THE HEALTH CONSEQUENCES OF SMOKING

CANCER AND CHRONIC LUNG DISEASE IN THE WORKPLACE

a report of the Surgeon General



U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Office on Smoking and Health
Rockville, Maryland 20857

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THE SECRETARY OF HEALTH AND HUMAN SERVICES
WASHINGTON D.C. 20201

MAY 8 1986

The Honorable Thomas P. O'Neill, Jr.
Speaker of the House of Representatives
Washington, D.C. 20515

Dear Mr. Speaker:

It is a pleasure to transmit to the Congress the final edition of the Surgeon General's Report on the Health Consequences of Smoking, as mandated by Section 8(a) of the Public Health Cigarette Smoking Act of 1969. This is the Public Health Service's 17th Report on this topic and, like earlier Reports, identifies cigarette smoking as one of this Nation's most serious public health problems.

This Report, which provides a detailed review of the relationship between smoking and hazardous substances in the workplace, is particularly disturbing because of the added health burden that many workers carry if they smoke cigarettes. As this Report makes clear, for some workers this added burden is substantial. No better example exists to illustrate this interaction than the case of asbestos workers. Current scientific evidence indicates that heavily exposed asbestos insulation workers who did not smoke may experience a 5-fold increase in lung cancer compared to nonsmoking, nonexposed workers. However, if this same worker also smoked, his lung cancer risk is increased more than 50-fold.

Also disturbing is the continued high rate of current cigarette use among blue collar workers compared to their white collar counterparts. These workers are more apt to be exposed to dusts and other harmful substances in their workplace environments. Programs to reduce workplace hazardous exposures are helping to offset these risks. For the majority of workers who smoke, cigarette smoking poses a greater risk to health than does occupational exposure. Thus, elimination of cigarette smoking among such workers can have a profound effect on improving their health.

This Department has a strong commitment to prevention and health promotion. It is essential that workplace health promotion programs have a strong focus on reducing cigarette smoking among employees to the extent possible. These efforts can not only have an effect on the health of the individual, but may also have a substantial impact by reducing absenteeism on the job, thereby improving productivity and reducing health care costs.

Cigarette smoking is associated with an estimated $23 billion in health care costs annually and over $30 billion in lost productivity and wages. To a certain degree we all share these costs whether we smoke or not. Programs that reduce smoking, therefore, can have a benefit to all our society.

Sincerely,

Otis R. Bowen, M.D.
Secretary

Enclosure

THE SECRETARY OF HEALTH AND HUMAN SERVICES
WASHINGTON D.C. 20201

MAY 1 1986

The Honorable George Bush
President of the Senate
Washington, D.C. 20510

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FOREWORD

Over the past generation, the actions of labor unions, management, insurers, and Government have made substantial progress in reducing exposure to hazardous substances in the workplace. This Report acknowledges this progress, and demonstrates clearly that these efforts to protect the American worker must continue. There can be no relaxation in our efforts to continue the safeguards already in place or to seek new safeguards as new hazards are identified.

This Report also establishes that for these efforts to protect the worker to fully succeed, these same forces of labor, management, insurers, and Government must become equally engaged in attempts to reduce the prevalence of cigarette smoking, particularly among those working populations most at risk. For the majority of workers who smoke, cigarette smoking poses a greater risk to health than does occupational exposure.

This 1985 Report of the Surgeon General examines in greater depth than ever before the relationships between cigarette smoking and occupational exposures; it is a document of singular importance. As with previous Reports, a large number of experts and scientists recruited from both within and outside the Federal service have participated in developing and reviewing the content of this Report. I express here my respect and gratitude for their efforts.

Donald Ian Macdonald, M.D.
Acting Assistant Secretary
for Health

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PREFACE

The 1985 Report on the Health Consequences of Smoking presents a comprehensive review of the interaction of cigarette smoking with occupational exposures in the production of cancer and chronic lung disease.

Cigarette smoking and its relationship to cancer and chronic obstructive lung disease (COLD) were extensively reviewed in the 1982 and 1984 Surgeon General's Reports, respectively. In the 1982 Report, cigarette smoking was judged to be the leading cause of cancer mortality in the United States; a causal association was found between smoking and cancer of the lung, larynx, oral cavity, and esophagus, and smoking was identified as a contributory factor in the development of cancer of the bladder, kidney, and pancreas. In 1984, cigarette smoking was identified as the major cause of COLD, which includes chronic bronchitis and emphysema, among both men and women in the United States. The contribution of other factors in COLD morbidity and mortality was found to be far less important than that of cigarette smoking.

This Report examines the evidence available on the role played by cigarette smoking and occupational exposure in the development of cancer and chronic lung disease. Cancer and chronic lung disease are major causes of death in the United States, accounting for well over 25 percent of all deaths annually. Cancer mortality rates have shown a steady increase, unlike rates for the major cardiovascular diseases, which have declined over the last two decades. Chronic lung disease, now the fifth leading cause of mortality, has been increasing more rapidly than other major causes of death. It is estimated that more than 10 million Americans report suffering from these diseases.

Findings of the 1985 Report

The major overall conclusions of this Report are these:

For the majority of American workers who smoke, cigarette smoking represents a greater cause of death and disability than their workplace environment.

In those worksites where well-established disease outcomes occur, smoking control and reduction in exposure to hazardous agents are effective, compatible, and occasionally synergistic

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approaches to the reduction of disease risk for the individual worker.

Smoking and occupational exposures can interact synergistically to create more disease than the sum of the separate exposures. This kind of interaction is exemplified by the relationship between asbestos exposure and smoking. A study of heavily exposed asbestos insulation workers, more than 20 years after onset of exposure, demonstrated a fivefold increased risk for lung cancer among nonsmoking asbestos workers compared with nonsmokers without asbestos exposure. We know that in non-asbestos-exposed populations, smoking increases the lung cancer risk approximately tenfold. The risk is increased more than fiftyfold if the asbestos workers also smoke. This risk in cigarette-smoking asbestos workers is greater than the sum of the risk of the independent exposures, and is approximated by multiplying the risks of the two separate exposures. In other words, for those workers who both smoke and are exposed to asbestos, the risk of developing and dying from lung cancer is 5,000 percent greater than the risk for individuals who neither smoke nor are exposed. Thus, the interaction of cigarette smoking and asbestos exposure is multiplicative. For asbestos workers, the risk of developing and dying of lung cancer increases with an increasing number of cigarettes smoked per day and with an increasing asbestos exposure. For example, the risk is 87 times greater for those workers who smoke more than one pack per day. The risk declines among workers who are able to stop smoking, compared with the risk for those who continue to smoke. An interaction for the production of lung cancer also exists between cigarette smoking and the radon daughters exposure of miners, although the exact nature of this interaction is not clear.

Both cigarette smoking and exposure to certain occupational hazards increase the risk for chronic lung disease. These risks can occur independently or may combine to produce a greater degree of lung injury than would have occurred from either exposure separately. While many exposures are capable of producing chronic lung injury, either independently or in combination, smoking appears to be the more important exposure for the majority of U.S. workers.

Differences in Smoking Behavior Between White-Collar Workers and Blue-Collar Workers

This Report also presents detailed findings with regard to differences in smoking prevalence between blue-collar workers and white-collar workers. Blue-collar workers are more likely to be exposed to workplace agents, which, in combination with their higher smoking rates, may place these workers at considerable excess risk for cancer

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and chronic lung disease. Although these differences exist among both men and women, they are more pronounced among men.

The differences in the prevalence of smoking between blue-collar workers and white-collar workers may underestimate the differences found among specific populations of occupationally exposed workers. As noted in this Report, individual studies among certain workers report current smoking rates well in excess of 50 percent. In addition, in one of the largest studies of asbestos workers, more than 80 percent of the men in the cohort had been regular cigarette smokers during their lifetime and only 11 percent were classified as never having smoked regularly. These differences in smoking behavior make the control for smoking behavior an important part of the design of studies of the relationship of occupational exposures and cancer or chronic lung disease.

On the average, blue-collar men initiate smoking approximately 14 months earlier than white-collar men. We know from existing studies that an earlier age of initiation is strongly correlated with increased mortality for lung cancer and chronic lung disease as well as for most other smoking-related diseases. Even with this earlier age of initiation, a substantial fraction of blue-collar workers begin smoking coincident with their entry into the workforce, and blue-collar workers are less likely than white-collar workers to be able to successfully quit smoking.

Smoking Control in the Workplace

The potential role of the workplace in promoting initiation and fostering the continuation of smoking behavior represents a kind of interaction between smoking and the workplace that may affect large numbers of U.S. workers. It seems clear that the responsibility for health in the workplace includes at minimum a work environment that does not promote smoking or interfere with cessation.

The worksite offers an opportunity for implementation of smoking cessation programs. A number of studies cited in this Report found worksite-based programs to be more successful than clinic-based programs, probably owing to their more intensive nature and because many employer-sponsored programs offer economic and other incentives, thus enhancing their success.

The goal in public health, both in the worksite and outside it, is the reduction and elimination of disease and the promotion of healthy behavior. The content of this Report makes it clear that the elimination of chronic lung disease and cancer from the workplace cannot succeed without a companion effort to alter the smoking behavior of workers. It is precisely those occupations in which the greatest occupational hazards have existed that smoking cessation also yields the greatest return for individual worker's health. It

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should be obvious that smoking cessation efforts are an adjunct to, and not a substitute for, occupational environmental controls. Correspondingly, a concern about workers' health that limits itself to the control of environmental exposure levels disregards the major health benefits of smoking cessation.

C. Everett Koop, M.D.
Surgeon General

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CHAPTER 1

INTRODUCTION, OVERVIEW, AND SUMMARY AND CONCLUSIONS

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Historical Perspective

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Introduction

Development and Organization of the 1985 Report

The 1985 Report was prepared by the Office on Smoking and Health of the U.S. Department of Health and Human Services as part of the Department's responsibility, under Public Law 91-222, to report new and current information on smoking and health to the United States Congress. The scientific content of this Report is the collective work of 100 scientists in the fields of both smoking and occupational health. Individual manuscripts were written by experts who are recognized for their understanding of specific content areas. Each chapter was subjected to an intensive peer review, whereby comments were solicited from four to six individuals knowledgeable in that particular area. After these comments were incorporated, the entire Report was submitted to distinguished experts representing a balance of opinion in occupational disease and smoking and health. Concurrent with this latter review, the manuscript was also submitted to various U.S. Public Health Service agencies for review.

Throughout the entire report compilation process the Office on Smoking and Health had the advice and consultation of four internationally known scientists. These individuals represent expertise in the fields of both smoking and occupation. They are Dr. Lester Breslow, University of California at Los Angeles, Dr. Marcus Key, University of Texas Health Science Center, Dr. Irving Selikoff, the Mount Sinai Medical Center, and Dr. Jesse Steinfeld, Medical College of Georgia. From the outset, this panel of experts was instrumental in recommending the Report content and outline, suggesting individual authors and reviewers, and providing overall guidance during each stage of the compilation process. Each also served as an overall reviewer of the completed manuscript.

The 1985 Report contains a Foreword by the Acting Assistant Secretary for Health, a Preface by the Surgeon General of the U.S. Public Health Service, and the following chapters:

- Chapter 1. Introduction, Overview, and Summary and Conclusions
- Chapter 2. Occupation and Smoking Behavior in the United States
- Chapter 3. Evaluation of Smoking-Related Cancers in the Workplace
- Chapter 4. Evaluation of Chronic Lung Disease in the Workplace
- Chapter 5. Chronic Bronchitis: Interaction of Smoking and Occupation
- Chapter 6. Asbestos-Exposed Workers
- Chapter 7. Respiratory Disease in Coal Miners
- Chapter 8. Silica-Exposed Workers

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- Chapter 9. Occupational Exposures to Petrochemicals, Aromatic Amines, and Pesticides
- Chapter 10. Cotton Dust Exposure and Cigarette Smoking
- Chapter 11. Ionizing Radiation and Lung Cancer
- Chapter 12. Smoking Intervention Programs in the Workplace

Historical Perspective

More than two centuries ago, the relationship between occupational exposure and health outcome was presented by a noted English practitioner of surgery. Dr. Percivall Pott (1733–1788), in his *Chirugical Observations* (1775), described this first scientific observation as a "superficial, painful ragged, ill-looking sore with hard and rising edges" that appeared in chimney sweeps, who almost always began working when they were very young and small enough to fit down a chimney. This malady was appropriately tagged "chimney sweep's cancer." Soon after the turn of the 19th century, additional reports confirmed Dr. Pott's observations.

