors.

The limitations posed by sample size must also be considered in interpreting the results of modeling. In studies of occupational

groups, the number of subjects is most often determined by the size of the workforce and by feasibility considerations, and rarely on the basis of more formal sample size calculations with statistical methods. The statistical power of tests for interaction tends to be low (Greenland 1983), and potentially important interactions may not attain conventional levels of statistical significance without a sufficiently large population.

Analysis of epidemiological data can also provide estimates of the effects of exposure at the individual level and at the group level (Kleinbaum et al. 1982). Measures of association between exposure and disease estimate the excess risk incurred by exposed individuals. Measures of impact combine measures of association with the prevalence of exposure and estimate the contribution of specific exposures to the disease burden in a population. The most widely used is the population attributable risk or etiologic fraction. These measures can be used to gauge the relative importance of cigarette smoking and occupational agents.

Specific Investigation Issues

Population Selection

The most widely employed design for investigating occupational lung disease, the cross-sectional study or survey, may be biased when subjects are selected from the active workforce. The individuals examined at any particular time in a cross-sectional study may be regarded as survivors from the entire population that entered the particular workplace. Individuals with illness tend to leave the workforce, whereas healthy individuals tend to remain. This bias, often called the healthy worker effect, must be considered in both longitudinal and cross-sectional designs (Fox and Collier 1976; Wen et al. 1983). The implications for surveys of occupational lung disease are evident and have been widely discussed (McDonald 1981; Field 1981; Lebowitz 1981). If only employed workers are considered and individuals with occupational lung disease leave the workforce, the measures of association will underestimate the true effect of exposure. In fact, the leaving of employment by people who are ill has been demonstrated in several industries (Fox and Collier 1976; Musk et al. 1977; McDonald 1981; Soutar and Maclaren 1982; Eisen et al. 1983). The resulting bias should be evaluated by examining retirees and others who have left.

The role of cigarette smoking in determining the magnitude of the healthy worker effect has not been fully evaluated. Overall mortality ratios for cigarette smokers are greater below age 65 (US DHEW 1979b), and cardiovascular diseases, respiratory diseases, and lung cancer generally contribute prominently to the reduced all-cause mortality of the healthy worker effect (Fox and Collier 1976; Wen et al. 1983). Thus, cigarette smokers would be anticipated to leave the

workforce prematurely more often than nonsmokers. A recent study of Vermont granite workers provides data that conflict with this hypothesis, however. Eisen and colleagues (1983) compared men who remained in the industry during a 5-year followup period with those who terminated. The rate of FEV_1 loss was greater in those who left the industry, but their cumulative cigarette consumption was not significantly greater than that of those who stayed. These data do illustrate the selection bias that results from differential termination of employment, contingent on the development of disease.

Eisen and colleagues (1983, 1984) have explored other sources of bias in respiratory disease surveys. In the granite workers' study, men whose spirometric testing repeatedly failed to meet criteria for acceptability had a more rapid decline of FEV_1 than those with a better performance. This finding suggests that the exclusion of subjects whose lung function testing is judged unacceptable may introduce bias toward the null.

External Control Populations

When subjects are selected for an epidemiological investigation, a population, not exposed to the agent of interest but similar in other respects to those who are, may not be available for comparison purposes. In this circumstance, an investigator may consider only the exposed subjects and evaluate the dose–response relationships if the necessary data are available, or identify an external population as controls. If the latter approach is used, the control population must be comparable to the exposed group on potential confounding factors such as age, sex, race, and cigarette smoking. At times, appropriate external populations may not be readily identified.

Nevertheless, external control populations are frequently used. In mortality studies, the use of general population rates for calculation of "expected" deaths assumes that the general public is the control group. Frequently, lung function levels in exposed people are compared with those predicted from tests performed on "normal" populations, most often asymptomatic nonsmokers without respiratory disease (Clausen 1982). Recently, Peterson and Castellan (1984) reported the prevalence of chest symptoms, as measured with a modified Medical Research Council questionnaire, in 1,372 blue-collar workers employed in plants considered to be free of respiratory hazards. The data are illustrative of the effects of smoking on the prevalence of major respiratory symptoms; even in this young, employed population, all of the symptoms examined were more common in current and former smokers. The authors provided smoking-specific prediction equations and suggested that these data can be used for comparative purposes.