Only shortly before Dr. Pott's description was published, Dr. John Hill (1716?–1775), in his *Cautions Against the Immoderate Use of Snuff,* described an association between tobacco use and cancer. Hill reported on two case histories and observed that "snuff is able to produce . . . swellings and excrescences" in the nose, and he believed them to be cancerous.

Although Dr. Pott's startling report and description of the deplorable use of children as chimney sweeps was published in 1775, it was not until nearly a century and a half later, in 1914, that Yamagawa and Ichikawa were able to demonstrate the carcinogenic nature of the hydrocarbons in soot and tar. Almost 20 years later, in 1933, the proximate carcinogen 3,4-benzypyrene was isolated from coal tar by Cook, Hewett, and Hieger.

Also in the 1920s and 1930s, scientists began investigating the possible association between cigarette smoking and cancer, and near the end of World War II, several scientists had noted the higher percentages of cigarette smokers among cancer patients, particularly those with lung cancer. In 1962, when the Surgeon General's Advisory Committee on Smoking and Health began weighing the scientific evidence for its 1964 Report, the causal significance of the association of cigarette smoking and disease was evaluated by strict criteria, none of which taken alone was sufficient for a causal judgment. These criteria today form the basis for the continued judgment that cigarette smoking is causally related to a number of disease processes.

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Overview

Cigarette smoking is clearly the major cause of lung cancer and chronic lung disease identified for the U.S. population. The role that cigarette smoking plays in the development of cancer was extensively reviewed in 1982 Report of the Surgeon General and chronic obstructive lung disease was reviewed in 1984. However, cigarette smoking is not the only cause of lung cancer or chronic lung disease in the U.S. population. A number of occupational exposures are well established as causes of cancer and chronic lung disease, and it is reasonable to expect that ongoing investigation of workplace exposures will continue to expand our understanding of the hazards of specific exposures and increase our ability to protect U.S. workers.

This Report examines the contributions of cigarette smoking and a number of workplace exposures to lung cancer and chronic lung disease among occupations in which specific hazardous exposures are known to occur. It is possible from the data presented to identify a causal role for both smoking and certain workplace exposures in lung cancer and disability from chronic lung disease. It is also known that the occupational hazards reviewed in this Report frequently occur on a substrate of risk and injury produced by cigarette smoking. The combination of exposures may influence the nature or extent of the disease produced by the isolated exposures (interact); both may act to produce the same disease, or may produce separate injuries to the lung that in combination result in more severe disability than would be expected from the isolated injuries. In addition, the worksite may represent a setting in which a substantial number of workers begin to smoke, and may provide an environment that either supports or discourages the efforts of individual workers to stop smoking. The ability to alter the adverse health outcomes of workers exposed to occupational hazards requires both an understanding of the disease risks that result from individual and combined exposure and a knowledge of how changes in the worksite can alter the pattern of disease occurrence.

Many of the major improvements in public health during the last century and the first part of this century were produced through the control of infectious diseases. The key to this success frequently was the identification of the causal agent, with the subsequent elimination of exposure to the agent or immunization against the agent. The criteria for establishing the causality of an infectious agent were expressed by Robert Koch in 1877 and are commonly referred to as Koch's postulates. They are the following:

1. The agent must be shown to be present in every case of the disease by isolation in pure culture.
2. The agent must not be found in cases of other disease.

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3. Once isolated, the agent must be capable of reproducing the disease in animal experiments.
4. The agent must be recovered from the experimental disease produced.

These postulates served well in identifying the causal agents in acute infectious processes; frequently their identification was a critical part of their successful control.

The major diseases responsible for death and disability in the latter half of the 20th century are chronic heart and lung disease and cancer. These diseases, which now account for over half of all deaths in the United States annually, are commonly the result of chronic exposures to noninfectious occupational and lifestyle influences, may be caused by a number of agents acting independently, and may also result from more than one agent contributing to the disease process in any given individual. For these reasons, Koch's postulates have little relevance for establishing causality in lifestyle and occupational exposures, and new criteria for causality have been developed. These criteria rely heavily on epidemiologic data and include an examination of the consistency, strength, specificity, coherence, and temporal relationship of the association between the agent and the disease as well as the evidence of the biologic mechanisms by which the agent produced the disease.

The multifactorial etiology and chronic exposures that characterize cancer and chronic lung disease also have implications for control of these diseases in the worksite. One of the important public health achievements of this century has been the identification of hazardous agents in the workplace, with subsequent reductions in these exposures through changes in environmental levels of the agent, modification of work practices, and alteration of manufacturing practices. These changes were the result of regulation and voluntary agreement, and they reflect the action and concern of labor, management, Government, and the insurance industry. The result, in some industries, has been a dramatic reduction in the exposure to hazardous agents in the worksite and in the disease that would have been produced by these exposures.

As this Report clearly documents, however, cigarette smoking may alter the amount of disease or level of disability produced by hazardous occupational exposures. For cancer, this alteration may come in the form of adding an additional number of cancer cases, or of the combined exposure synergistically increasing the number of cancers. On an individual level, our understanding of the process of carcinogenesis suggests that both agents may contribute to individual cancer rather than some cases being caused exclusively by an occupation exposure and other cases being caused exclusively by cigarette smoking.

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For lung disease, the combination of cigarette smoking and exposure to a hazardous workplace agent may combine to produce similar injuries or may produce independent disease processes in the same lung that result in greater disability than with either exposure separately.

The public health importance of interaction between smoking and an occupational exposure is typified by the relationship between cigarette smoking and asbestos exposure among asbestos workers. A number of studies published in this country and abroad have demonstrated an approximately fivefold excess risk for lung cancer among nonsmoking asbestos insulation workers. Smoking in non-asbestos-exposed populations increases the lung cancer risk by approximately tenfold. However, the risk is more than fiftyfold greater if the asbestos worker also smokes. The risk in cigarette-smoking asbestos workers is greater than the sum of the risk of the independent exposures, and is approximated by multiplying the risks of the two separate exposures. Thus, the interaction of cigarette smoking and asbestos exposure is multiplicative in nature. To state this in another way, for those workers who both smoke and are exposed to asbestos, the risk of developing and dying from lung cancer is 5,000 percent greater than the risk for individuals who neither smoke nor are exposed. Among these asbestos workers, the extent of disease produced by asbestos is conditioned by the smoking habits of the asbestos-exposed population. As is also evident, attempts to control asbestos-related lung cancer can have a maximal impact only if they include successful programs to change smoking behavior as well as efforts aimed at reducing levels of asbestos dust exposure.

Elimination of the contribution made by smoking to disease and disability in the worksite is beneficial, even in the absence of synergistic interaction between smoking and workplace exposures. Even with an additive risk for an exposed population, both agents probably contribute to the cancer that develops in an individual, and removing that contribution is an important benefit to that individual. In addition, a given degree of impairment produced by an occupational agent will result in less disability in an individual without concomitant lung injury due to smoking than in a worker who has chronic obstructive lung disease due to smoking.

The focus on individuals rather than on populations when considering strategies to control occupationally related diseases also helps clarify the concept of a "safe" worksite. The same number of lung cancers may occur in a population with a high smoking prevalence and a low asbestos exposure and a population with a low smoking prevalence and a high asbestos exposure. This similarity of population risks does not suggest that the level of acceptable or "safe" dust exposure can be adjusted on the basis of the smoking

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prevalence in the population. It may be reasonable to select nonsmokers for jobs in which smokers would be at much greater risk, but this approach should never be used as a justification for accepting occupational exposure levels that result in risk for those exposed. The goal should always be the elimination of as much of the disease as possible in the working population rather than the lowering of the disease rate to the population norm.

Factors in the worksite may also influence smoking initiation and smoking cessation. Chapter 2 of this Report updates the previously reported increased smoking prevalence among blue-collar workers compared with white-collar workers. It also reports two analyses that suggest the workplace may play an important role in smoking behavior. The mean age of initiation reported confirms that the majority of smokers begin smoking prior to or during high school. However, a substantial fraction also begin to smoke after high school. Little is known about the influences that may predispose individuals to become smokers at this age. One of the major life experiences occurring at the same time is entry into the workforce, particularly for blue-collar and clerical workers, and the work environment may be a major factor capable of predisposing an individual toward or away from becoming a smoker.

A second important consideration that emerges from chapter 2 is the markedly lower prevalence of successful smoking cessation among blue-collar workers compared with white-collar workers. This difference in cessation is not explained by differences in rates of initiation, and almost equal percentages of current smokers have made a serious attempt to quit and failed. This suggests that the majority of both groups of workers have attempted to become nonsmokers, but blue-collar workers have been less successful. Once again, a potential role for the workplace environment in reinforcing or inhibiting successful cessation may help to explain these differences in the prevalence of former smokers.

If a workplace is to be considered "safe," one very important criterion is the absence of exposures to agents that can cause disease. Equally important, however, is that safety should include a workplace that neither encourages initiation nor discourages cessation of cigarette smoking. As demonstrated in the final chapter of this Report, the worksite may provide a focus for the promotion of healthy behavioral change in the workforce, but at a minimum, should not be a focus that encourages behaviors that compromise a worker's health.

Summary and Conclusions of the 1985 Report

The major conclusions of this Report are clear. They are the following:

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For the majority of American workers who smoke, cigarette smoking represents a greater cause of death and disability than their workplace environment.

In those worksites where well-established disease outcomes occur, smoking control and reduction in exposure to hazardous agents are effective, compatible, and occasionally synergistic approaches to the reduction of disease risk for the individual worker.

Individual chapter summaries and conclusions follow.

Occupation and Smoking Behavior in the United States: Current Estimates and Recent Trends

1. Among men, a substantially higher percentage of blue-collar workers than white-collar workers currently smoke cigarettes. Operatives and kindred workers have the highest rate of current smoking (approaching 50 percent), with professional, technical, and kindred workers having the lowest rates of current smoking (approximately 26 percent).
2. Among women, blue-collar versus white-collar differences are less pronounced, but still show a higher percentage of current smokers among blue-collar workers. Occupational categories with the highest rates of current smoking include craftsmen and kindred workers (approximately 45 percent current smokers) and managers and administrators (38 percent), with the lowest rate of current smoking occurring among women employed in professional, technical, and kindred occupations (26 percent).
3. Occupational differences in daily cigarette consumption are generally modest. For both men and women, the highest daily consumption of cigarettes occurs among managers and administrators and craftsmen and kindred workers.
4. Blue-collar workers (both men and women) report an earlier onset of smoking than white-collar workers. A substantial fraction of smokers report initiation of smoking at ages coincident with their entry into the workforce.
5. Blue-collar occupations have a lower percentage of former smokers than white-collar occupations; this difference is most pronounced among men. Among women, the pattern for homemakers closely parallels that of white-collar women.
6. Black workers have higher smoking rates than white workers, with black male blue-collar workers exhibiting the highest smoking rate. Black workers also have lower quit rates than white workers. In contrast, white workers of both sexes are more likely to be heavy smokers regardless of occupational category.

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Evaluation of Smoking-Related Cancers in the Workplace

1. Cigarette smoking and occupational exposures may interact biologically, within a given statistical model and in their public health consequences. The demonstration of an interaction at one of these levels does not always characterize the nature of the interaction at the other levels.
2. Information on smoking behaviors should be collected as part of the health screening of all workers and made a part of their permanent exposure record.
3. Examination of the smoking behavior of an exposed population should include measures of smoking prevalence, smoking dose, and duration of smoking.
4. Differences in age of onset of exposure to cigarette smoke and occupational exposures should be considered when evaluating studies of occupational exposure, particularly when the exposed population is relatively young or the exposure is of relatively recent onset.

Evaluation of Chronic Lung Disease in the Workplace

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

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independent and interactive effects should be evaluated. The 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.

Chronic Bronchitis: Interaction of Smoking and Occupation

1. Chronic simple bronchitis has been associated with occupational exposures in both nonsmoking exposed workers and populations of exposed smokers in excess of rates predicted from the smoking habit alone. Among these exposures are coal, grain, silica, the welding environment, and to a lesser extent, sulfur dioxide and cement.
2. The evidence indicates that the effects of smoking and those occupational agents that cause bronchitis are frequently additive in producing symptoms of chronic cough and expectoration. Smoking has commonly been demonstrated to be the more important factor in producing these symptoms.

Asbestos-Exposed Workers

1. Asbestos exposure can increase the risk of developing lung cancer in both cigarette smokers and nonsmokers. The risk in cigarette-smoking asbestos workers is greater than the sum of the risks of the independent exposures, and is approximated by multiplying the risks of the separate exposures.
2. The risk of developing lung cancer in asbestos workers increases with increasing number of cigarettes smoked per day and increasing cumulative asbestos exposure.
3. The risk of developing lung cancer declines in asbestos workers who stop smoking when compared with asbestos workers who continue to smoke. Cessation of asbestos exposure may result in a lower risk of developing lung cancer than continued exposure, but the risk of developing lung cancer appears to remain significantly elevated even 25 years after cessation of exposure.
4. Cigarette smoking and asbestos exposure appear to have an independent and additive effect on lung function decline. Nonsmoking asbestos workers have decreased total lung capacities (restrictive disease). Cigarette-smoking asbestos workers develop both restrictive lung disease and chronic obstructive lung disease (as defined by an abnormal FEV_1/FVC), but the evidence does not suggest that cigarette-smoking asbestos

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workers have a lower FEV_1/FVC than would be expected from their smoking habits alone.

5. Both cigarette smoking and asbestos exposure result in an increased resistance to airflow in the small airways. In the absence of cigarette smoking, this increased resistance in the small airways does not appear to result in obstruction on standard spirometry as measured by FEV_1/FVC.
6. Asbestos exposure is the predominant cause of interstitial fibrosis in populations with substantial asbestos exposure. Cigarette smokers do have a slightly higher prevalence of chest radiographs interpreted as interstitial fibrosis than nonsmokers, but neither the frequency of these changes nor the severity of the changes approach levels found in populations with substantial asbestos exposure.
7. The promotion of smoking cessation should be an intrinsic part of efforts to control asbestos-related death and disability.

Respiratory Disease in Coal Miners

1. Coal dust exposure is clearly the major etiologic factor in the production of the radiologic changes of coal workers' pneumoconiosis (CWP). Cigarette smoking probably increases the prevalence of irregular opacities on the chest roentgenograms of smoking coal miners, but appears to have little effect on the prevalence of small rounded opacities or complicated CWP.
2. Increasing category of simple radiologic CWP is not associated with increasing airflow obstruction, but increasing coal dust exposure is associated with increasing airflow obstruction in both smokers and nonsmokers.
3. Since the introduction of more effective controls to reduce the level of coal dust exposure at the worksite, cigarette smoking has become the more significant contributor to reported cases of disabling airflow obstruction among coal miners.
4. Cigarette smoking and coal dust exposure appear to have an independent and additive effect on the prevalence of chronic cough and phlegm.
5. Increasing coal dust exposure is associated with a form of emphysema known as focal dust emphysema, but there is no definite evidence that extensive centrilobular emphysema occurs in the absence of cigarette smoking.
6. The majority of studies have shown that coal dust exposure is not associated with an increased risk for lung cancer.
7. Reduction in the levels of coal dust exposure is the only method available to reduce the prevalence of simple or complicated CWP. However, the prevalence of ventilatory disabilities in coal miners could be substantially reduced by reducing the prevalence of cigarette smoking, and efforts aimed at reducing

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ventilatory disability should include efforts to enhance successful smoking cessation.

Silica-Exposed Workers

1. Silicosis, acute silicosis, mixed-dust silicosis, silicotuberculosis, and diatomaceous earth pneumoconiosis are causally related to silica exposure as a sole or principal etiological agent.
2. Epidemiological evidence, based on both cross-sectional and prospective studies, demonstrates that silica dust is associated with chronic bronchitis and chronic airways obstruction. Silica dust and smoking are major risk factors and appear to be additive in producing chronic bronchitis and chronic airways obstruction. Most studies indicate that the smoking effect is stronger than the silica dust effect.
3. Pathological studies describe mineral dust airways disease, which is morphologically similar to the small airways lesions caused by cigarette smoking.
4. A number of studies have demonstrated an increased risk of lung cancer in workers exposed to silica, but few of these studies have adequately controlled for smoking. Therefore, while the increased standardized mortality ratios for lung cancer in these populations suggest the need for further investigation of a potential carcinogenic effect of silica exposure (particularly in a combined exposure with other possible carcinogens), the evidence does not currently establish whether silica exposure increases the risk of developing lung cancer in man.
5. Smoking control efforts should be an important concomitant of efforts to reduce the burden of silica-related illness in working populations.

Occupational Exposures to Petrochemicals, Aromatic Amines, and Pesticides

1. The biotransformation of industrial toxicants can be modified at least to some extent by the constituents of tobacco smoke through enzyme induction or possibly inhibition. Both tobacco smoke and some industrial pollutants contain substances capable of initiating and promoting cancer and damaging the airways and lung parenchyma. There is, therefore, an ample biologic basis for suspecting that important interactive effects between some workplace pollutants and tobacco smoke exist.
2. In mortality studies of coke oven workers and gas workers, convincing evidence has indicated that work exposures to oven effluents are causing an excess risk of lung cancer in spite of the lack of adequate information on smoking. Other mortality studies that suggest small increases in smoking-related dis-

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eases, such as pancreatic cancer in refinery workers, cannot be interpreted without more information on smoking.

3. For bladder cancer, the interactions between smoking and occupational exposure are unclear, with both additive and antagonistic interactions having been demonstrated.
4. The risk of pulmonary disability in rubber workers was increased when smoking and occupational exposure to particulates were combined. There are few empirical animal experiments that demonstrate interactive effects between cigarette smoking and various industrial chemicals for lung disease.

Cotton Dust Exposure and Cigarette Smoking

1. Byssinosis prevalence and severity is increased in cotton textile workers who smoke in comparison with workers who do not smoke.
2. Cigarette smoking seems to facilitate the development of byssinosis in smokers exposed to cotton dust, perhaps by the prior induction of bronchitis. Cotton mill workers of both sexes who smoke have a consistently greater prevalence of bronchitis than nonsmokers.
3. The importance of cigarette smoking to byssinosis prevalence seems to grow with rising dust levels (a smoking–cotton dust interaction). At the highest dust levels, cigarette smoke was found to interact with cotton dust exposure to substantially increase the acute symptom prevalence.
4. Nonsmokers with byssinosis have lower preshift lung function and a greater cross-shift decline in lung function than asymptomatic workers, and those workers with bronchitis generally have lower preshift lung function than those without bronchitis. In general, smokers have lower lung function than nonsmokers among cotton workers, both in those with bronchitis and in those with byssinosis.
5. Although the average forced expiration values measured at the start of a shift are reduced among smokers, the cross-shift decline in function does not seem to be affected by smoking status.
6. The contribution of the acute byssinotic symptoms (grades 1/2 and 1) to the subsequent development of what have been termed the chronic forms (grade 3) of byssinosis (which include airways obstruction) is not well documented; however, chronic airflow obstruction has been found more frequently in cotton textile workers than in control populations, and this lung function loss appears to be additive to that caused by cigarette smoking.
7. Cotton dust exposure is significantly associated with mucous gland volume and peripheral goblet cell metaplasia in non-

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smokers, a pathology consistent with bronchitis. Among cigarette smokers, the interaction of cotton textile exposure and smoking is demonstrable for goblet cell hyperplasia. Centrilobular emphysema is found only in association with cigarette smoking and pipe smoking. There is no emphysema association found with cotton dust exposure.

8. The evidence does not currently suggest an excess risk of lung cancer among cotton textile workers.

Ionizing Radiation and Lung Cancer

1. There is an interaction between radon daughters and cigarette smoke exposures in the production of lung cancer in both man and animals. The nature of this interaction is not entirely clear because of the conflicting results in both epidemiological and animal studies.
2. The interaction between radon daughters and cigarette smoke exposures may consist of two parts. The first is an additive effect on the number of cancers induced by the two agents. The second is the hastening effect of the tumor promoters in cigarette smoke on the appearance of cancers induced by radiation, so that the induction-latent period is shorter among smokers than nonsmokers and the resultant cancers are distributed in time differently between smokers and nonsmokers, appearing earlier in smokers.

Smoking Intervention Programs in the Workplace

1. Smoking modification and maintenance of nonsmoking status among initial quitters has the promise of being more successful in worksite programs than in clinic-based programs. Higher cessation rates in worksite programs are achieved with more intensive programs.
2. Incentives for nonsmoking appear to be associated with higher participation and better success rates. Further research is needed to specify the optimal types of incentive procedures.
3. Success of a worksite smoking program depends upon three primary factors: the characteristics of the intervention program, the characteristics of the organization in which the program is offered, and the interaction between these factors.
4. Research is needed on recruitment strategies and participation rates in worksite smoking programs and on the impact of interventions on the entire workforce of a company.
5. More investigations are needed on worksite characteristics associated with the success of occupational programs and on comprehensive programs including components such as quit-smoking contests, no-smoking policies, physician messages, and self-help materials in addition to smoking cessation clinics.

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6. The implementation of broadly based health promotion efforts in the workplace should be encouraged, with smoking interventions representing a major component of the larger effort to improve health through a worksite focus.

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CHAPTER 2

OCCUPATION AND SMOKING BEHAVIOR IN THE UNITED STATES: CURRENT ESTIMATES AND RECENT TRENDS

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Introduction

Estimates of current smoking behavior reported in this section of the Surgeon General's Report were obtained from the 1978, 1979, and 1980 National Health Interview Surveys (NHIS). A data tape was prepared by the National Center for Health Statistics to allow linkages across surveys, thereby permitting analyses of the combined 1978–1980 NHIS (n=49,715). The majority of the analysis presented in this chapter were conducted on the population aged 20 to 64 (n=38,527). Given the large samples and exceptionally high response rates of NHIS, these estimates are generally regarded as the best available estimates of national smoking patterns. To examine recent 10-year changes in smoking behavior by occupational category, the 1978–1980 NHIS estimates have also been compared with the 1970 NHIS estimates for selected smoking variables. A more detailed description of the NHIS data base is provided in the Technical Addendum to this section.

Patterns of Employment

Before characterizing the smoking behavior of the U.S. adult workforce, it will be useful to describe the patterns of employment for men and women. As is shown in Table 1, men are more likely to be employed in professional and technical, management, and blue-collar occupations. Women are more likely to be employed in professional and technical and clerical and service occupations or to be homemakers. Although there was an increase in participation by women in white-collar occupations between 1970 and 1980, the ranking of occupational categories by their relative frequency for both sexes remained about the same in 1980 as it did in 1970. Because of their low relative frequency, farm, sales, and clerical workers, laborers, and service workers have less impact on the smoking behavior of the total male workforce, and female farm workers, laborers, craftsmen and kindred workers, sales workers, and managers and administrators have a modest impact on the smoking behavior of the total female workforce.

Smoking Prevalence

Surveys have repeatedly shown that blue-collar workers are more likely than white-collar workers to smoke cigarettes (US DHEW 1979). Recent estimates from NHIS continue to substantiate this finding (Table 2). Overall, smoking rates for blue-collar men (47.1 percent) exceed that of white-collar men (33.0 percent). The same pattern holds for women, but is less pronounced, with smoking rates among blue-collar women (38.1 percent) exceeding that of white-collar women (31.9 percent). Among women, this white-collar–blue-

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TABLE 1.—Estimates of the occupational distribution of men and women, aged 20 to 64 years, United States, 1970–1980

Occupation	Men		Women	
	1970	1978–80	1970	1978–80
Currently employed	87.8	85.1	47.9	57.3
White-collar total	39.2	39.2	31.1	40.5
Professional, technical, and kindred workers	14.2	14.9	7.9	11.4
Managers and administrators, except farm	13.3	13.5	2.6	4.9
Sales workers	5.0	5.3	3.4	3.6
Clerical and kindred workers	6.8	5.5	17.1	20.6
Blue-collar total	43.1	40.8	9.0	9.3
Craftsmen and kindred workers	19.9	20.7	0.8	1.5
Operatives and kindred workers	18.1	14.6	8.0	7.2
Laborers, except farm	5.1	5.5	0.2	0.6
Service	5.4	6.1	10.3	10.8
Farm	3.7	2.9	0.5	0.6
Unemployed	3.6	4.1	3.2	4.3
Usual activity, homemaking	—	—	52.5	41.7

NOTE. The white-collar, blue-collar, service, and farm occupational categories are mutually exclusive; however, those classified as "Homemaking" or "Unemployed" may also be classified in an occupational group on the basis of a recent or part-time job, resulting in a small degree of overlap between categories.

SOURCE: National Center for Health Statistics, National Health Interview Surveys, 1970 and 1978–1980 (combined). (See Technical Addendum.)

collar difference exists only for the younger age group (aged 20 to 44); for older women (aged 45 to 64) there is virtually no difference in smoking prevalence between these two categories of workers.