Colinearity of Aging, Cigarette Smoking, and Occupational Exposure Effects

From approximately age 25, measures of ventilatory function gradually and progressively decline. In nonsmokers, the rate of loss is approximately 20 to 30 mL annually for FEV_1 and FVC (US DHHS 1984). The decline in FEV_1 with age may not be a linear function with a constant decline each year, but rather, the absolute rate of annual decline may vary with age. In addition, the rate of decline in lung function with age derived from cross-sectional studies may be an overestimate of the actual rate of decline because of possible differences in lung function among different birth cohorts in cross-sectional studies. Some cigarette smokers lose function at much more rapid rates and ultimately develop COLD, unless they stop smoking (US DHHS 1984). Presumably, a similar insidious excess loss of function antedates the appearance of clinically evident chronic occupational lung disease.

This simultaneous contribution of aging, smoking, and occupational exposure to lung function loss represents a formidable analytical problem. Further complicating its solution is the temporal colinearity or correlation of these three independent factors; age, cumulative smoking, and cumulative exposure all increase with the passage of time. Failure to address this colinearity may lead to confounding and to an incorrect assessment of the effect of exposure.

This problem is most often addressed by using external standard populations to control for aging and, at times, cigarette smoking, or by multiple regression modeling (Berry 1981b). In the first approach, expected lung function levels in the exposed workers are calculated with prediction equations developed in other populations; sex, age, race, and cigarette smoking habits may all be considered in the calculations. For example, Beck and colleagues (1984) conducted a cross-sectional survey of cotton textile workers in Columbia, South Carolina. Spirometric test results for the cotton workers were compared with the expected values calculated from survey data collected in two towns in Connecticut and one town in South Carolina. For each cotton worker, an expected value was predicted on the basis of sex, age, height, and weight, with regression equations derived from asymptomatic nonsmokers in the control communities. Deviations from the expected value were then examined within the strata defined by smoking. This approach is effective when appropriate external populations are available. Prediction equations developed for clinical purposes are frequently used, primarily owing to availability; investigators should, however, consider the comparability of the exposed workers with the "normal" population from which the prediction equations were derived.

Multiple regression techniques permit a simultaneous examination of the effects of age, exposure, and smoking, as well as their

interactions, on lung function measures. Comprehensive treatments of these methods have been published (Draper and Smith 1966; Kleinbaum and Kupper 1978), and only their use for lung function data is considered here. With this approach, the lung function measures are the dependent variables, and age, smoking, and exposure are the independent variables in a model of this form: $Y=\alpha+B_1X_1+B_2X_2+B_3X_3+ \ldots B_iX_i+\epsilon$; where Y is a lung function parameter, α is a constant term, X_1 through X_i are the independent variables and B_1 through B_i are their regression coefficients, and ϵ is a term for error. The regression coefficients describe the change in Y per unit change in a particular X_i, with all other independent variables held constant. An estimated regression equation is generally obtained by the least squares criterion.

Most standard statistical packages for computers include this technique, and it can be readily applied to a data set. However, the results of such modeling may be misleading, and the plausibility of such models should be assessed by careful examination of the raw data and residuals and by other formal means. In addition, model development should be guided by biological rather than primarily statistical considerations; that is, the investigator should specify the regression model in the most appropriate fashion biologically, rather than rely on statistical procedures for variable selection. Colinearity of the age, smoking, and exposure effects may limit the multiple regression approach. High correlation in a data set between any two of these factors may prevent assessment of their independent effects.

Quantification of Effects in Individuals

Properly designed epidemiological investigations can provide essential information about the occurrence of chronic occupational lung diseases in populations. They can establish that an occupational exposure is hazardous, quantify the risk associated with exposure, describe the agent's contribution to the disease burden in the population, and document the consequences of reducing the exposures. For an individual, epidemiologically derived estimates of relative risk generally indicate the excess risk incurred by virtue of exposure to a particular agent, as compared with nonexposure. But such a measure of relative risk cannot be interpreted directly as a quantitative indicator of the chance that a particular individual's exposure to the agent was responsible for the occurrence of the disease concerned. Statements concerning causality in an individual case are particularly difficult when the disease of interest has multiple causes and interactions among them are of potential importance.