For men, the highest rates of current smoking occur among craftsmen and kindred workers, operatives and kindred workers, laborers, service workers, and the unemployed. The lowest smoking rates for men occur among professional, technical, and kindred workers, managers and administrators, clerical and kindred workers, and farm workers.

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TABLE 2.—Estimates of the percentage of current smokers by sex, age, and occupation, aged 20 to 64 years, United States, 1978–1980

Occupation	Women			Men		
	Total	20–44	45–64	Total	20–44	45–64
Total	33.2	34.2	31.4	40.9	41.4	39.8
Currently employed	33.3	34.0	31.8	39.9	40.9	37.7
White-collar total	31.9	31.9	31.9	33.0	33.5	32.2
Professional, technical, and kindred workers	26.5	26.1	27.9	25.7	25.3	26.6
Managers and administrators, except farm	38.3	37.8	39.2	36.3	38.9	32.2
Sales workers	33.3	33.2	33.5	40.6	42.0	38.0
Clerical and kindred workers	33.2	33.9	31.4	37.7	36.4	40.4
Blue-collar total	38.1	41.3	31.9	47.1	48.7	43.6
Craftsmen and kindred workers	44.6	45.4	43.0*	46.1	47.8	42.6
Operatives and kindred workers	37.0	40.2	30.8	48.6	50.4	44.5
Laborers, except farm	36.2	43.0*	14.1*	46.8	47.3	45.1
Service	37.4	39.8	32.7	47.5	48.3	46.0
Farm	22.6	31.3*	7.1*	31.5	28.9	34.5
Unemployed	39.6	41.7	30.4	53.1	53.9	50.8
Usual activity, homemaking	33.0	35.1	30.4	—	—	—

* <100 cases in the denominator (unweighted sample).

SOURCE: National Center for Health Statistics, National Health Interview Surveys, 1978–1980 (combined). (See Technical Addendum.)

For women 20 to 64 years of age, the highest smoking rates are found among craftsmen and kindred workers and managers and administrators. Among women 20 to 44 years of age, there are also relatively high smoking rates among operatives and kindred workers, service workers, and the unemployed. The lowest rates of current smoking occur among professional, technical, and kindred workers, regardless of age. For homemakers, the category representing nearly 42 percent of all women aged 20 to 64, the prevalence of smoking among those aged 20 to 44 is midway between the

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prevalence rates for white-collar and blue-collar occupations. However, among women 45 to 64 years of age, smoking rates vary little by occupational group (with the single exception of managers and administrators), with white collar-workers, blue-collar workers, and homemakers all having approximately the same smoking prevalence.

Among men, a more detailed breakdown of smoking by occupation (Table 3) shows that painters, truck drivers, construction workers, carpenters, auto mechanics, and guards and watchmen have the highest rates of current smoking (among occupations having 100 or more cases in the 1978–1980 NHIS), each exceeding 50 percent. In contrast, electrical and electronic engineers, lawyers, and secondary school teachers have the lowest rates of current smoking, all under 25 percent.

Among women, waitresses have a noticeably higher rate of current smoking than other groups (Table 4), followed by cashiers, assemblers, nurses aides, machine operators, practical nurses, and packers and wrappers—all of whom have rates of current smoking that equal or surpass 40 percent. The lowest rates of smoking occur among women employed as elementary school teachers, food service workers, bank tellers, and sewers and stitchers.

Because of the exemplar role of physicians and nurses in regard to health, their smoking rates are of special interest. Although the sample is relatively small, physicians have among the lowest rates of current smoking (18.1 percent). Among nurses, the pattern of smoking reflects the white-collar–service worker distinction; registered nurses have among the lowest rates of current smoking, but practical nurses have among the highest rates (Table 4).

Daily Cigarette Consumption

For men, occupational differences in cigarette consumption do not follow the same patterns observed for prevalence. On the average, adult male white-collar smokers consume 24 cigarettes per day, essentially the same as the number of cigarettes consumed by blue-collar smokers (23.3) (Table 5). In virtually all occupational subgroups, adult men report an average daily consumption exceeding 20 cigarettes. Consumption levels are highest among managers and administrators and sales workers. These numbers represent daily cigarette consumption and need to be interpreted with some caution, as there may be a substantial underreporting of cigarette consumption, and the tendency to underreport may not be constant across occupational categories.

For women, no difference in consumption is found between white-collar and blue-collar smokers. On the average, white-collar female smokers consume 19.5 cigarettes per day, compared with 19.8

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TABLE 3.—Specific occupations with highest and lowest estimates of current smoking, men, aged 20 to 64 years, United States, 1978–1980

Occupation	Current smokers (percentage)
Highest rates	
1. Painters, construction and maintenance (510)	55.1
2. Truck drivers (715)	53.6
3. Construction laborers, except carpenters' helpers (751)	53.0
4. Carpenters (415)	50.8
5. Auto mechanics (473)	50.5
6. Guards and watchmen (962)	50.5
7. Janitors and sextons (903)	49.8
8. Assemblers (602)	48.7
9. Electricians (430)	48.3
10. Sales representatives, wholesale trade (282)	48.1
Lowest rates	
1. Electrical and electronic engineers (012)	16.2
2. Lawyers (031)	21.9
3. Secondary school teachers (144)	24.9
4. Accountants (001)	26.8
5. Real estate agents and brokers (270)	27.8
6. Farmers (801)	28.1

NOTE: Adapted from Table 22 in Technical Addendum. Only those occupations with at least 100 men (aged 20 to 64) in the 1978–1980 NHIS are included. Numbers in parentheses denote code values from the U.S. Bureau of the Census 1970 classification of occupations.

SOURCE: National Center for Health Statistics, National Health Interview Surveys, 1978–1980 (combined). (See Technical Addendum.)

cigarettes for blue-collar smokers, 19.4 cigarettes for homemakers, and 19.0 cigarettes for service workers. Female smokers employed as managers or administrators or as craftsmen or kindred workers report the highest consumption levels, averaging more than 20 cigarettes per day; women employed in professional, technical, or kindred occupations report lower average daily consumption. However, like the men, these differences are not large, averaging fewer than two to four cigarettes per day.

The higher the average daily consumption of cigarettes within an occupational group, the more likely it is that this group will also contain a higher percentage of heavy smokers (more than 20 or more than 40 cigarettes a day). Overall, 72 percent of the male smokers employed in white-collar occupations reported smoking more than 20

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TABLE 4.—Specific occupations with highest and lowest estimates of current smoking, women, aged 20 to 64 years, United States, 1978–1980

Occupation	Current smokers (percentage)
Highest rates	
1. Waitresses (915)	51.1
2. Cashiers (310)	44.2
3. Assemblers (602)	42.9
4. Nurses aides, orderlies, and attendants (925)	41.0
5. Machine operatives (690)	41.0
6. Practical nurses (926)	40.3
7. Packers and wrappers, excluding meat/produce (643)	40.0
8. Checkers, examiners, and inspectors; manufacturing (610)	39.3
9. Managers and administrators n.e.c.[1] (245)	38.0
10. Hairdressers and cosmetologists (944)	37.5
Lowest rates	
1. Elementary school teachers (142)	19.8
2. Food service workers (916)	24.6
3. Secondary school teachers (144)	24.8
4. Bank tellers (301)	25.7
5. Sewers and stitchers (663)	25.8
6. Registered nurses (075)	27.2
7. Child care workers, excluding private households (942)	28.9

NOTE: Adapted from Table 22 in Technical Addendum. Only those occupations with at least 100 women (aged 20 to 64) in the 1978–1980 NHIS are included. Numbers in parentheses denote code values from the U.S. Bureau of the Census 1970 classification of occupations.

[1] Not elsewhere classified.

SOURCE: National Center for Health Statistics, National Health Interview Surveys, 1978–1980 (combined). See Technical Addendum.

cigarettes a day, and over 21 percent reported smoking 40 or more cigarettes a day (Table 6). Comparable figures for blue-collar smokers are 72 percent and 18 percent, respectively.

Among adult women (Table 7), the percentage of heavy smokers is generally lower than for men, with women employed as craftsmen or kindred workers reporting higher percentages of heavy smoking than other female occupational groups. The pattern for homemakers closely parallels that of white-collar workers, but service workers have slightly lower rates of heavy smoking than white-collar workers. For both men and women, and across virtually all occupational groups, smokers 45 years of age or older are more likely

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TABLE 5.—Estimates of average daily cigarette consumption among current smokers by sex, age, and occupation, aged 20 to 64 years, United States, 1978–1980

Occupation	Women			Men		
	Total	20–44	45–64	Total	20–44	45–64
Total	19.3	19.1	19.8	23.2	22.2	25.1
Currently employed	19.2	19.0	19.8	23.4	22.4	25.6
White-collar total	19.5	19.1	20.4	24.0	22.6	26.9
Professional, technical, and kindred workers	18.3	17.9	19.3	21.5	19.8	25.4
Managers and administrators, except farm	21.1	20.6	22.0	26.2	25.2	28.1
Sales workers	19.1	18.0	21.0	25.1	22.7	30.3
Clerical and kindred workers	19.6	19.4	20.1	22.3	21.8	23.2
Blue-collar total	19.8	19.9	19.4	23.3	22.6	25.1
Craftsmen and kindred workers	22.4	22.3	22.5	24.4	23.7	26.1
Operatives and kindred workers	19.2	19.5	18.4	22.4	21.7	24.2
Laborers, except farm	18.9	18.1	25.6	21.5	20.9	23.6
Service	19.0	19.0	18.9	21.5	19.9	24.7
Farm	18.0	18.0	18.0	20.9	20.2	21.7
Unemployed	21.2	21.2	21.3	21.5	20.1	26.0
Usual activity, homemaking	19.4	19.4	19.4	—	—	—

SOURCE: National Center for Health Statistics, National Health Interview Surveys, 1978–1980 (combined). (See Technical Addendum.)

to report a higher percentage of heavy smokers than their 20- to 44-year-old counterparts.

Age of Initiation

Men employed as blue-collar workers initiate smoking approximately 14 months earlier, on the average, than men employed in white-collar occupations (Table 8). The earliest ages of initiation are

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TABLE 6.—Estimates of the percentage of current smokers who smoke more than 20 or more than 40 cigarettes daily, by age and occupation, men, aged 20 to 64 years, United States, 1978–1980

Occupation	Total		20–44		45–64	
	≥20	≥40	≥20	≥40	≥20	≥40
Total	70.6	18.8	68.5	15.7	74.8	24.5
Currently employed	71.4	19.1	69.3	16.1	76.0	25.7
White-collar total	72.1	21.1	69.5	16.9	77.6	29.5
Professional, technical, and kindred workers	66.5	17.3	61.9	12.9	76.7	26.8
Managers and administrators, except farm	79.1	24.5	77.7	20.0	81.6	33.3
Sales workers	74.2	23.7	70.0	17.8	83.0	36.1
Clerical and kindred workers	64.2	17.2	64.1	16.2	64.6	19.0
Blue-collar total	71.8	18.3	70.1	16.1	76.3	24.1
Craftsmen and kindred workers	75.3	21.2	73.6	18.7	79.6	27.2
Operatives and kindred workers	69.4	15.6	68.3	13.5	72.1	21.4
Laborers, except farm	65.7	15.1	63.1	14.2	74.6	17.9
Service	66.6	16.0	63.0	11.5	73.6	24.7
Farm	62.1	16.5	56.3*	16.6*	68.0*	16.4*
Unemployed	65.9	16.3	61.3	12.9	81.1*	27.6*
Usual activity, homemaking	—	—	—	—	—	—

* < 100 cases in the denominator (unweighted sample).

SOURCE: National Center for Health Statistics, National Health Interview Surveys, 1978–1980 (combined). (See Technical Addendum.)

reported by men employed as laborers (16.5 years), operatives or kindred workers (16.6 years), or craftsmen or kindred workers (16.8 years). Men employed in professional, technical, or kindred occupations, or as managers or administrators, sales workers, or clerical or kindred workers report later onset of smoking, ranging between 17.7 and 18.1 years of age.

For women, blue-collar and service workers report a somewhat earlier onset of smoking than white-collar workers or homemakers

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TABLE 7.—Estimates of the percentage of current smokers who smoke more than 20 or more than 40 cigarettes daily, by age and occupation, women, aged 20 to 64 years, United States, 1978–1980

Occupation	Total		20–44		45–64	
	≥ 20	≥ 40	≥ 20	≥ 40	≥ 20	≥ 40
Total	58.6	11.4	57.1	10.8	61.3	12.4
Currently employed	58.5	11.3	57.2	10.9	61.7	12.3
White-collar total	59.4	11.8	57.8	11.0	63.2	13.8
Professional, technical, and kindred workers	52.8	10.8	52.0	9.8	55.0	13.8
Managers and administrators, except farm	63.4	15.6	59.0	14.6	71.8	17.5
Sales workers	56.8	9.9	55.0	6.5	59.9*	16.0*
Clerical and kindred workers	61.6	11.5	60.6	11.3	64.3	12.0
Blue-collar total	62.0	11.2	61.2	11.5	64.0	10.6
Craftsmen and kindred workers	70.0	18.2	67.4*	18.2*	75.5*	18.1*
Operatives and kindred workers	60.4	9.9	60.3	10.5	60.7	8.4
Laborers, except farm	56.7*	6.0*	55.2*	5.0*	70.9*	15.6*
Service	54.6	11.6	53.6	11.9	57.1	11.0
Farm	65.4*	4.9*	63.5*	5.5*	80.2*	0.0*
Unemployed	62.1	14.8	61.7	14.4	64.4*	17.0*
Usual activity, homemaking	59.1	11.3	58.4	10.9	60.0	11.8

* < 100 cases in the denominator (unweighted sample).

SOURCE: National Center for Health Statistics, National Health Interview Surveys, 1978–1980 (combined). (See Technical Addendum.)

(about 6 months). The earliest age of initiation occurs among women employed as laborers (17.4 years of age) or operatives or kindred workers (18.5 years of age), and the latest age of initiation occurs among women employed in professional, technical, or kindred occupations (19.4 years of age). Across all occupational categories, men report an earlier age of initiation than women; this difference is most pronounced within the 45 to 64 age group.

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TABLE 8.—Estimates of average age of initiation of smoking among current and former smokers by sex, age, and occupation, aged 20 to 64 years, United States, 1978–1980

Occupation	Women			Men		
	Total	20–44	45–64	Total	20–44	45–64
Total	19.1	18.0	21.2	17.2	16.9	17.6
Currently employed	19.0	18.1	21.0	17.3	17.0	17.7
White-collar total	19.1	18.4	20.9	17.9	17.6	18.3
Professional, technical, and kindred workers	19.4	18.8	21.2	18.1	17.7	18.7
Managers and administrators, except farm	18.9	18.1	20.7	17.8	17.6	18.0
Sales workers	19.2	18.0	21.2	17.8	17.5	18.4
Clerical and kindred workers	19.0	18.2	20.9	17.7	17.3	18.3
Blue-collar total	18.6	17.4	21.3	16.7	16.5	17.1
Craftsmen and kindred workers	19.2	17.6	22.9	16.8	16.5	17.3
Operatives and kindred workers	18.5	17.4	21.1	16.6	16.4	17.1
Laborers, except farm	17.4	17.6	16.5	16.5	16.4	16.6
Service	18.8	17.7	21.4	17.2	16.9	17.9
Farm	18.4	18.4	18.4	17.0	16.4	17.5
Unemployed	18.2	17.5	21.1	16.9	16.4	18.2
Usual activity, homemaking	19.3	17.8	21.3	—	—	—

SOURCE: National Center for Health Statistics, National Health Interview Surveys, 1978–1980 (combined). (See Technical Addendum.)

An important inference of the age of initiation reported in Table 8 is that a substantial fraction of smokers report beginning to smoke at ages when they would be first entering the workforce. This suggests that a set of influences that promote initiation may be present in the initial socialization into the workforce.

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Quitting Behavior

Because cigarette smoking usually begins between the ages of 12 and 25 (US DHEW 1979; US PHS 1973, 1976) the prevalence of smoking among people 25 years of age or older is determined in large part by the rate at which they stop smoking (or die). The percentage of former smokers (as a portion of "ever smoked") by occupational group is reported in Table 9. For men, relatively higher percentages of former smokers are found among professional, technical, and kindred workers (55.2 percent) and managers and administrators (47.7 percent)—the same occupational groups reporting lower rates of current smoking (Table 2). The striking feature for women is the uniformly lower percentage of former smokers when compared with men. However, even here the same general pattern can be found; occupations that have lower rates of current smoking also tend to have a higher percentage of former smokers. In general, there are substantial differences by occupational category, with white-collar workers of both sexes having a higher percentage of former smokers than blue-collar workers. This white-collar–blue-collar difference is most pronounced among men. Among women, homemakers tend to mirror the pattern of white-collar women.

It does not appear that the lower percentage of former smokers in blue-collar occupations occurs simply because blue-collar workers are less likely than white-collar workers to attempt to quit. Among men, white-collar current smokers are more likely to report "a serious attempt" to quit smoking (Table 10), but these differences are typically only half as large as the white-collar–blue-collar differences in the proportion of former smokers. Among women, the white-collar–blue-collar differences are relatively small and show a mixed pattern.

Recent Changes in Smoking Behavior

A comparison of smoking estimates for the period 1970–1980 reveals several interesting changes by occupational group and sex (Table 11). Among men, there was a 19 percent proportionate decline in smoking prevalence between 1970 and 1980 for white-collar workers (40.8 vs. 33.0 percent), compared with a 14 percent decline for blue-collar workers (55.0 vs. 47.1 percent). Occupations with the largest decline in male smoking include professional, technical, and kindred occupations (21 percent decline) and farm workers (20.7 percent decline); the unemployed (3.6 percent) and service workers (10.9 percent) had the smallest proportionate declines in smoking prevalence.

Among white-collar women, there was a proportionate reduction in smoking prevalence of 11.6 percent between 1970 and 1980 (36.1

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TABLE 9.—Estimates of the percentage of former smokers by sex, age, and occupation, aged 20 to 64 years, United States, 1978–1980

Occupation	Women			Men		
	Total	20–44	45–64	Total	20–44	45–64
Total	33.2	30.2	35.7	40.0	34.2	48.7
Currently employed	31.4	30.1	34.2	40.8	35.1	50.5
White-collar total	33.8	32.7	36.4	48.1	42.7	56.4
Professional, technical, and kindred workers	41.1	40.1	43.8	55.2	51.8	61.3
Managers and administrators, except farm	30.2	30.9	28.6	47.7	39.9	57.9
Sales workers	32.0	30.9	34.1	39.1	32.8	49.1
Clerical and kindred workers	31.3	29.4	35.9	40.9	36.4	47.8
Blue-collar total	24.9	22.8	29.8	34.8	29.5	45.4
Craftsmen and kindred workers	23.8	24.9	21.4*	36.7	31.1	46.8
Operatives and kindred workers	24.6	21.8	30.9	33.8	28.8	44.1
Laborers, except farm	30.7*	27.0*	53.5*	29.7	25.0	41.9
Service	26.2	24.2	62.2	32.0	27.0	40.0
Farm	32.5*	25.0*	30.5*	45.7	38.3	51.5
Unemployed	25.7	22.7	39.7	30.0	26.0	40.6
Usual activity, homemaking	33.5	30.9	37.2	—	—	—

* < 100 cases in the denominator (unweighted sample).
SOURCE: National Center for Health Statistics, National Health Interview Surveys, 1978–1980 (combined). (See Technical Addendum.)

vs. 31.9 percent), but blue-collar women showed virtually no change in smoking prevalance (1.0 percent proportionate increase).

The greater rate of decline in smoking prevalence for men has produced two fundamental changes in the occupational smoking patterns in this country. In 1970, men employed in professional, technical, or kindred occupations or as managers or administrators had a higher rate of smoking than their female counterparts. By the end of the decade, this pattern had been reversed; a slightly higher percentage of women in these two occupational groups now smoke

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TABLE 10.—Estimates of the percentage of current smokers who have ever seriously attempted to quit by sex, age, and occupation, aged 20 to 64 years, United States, 1978–1980

Occupation	Women			Men		
	Total	20–44	45–64	Total	20–44	45–64
Total	59.3	60.6	56.8	60.2	59.1	62.4
Currently employed	58.4	60.3	54.1	60.1	59.2	62.0
White-collar total	59.7	61.7	54.8	63.6	62.7	65.3
Professional, technical, and kindred workers	62.2	62.2	62.1	68.8	66.6	73.8
Managers and administrators, except farm	61.0	64.4	54.8	60.2	59.5	61.5
Sales workers	59.3	63.4	52.0	60.9	59.2	64.5
Clerical and kindred workers	58.3	60.6	52.5	64.8	66.6	61.3
Blue-collar total	58.7	58.8	58.4	58.6	57.7	61.0
Craftsmen and kindred workers	57.1	52.2*	67.9*	59.4	58.9	60.7
Operatives and kindred workers	58.8	60.1	55.6	57.9	56.7	61.1
Laborers, except farm	62.6*	61.9*	68.9*	57.4	56.0	62.2
Service	57.4	58.9	54.0	55.1	53.7	57.9
Farm	77.5*	77.3*	78.9*	61.0	61.3*	60.7*
Unemployed	66.4	64.9	74.8*	60.9	58.5	69.1*
Usual activity, homemaking	60.8	60.9	60.7	—	—	—

* < 100 cases in the denominator (unweighted sample).

SOURCE: National Center for Health Statistics, National Health Interview Surveys, 1978–1980 (combined). (See Technical Addendum.)

cigarettes. If the previous 10-year trends prevail, by the end of this decade women are likely to reach parity with men in the prevalence of smoking among blue-collar workers (as an aggregate) and clerical and kindred workers, and to surpass men in smoking prevalence in two additional occupational categories: craftsmen and kindred workers and laborers.

As is shown in Table 12, only one specific occupational group for men showed a net gain in smoking prevalence between 1970 and

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TABLE 11.—Estimates of the percentage of current smokers by sex and occupation, aged 20 to 64 years, United States, 1970–1980

Occupation	1970		1978–1980		Net change	
	M	W	M	W	M	W
Total	48.1	36.0	40.9	33.2	–7.2	–2.8
Currently employed	47.9	36.5	39.9	33.3	–8.0	–3.2
White-collar total	40.8	36.1	33.0	31.9	–7.8	–4.2
Professional, technical, and kindred workers	32.5	29.0	25.7	26.5	–6.8	–2.5
Managers and administrators, except farm	44.3	42.8	36.3	38.3	–8.0	–4.5
Sales workers	48.5	37.8	40.6	33.3	–7.9	–4.5
Clerical and kindred workers	45.4	37.9	37.7	33.2	–7.7	–4.7
Blue-collar total	55.0	37.7	47.1	38.1	–7.9	+0.4
Craftsmen and kindred workers	53.2	40.1	46.1	44.6	–7.1	+4.5
Operatives and kindred workers	56.4	37.7	48.6	37.0	–7.8	–0.7
Laborers, except farm	57.2	28.2*	46.8	36.2	–10.4	+8.0
Service	53.3	39.4	47.5	37.4	–5.8	–2.0
Farm	39.7	20.8	31.5	22.6	–8.2	+1.8
Unemployed	55.9	42.3	53.9	39.6	–2.0	–2.7
Usual activity, homemaking	—	35.3	—	33.0	—	–2.3

* . . 100 cases in the denominator (unweighted sample).

SOURCE: National Center for Health Statistics, National Health Interview Surveys, 1970 and 1978–1980 (combined). (See Technical Addendum.)

1980 (i.e., electricians), but painters, farm laborers, stock clerks and storekeepers, and deliverymen and routemen had net reductions in excess of 10 percentage points. Among women (Table 13), three occupational groups showed a net increase in smoking prevalence between 1970 and 1980 (practical nurses, cashiers, and packers and wrappers), but relatively large net declines in smoking prevalence occurred among receptionists, waitresses, bank tellers, secretaries, and hairdressers and cosmetologists.

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TABLE 12.—Specific occupations with largest estimated net changes in smoking prevalence between 1970 and 1980, men, aged 20 to 64 years, United States

Occupation	Net change (1970–1980) in current smoking
Largest net gains	
1. Electricians (430)/(421)	+3.9
Largest net reductions	
1. Painters, construction and maintenance (510)/(495)	-17.1
2. Farm laborers, wage workers (822)/(902)	-14.5
3. Stockclerks and storekeepers (381)/(350)	-12.0
4. Deliverymen and routemen (705)/(650)	-11.6
5. Foremen n.e.c.[1] (441)/(430)	-8.9
6. Machinists (461)/(465)	-8.7
7. Checkers, examiners, and inspectors; manufacturing (610)/(643)	-8.7
8. Managers and administrators n.e.c.[1] (245)/(290)	-8.1
9. Assemblers (602)/(631)	-7.0
10. Accountants (001)/(000)	-6.8

NOTE: Adapted from Table 23 in Technical Addendum. Only those occupations with at least 100 men (aged 20 to 64) in the 1978–1980 NHIS are included. Numbers in parentheses represent the occupational codes used in the 1970–1980 HIS and the 1970 HIS.