Judgments concerning the causation of disease in specific individuals are frequently necessary, however, for deciding claims made

through workmen's compensation, the courts, or other mechanisms (Hoffman 1984; Hadler 1984). Legal proof of causation hinges on a finding that the exposure more likely than not caused the disease (Danner and Sagall 1977; Hoffman 1984). Allocation of probability of causation when multiple agents interact is particularly problematic (Cox 1984), but frequently necessary. In particular, the evaluation of impairment in cigarette smokers exposed to harmful occupational agents requires judgment concerning the independent and combined effects of all exposures.

Accepted methods for accomplishing this quantification have not yet been developed. Enterline (1983) considered the problem for two agents that interact in a multiplicative fashion. Cox (1984) has suggested an approach that covers the situation of joint and interacting causes. Algorithms have been proposed for specific diseases, such as asbestosis (Mitchell et al. 1985), and for specific agents, such as radiation (NRC 1984). However, these approaches have only recently been proposed and their applicability remains to be established.

Some guidance can be found, however, in the pattern of physiological abnormality. For example, the impairment in a smoker with asbestosis, but with no evidence of airflow obstruction, can be attributed mostly to the pneumoconiosis. Correspondingly, the presence of airflow obstruction and an increased TLC in an asbestos worker who smokes and who has a normal chest x ray suggests that the impairment is largely attributable to cigarette smoking. The problem is more complicated in those situations where reduced expiratory airflow is present and TLC is decreased or in those pneumoconioses where reductions in the rate of expiratory airflow are part of the pattern of the pneumoconiosis. For example, reductions of FEV_1, FVC, and FEV_1/FVC may all be found in complicated silicosis and coal workers' pneumoconiosis, and these patterns are similar to those found in cigarette smokers. Emphysema decreases lung elastic recoil, whereas some pneumoconioses, such as asbestosis, increase it. These competing effects may result in a TLC that is increased, normal, or reduced in a smoker with COLD and pneumoconiosis, depending on which effect predominates. Thus, smokers with COLD and pneumoconiosis display diverse patterns of lung function abnormality. Evidence of airflow obstruction on spirometry may be accompanied by a reduced, normal, or increased TLC, and the diffusing capacity for carbon monoxide will generally be reduced regardless of the cause of the injury. In this setting, the diagnosis of pneumoconiosis can often be established from the chest x ray findings, but responsibility for impairment cannot readily be divided between COLD and pneumoconiosis. For chronic occupational lung diseases associated with airflow obstruction, even diagnosis may be difficult in an individual cigarette smoker.

A second method of separating the relative effects of two agents in a combined exposure is to use the known dose–response relationships for the agents. This approach is most useful when exposure to one agent has been slight in comparison with the exposure to the second agent. Difficulty arises when an individual has been exposed to biologically equivalent doses of both agents or when exposure to one of the agents cannot accurately be assessed.

Summary and Conclusions

During the 20th century, cigarette smoking has become prevalent among workers at risk for occupational lung disease. By itself, smoking causes pulmonary impairment; among people exposed to harmful occupational agents, the interactive effects of smoking may increase the number of individuals developing clinically significant impairment. For both clinicians and researchers, cigarette smoking by workers poses difficult and important challenges.

1. Existing resources for monitoring the occurrence of occupational lung diseases are not comprehensive and do not include information on cigarette smoking. Other approaches, such as registries, might offer more accurate data and facilitate research related to occupational lung diseases. Because of the variability in diagnostic criteria for chronic lung disease, in studies on occupational lung diseases emphasis should be placed on measures of physiological change, roentgenographic abnormality, and other objective measures.
2. Further studies that correlate lung function with histopathology should be carried out in occupationally exposed smokers and nonsmokers.
3. The effects of cigarette smoking on the chest x ray should be clarified. In particular, the sensitivity of the ILO classification to smoking-related changes should be further evaluated in healthy populations.
4. To determine if smoking is reported with bias by occupationally exposed workers, self-reported histories should be compared with biological markers of smoking in appropriate populations.
5. Mechanisms through which specific occupational agents and cigarette smoking might interact should be systematically considered. Both laboratory and epidemiological approaches should be used to evaluate such interactions.
6. Statistical methods for evaluating interaction require further development. In particular, the biological implications of conventional modeling approaches should be explored. Further, the limitations posed by sample size for examining independent and interactive effects should be evaluated. The

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consequences of misclassification by exposure estimates and of the colinearity of exposure variables should also be addressed.

7. The role of cigarette smoking in the "healthy worker effect" requires further evaluation.
8. Approaches for apportioning the impairment in a specific individual between occupational causes and cigarette smoking should be developed and validated.

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