[1] Not elsewhere classified.

SOURCE: National Center for Health Statistics, National Health Interview Surveys, 1970 and 1978–1980 (combined). (See Technical Addendum.)

The 10-year changes in daily consumption patterns show that among white-collar men, there was a 1.8 percent proportionate increase in the percentage of smokers who averaged 20 or more cigarettes a day, compared with a 3.3 percent increase for blue-collar men (Table 14). Professional, technical, and kindred workers, clerical and kindred workers, and the unemployed showed a net decrease in the percentage of smokers of 20 or more cigarettes a day. The overall pattern is one of modest differences.

For women, the proportionate increase in number of smokers of 20 or more cigarettes a day was 7.4 percent for white-collar workers (55.3 vs. 59.4 percent) and 4.8 percent for homemakers (56.4 vs. 59.1 percent). Service workers showed virtually no change between 1970 and 1980. Among blue-collar women however, the proportionate increase in smokers of 20 or more cigarettes a day was a much larger 20.4 percent (51.5 vs. 62.0 percent). High proportionate increases in 20-plus smokers occurred among women employed as operatives or

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TABLE 13.—Specific occupations with largest estimated net changes in smoking prevalence between 1970 and 1980, women, aged 20 to 64 years, United States

Occupation	Net change (1970–1980) in current smoking
Largest net gains	
1. Practical nurses (926)/(842)	+4.3
2. Cashiers (310)/(312)	+3.7
3. Packers and wrappers, except meat and produce (643)/(693)	+2.6
Largest net reductions	
1. Receptionists (364)/(341)	-10.6
2. Waitresses (915)/(875)	-9.0
3. Bank tellers (301)/(305)	-9.0
4. Secretaries n.e.c.[1] (372)/(342)	-8.1
5. Hairdressers and cosmetologists (944)/(843)	-7.4
6. Cooks, except private household (912)/(825)	-5.5
7. Typists (391)/(360)	-4.9
8. Managers and administrators n.e.c.[1] (245)/(290)	-4.2
9. Bookkeepers (305)/(310)	-4.2

NOTE: Adapted from Table 23 in Technical Addendum. Only those occupations with at least 100 women (aged 20 to 64) in the 1978–1980 NHIS are included. Numbers in parentheses represent the occupational codes used in the 1970–1980 HIS and the 1970 HIS.

[1] Not elsewhere classified.

SOURCE: National Center for Health Statistics, National Health Interview Surveys, 1970 and 1978–1980 (combined). (See Technical Addendum.)

kindred workers (37.8 percent) or craftsmen or kindred workers (33.2 percent). If these 10-year trends continue, by the end of this decade female blue-collar smokers may surpass their male counterparts in the percentage classified as moderate to heavy smokers (i.e., smoking more than 20 cigarettes a day).

Among men, the net change in smokers averaging more than 40 cigarettes a day generally parallels that of 20-plus smokers (Table 15). Only the unemployed show a net decrease in the percentage of current smokers averaging 40 or more cigarettes a day. Among women, the net changes in heavy smoking between 1970 and 1980 are relatively modest.

Birth Cohorts

Although there has been a 10-year decline in smoking prevalence for male blue-collar and white-collar workers and for female white-

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TABLE 14.—Estimates of percentage of current smokers who smoke 20 or more cigarettes daily, by sex and occupation, aged 20 to 64 years, United States, 1970–1980

Occupation	1970		1978–1980		Net change	
	M	W	M	W	M	W
Total	68.5	55.1	70.6	58.6	+2.1	+3.5
Currently employed	69.5	54.4	71.4	58.5	+1.9	+4.1
White-collar total	70.9	55.3	72.2	59.4	+1.3	+4.1
Professional, technical, and kindred workers	69.0	47.5	66.5	52.8	-2.5	+5.3
Managers and administrators, except farm	75.5	58.1	79.1	63.4	+3.6	+5.3
Sales workers	69.8	52.2	74.2	56.8	+4.4	+4.6
Clerical and kindred workers	66.0	58.2	64.2	61.6	-1.8	+3.4
Blue-collar total	69.5	51.5	71.8	62.0	+2.3	+10.5
Craftsmen and kindred workers	72.0	52.7 *	75.3	70.0	+3.3	+17.3
Operatives and kindred workers	68.3	51.1	69.4	60.4	+1.1	+19.3
Laborers, except farm	64.2	66.6 *	65.7	56.7 *	+1.5	-9.9
Service	65.2	53.2	66.6	54.6	+1.4	+1.4
Farm	60.5	50.1 *	62.1	64.4 *	+1.6	+15.3
Unemployed	67.5	49.7	65.9	62.1	-1.6	+12.4
Usual activity, homemaking	—	56.4	—	59.1	—	+2.7

* < 100 cases in the denominator (unweighted sample).

SOURCE: National Center for Health Statistics, National Health Interview Surveys, 1978–1980 (combined). (See Technical Addendum.)

collar workers, service workers, and homemakers, this does not necessarily indicate that rates of lung cancer (and other cigarette-linked diseases) will decline in the near future. What transpires during the next 10 to 20 years with regard to lung cancer incidence and mortality will be determined by those birth cohorts now entering the ages at which substantial numbers of lung cancer deaths occur. Figures 1 through 6, based on data from the combined 1978–1980 NHIS, present the prevalence of smoking among succes-

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TABLE 15.—Estimates of percentage of current smokers who smoke 40 or more cigarettes daily, by sex and occupation, aged 20 to 64 years, United States, 1970–1980

Occupation	1970		1978–1980		Net change	
	M	W	M	W	M	W
Total	15.7	8.0	18.8	11.4	+3.1	+3.4
Currently employed	15.9	7.8	19.1	11.3	+3.2	+3.0
White-collar total	18.4	8.1	21.1	11.8	+2.8	+3.7
Professional, technical, and kindred workers	14.9	4.9	17.3	10.8	−2.4	+5.9
Managers and administrators, except farm	22.8	9.8	24.5	15.6	−1.7	+5.8
Sales workers	18.4	7.2	23.7	9.9	+5.3	+2.7
Clerical and kindred workers	15.0	9.2	17.2	11.5	+2.2	+2.3
Blue-collar total	15.0	7.0	18.3	11.2	+3.3	+4.2
Craftsmen and kindred workers	16.1	9.6*	21.2	18.2	+5.1	+8.6
Operatives and kindred workers	14.8	6.6	15.6	9.0	+0.8	+2.4
Laborers, except farm	11.8	10.1*	15.1	6.0*	+3.3	−4.1
Service	14.5	8.5	16.0	11.6	+1.5	+3.1
Farm	10.3	10.1*	16.5	4.9*	+6.2	−5.2
Unemployed	18.4	10.9	16.3	14.8	−2.1	+3.9
Usual activity, homemaking	—	8.1	—	11.3	—	+3.2

* < 100 cases in the denominator (unweighted sample).

SOURCE: National Center for Health Statistics, National Health Interview Surveys, 1970 and 1978–1980 (combined). (See Technical Addendum.)

sive cohorts born during each decade of the first half of this century. The prevalence of smoking for each cohort is presented from 1900 to 1978 for men and women and for whites and blacks of both sexes. Men who are 50 to 60 years of age, the 1921–1930 birth cohort, are at the age at which the incidence of lung cancer increases rapidly.

Among white-collar workers (Figure 7), this cohort of men is currently smoking at a higher rate than the cohort they are replacing (1911–1920). The 1921–1930 cohort exhibits an exceptional-

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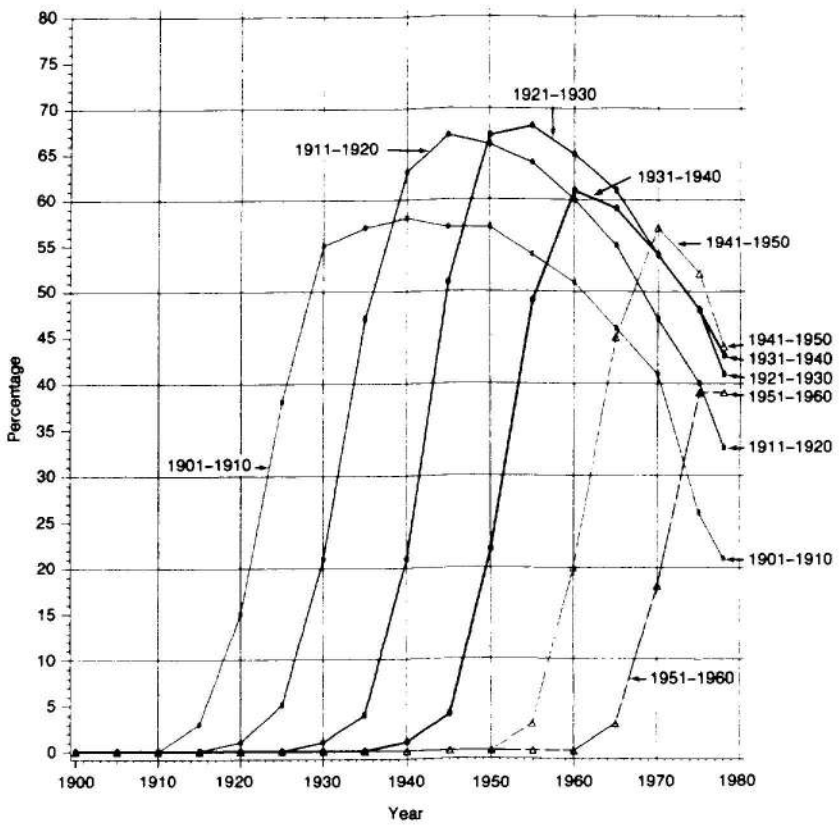


FIGURE 1.—Changes in the prevalence of cigarette smoking among successive birth cohorts of U.S. men, 1900–1978

SOURCE: Data from National Center for Health Statistics, National Health Interview Surveys, 1978–1980 (combined).

ly high peak prevalence of 74.6 percent—which has since declined to 36.3 percent—but is still higher than the current 28.3 percent prevalence estimate for the 1911–1920 cohort. However, one encouraging note is that the 1921–1930 cohort is currently smoking less frequently at age 50 to 60 than the 1911–1920 cohort did when they were 50 to 60 years of age (36.3 vs. 40.1 percent). If the 1921–1930 cohort of white-collar men achieves the same proportionate reduction in smoking during the next 10 years as the 1911–1920 cohort did during the previous 10 years, by 1990 the 1921–1930 birth cohort will be smoking at a lower rate than the 1911–1920 cohort did in 1978. In a continuation of this general trend, all cohorts of white-collar men

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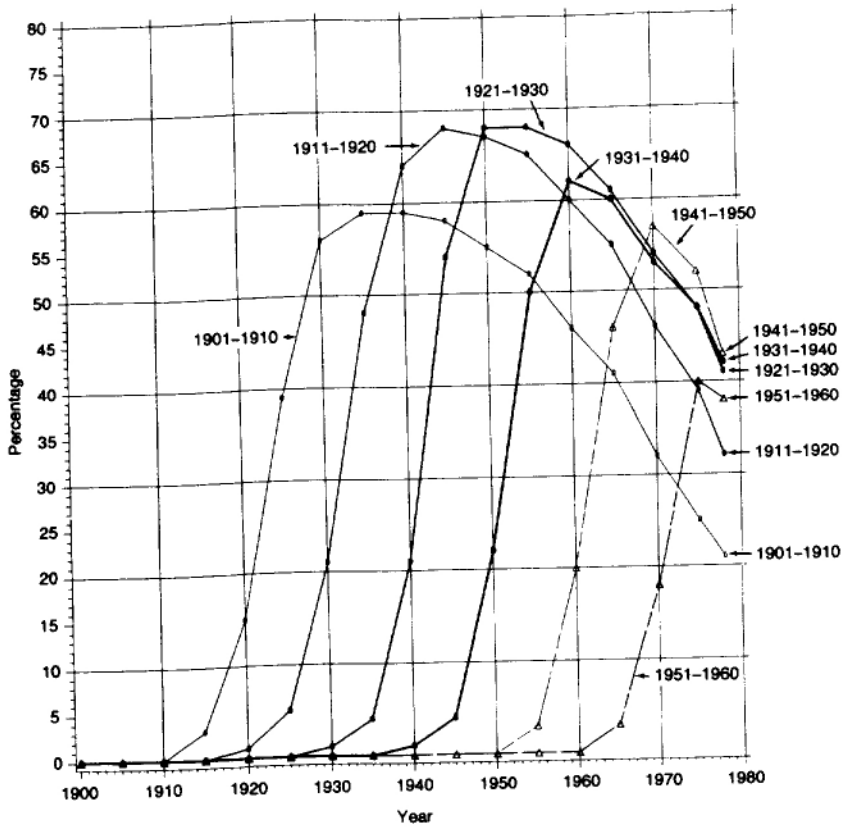


FIGURE 2.—Changes in the prevalence of cigarette smoking among successive birth cohorts of white U.S. men, 1900–1978

SOURCE: Data from National Center for Health Statistics, National Health Interview Surveys, 1978–1980 (combined).

after the 1921–1930 cohort have lower rates of smoking than previous cohorts at comparable ages, and also have successively lower rates of peak prevalence.

The same general pattern in evidence for white-collar men also applies to blue-collar men (Figure 8). The 1921–1930 birth cohort has a higher current and peak smoking prevalence than the 1911–1920 cohort they are replacing. However, the 1921–1930 cohort is currently smoking at a lower rate than the previous cohort (1911–1920) was at the same age (10 years ago). Similarly, the 1931–1940 cohort is currently smoking at a higher rate than the 1921–1930 cohort, but less frequently when compared with the 1921–1930 cohort 10 years

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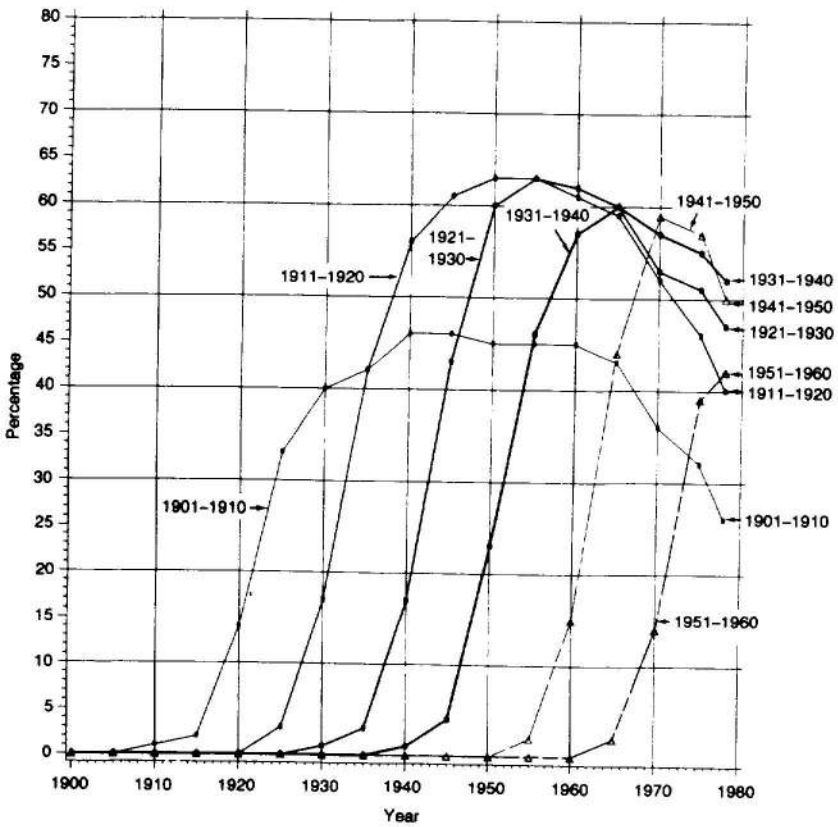


FIGURE 3.—Changes in the prevalence of cigarette smoking among successive birth cohorts of black U.S. men, 1900–1978

SOURCE: Data from National Center for Health Statistics, National Health Interview Surveys, 1978–1980 (combined).

earlier. After the 1921–1930 cohort, each successive birth cohort has a lower peak prevalence, suggesting less total cigarette exposure than for the previous cohort.

If present trends in male smoking continue, successive birth cohorts of white-collar and blue-collar workers will arrive at the ages of increasing lung cancer incidence with a lower rate of current smoking and lifetime exposure than the previous birth cohorts. For white-collar men, this pattern began with the 1911–1920 cohort, but blue-collar men exhibit this pattern beginning with the 1921–1930 cohort. This same pattern of decreasing smoking prevalence across successive birth cohorts also characterizes each main subcategory

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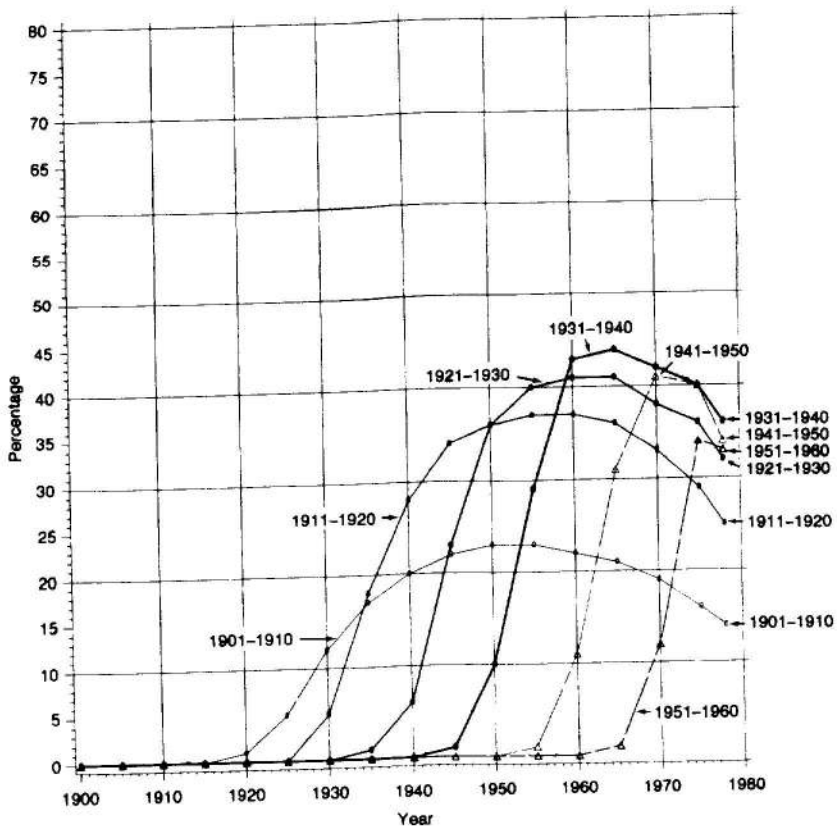


FIGURE 4.—Changes in the prevalence of cigarette smoking among successive birth cohorts of U.S. women, 1900–1978

SOURCE: Data from National Center for Health Statistics, National Health Interview Surveys, 1978–1980 (combined).

within the white-collar and blue-collar categories, including professional, technical, and kindred workers, managers and administrators, craftsmen and kindred workers, and operatives and kindred workers (See Technical Addendum, Figures 13 through 16).

Among white-collar women the same general pattern is found as is in evidence for men (Figure 9). The peak prevalence of smoking is highest in the 1931–1940 cohort; however, beginning with the 1921–1930 cohort, each successive birth cohort of women employed in white-collar occupations has a lower rate of smoking in 1978 than the previous cohort did 10 years earlier. This pattern is especially pronounced for the 1941–1950 and 1951–1960 cohorts, and is similar

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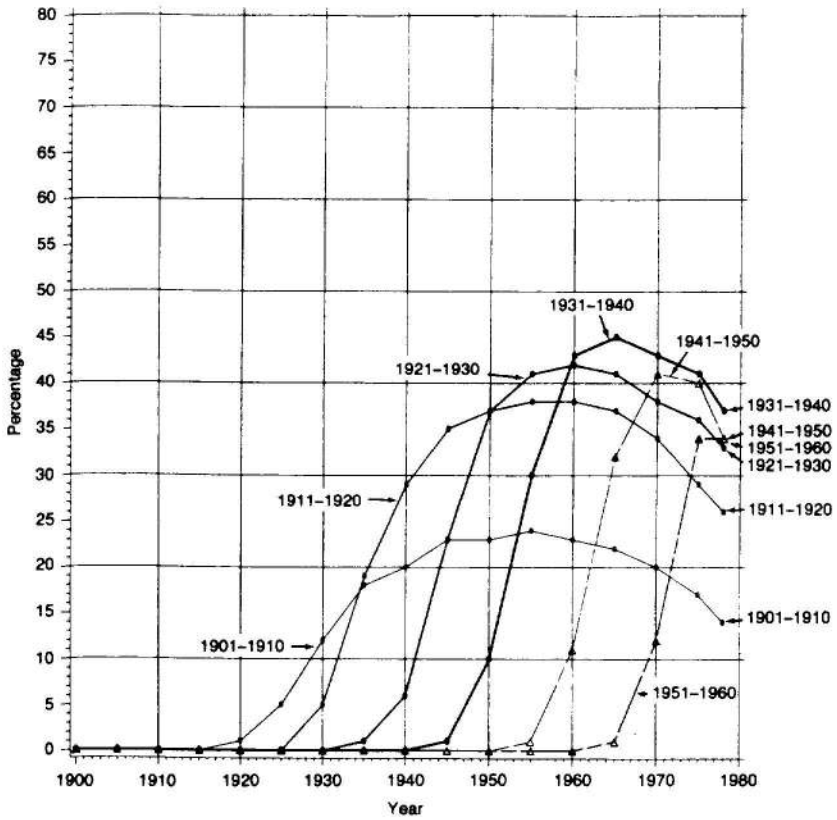


FIGURE 5.—Changes in the prevalence of cigarette smoking among successive birth cohorts of white U.S. women, 1900–1978

SOURCE: Data from National Center for Health Statistics, National Health Interview Surveys, 1978–1980 (combined).

to that found among professional, technical, and kindred workers and clerical and kindred workers (Technical Addendum, Figures 17 and 18). Among homemakers, the largest category of women aged 20 to 64, this same general pattern is also found (Figure 10).

Although the overall birth cohort patterns for white-collar women and homemakers are similar to those of men in regard to current smoking, one important difference should be noted. For men, the birth cohort with the highest peak prevalence is the 1921–1930 cohort, but for female white-collar workers and homemakers this occurs with the 1931–1940 cohort.

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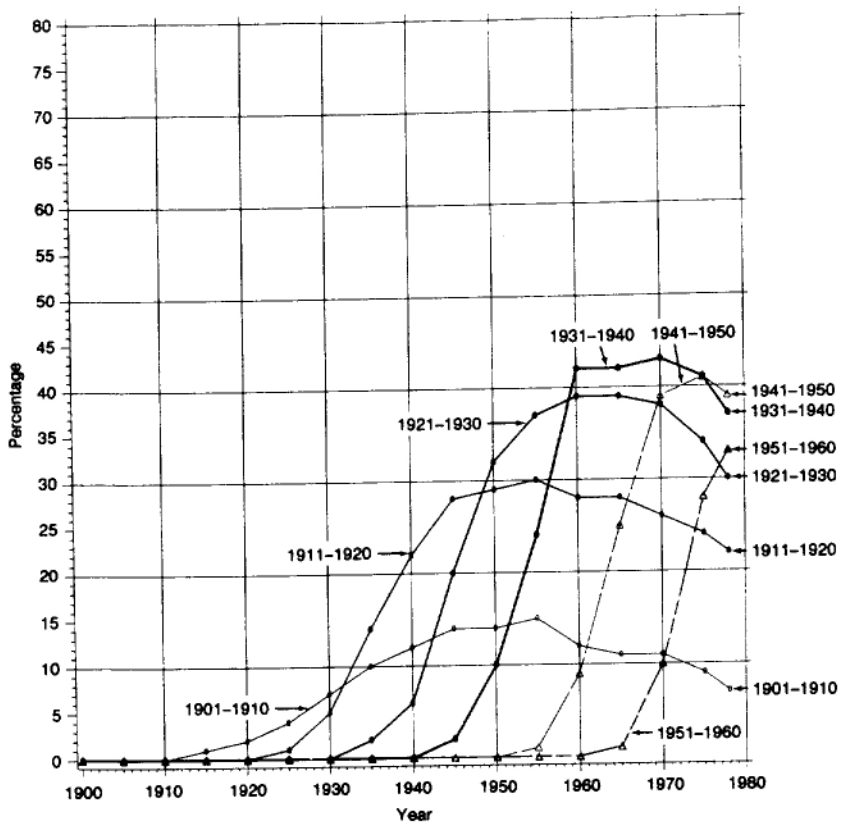


FIGURE 6.—Changes in the prevalence of cigarette smoking among successive birth cohorts of black U.S. women, 1900–1978

SOURCE: Data from National Center for Health Statistics, National Health Interview Surveys, 1978–1980 (combined).

In contrast with white-collar women and homemakers, the 1941–1950 cohort of blue-collar women has the highest peak prevalence (Figure 11). The 1931–1940 and 1941–1950 cohorts each exhibit approximately the same smoking rates in 1978 as did the previous cohort 10 years earlier. Only the 1951–1960 cohort of blue-collar women has significant potential to redirect this trend of increasing prevalence downward, and this will depend on whether this cohort can sustain its current downward trend in smoking prevalence.

Service workers represent another important category of employed women, and their birth cohort smoking patterns resemble white-collar workers in some ways and blue-collar workers in other

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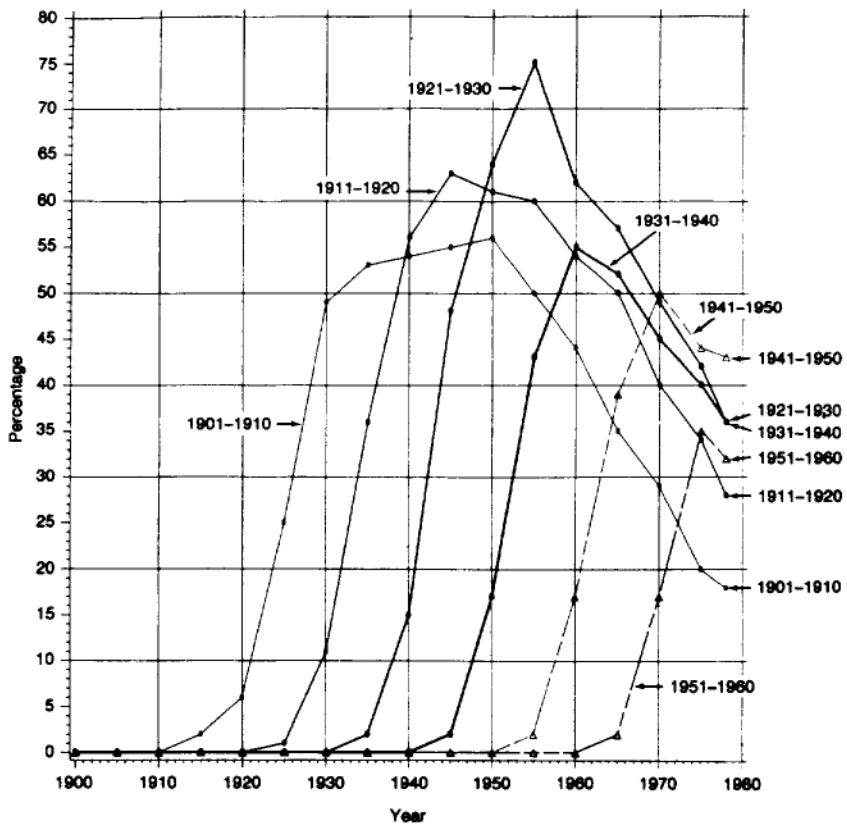


FIGURE 7.—Changes in the prevalence of cigarette smoking among successive birth cohorts of U.S. men employed in white-collar occupations, 1900–1978

SOURCE: Data from National Center for Health Statistics, National Health Interview Surveys, 1978–1980 (combined).

ways (Figure 12). Like white-collar women, female service workers reached their highest peak prevalence with the 1931–1940 birth cohort, and subsequent cohorts have experienced much lower peaks. However, like blue-collar women, the 1921–1930 cohort of female service workers continued to smoke at a higher rate in 1978 than the previous cohort at the same age. This pattern becomes more pronounced with the 1931–1940 cohort, but then reverses, with the 1941–1950 cohort reporting a lower smoking prevalence in 1978 than the previous cohort 10 years ago.

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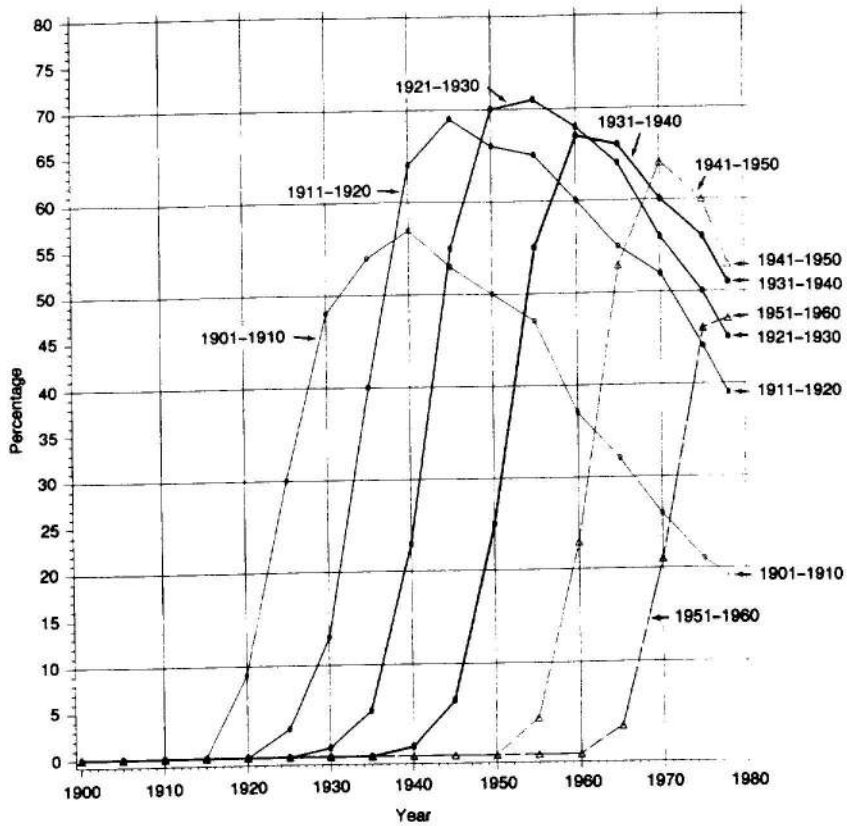


FIGURE 8.—Changes in the prevalence of cigarette smoking among successive birth cohorts of U.S. men employed in blue-collar occupations, 1900–1978

SOURCE: Data from National Center for Health Statistics, National Health Interview Surveys, 1978–1980 (combined).

Race

Among black men there are almost twice as many blue-collar workers as white-collar workers (Table 16). This contrasts with white men, who fall about equally into the white-collar and blue-collar categories. Additionally, blacks of both sexes are more heavily concentrated in the service category of workers, making this category an important one to consider when examining occupational differences in smoking by race. Black men are also almost twice as

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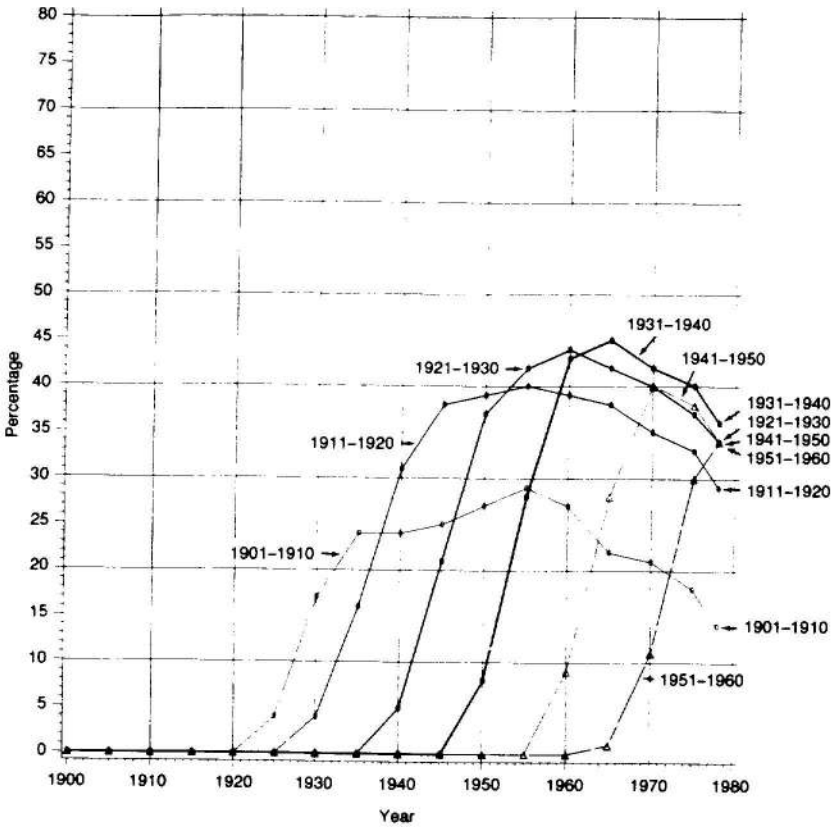


FIGURE 9.—Changes in the prevalence of cigarette smoking among successive birth cohorts of U.S. women employed in white-collar occupations, 1900–1978

SOURCE: Data from National Center for Health Statistics, National Health Interview Surveys, 1978–1980 (combined).

likely as white men to fall into the "Not Employed" category, which includes both unemployed people and those "not in the labor force."

The differences in smoking prevalence between black men and white men parallel the differences between blue-collar and white-collar workers (Table 17), with black men having a considerably higher smoking prevalence (47.7 percent) than white men (40.2 percent). Among men, blue-collar workers have considerably higher smoking rates than white-collar workers within each racial group, with black male blue-collar workers having the highest smoking prevalence (52.1 percent).

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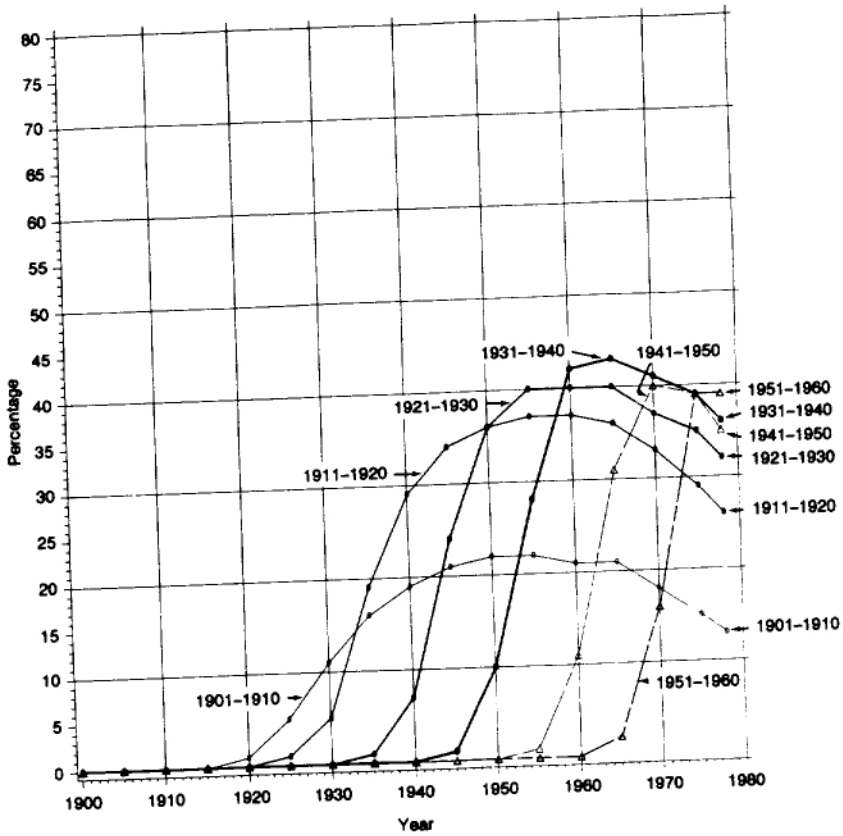


FIGURE 10.—Changes in the prevalence of cigarette smoking among successive birth cohorts of U.S. women classified as homemakers, 1900–1978

SOURCE: Data from National Center for Health Statistics, National Health Interview Surveys, 1978–1980 (combined).

Among black women, there is little difference in smoking prevalence between occupations, although homemakers have a somewhat higher smoking rate (Table 17). However, among white women, the expected white-collar, blue-collar, service worker differences prevail, with blue-collar and service workers having a higher smoking prevalence (39.6 and 38.7 percent, respectively) than white collar workers (32.0 percent).

As shown in Table 17, black workers are considerably less likely than their white counterparts to be heavy smokers (smoking 20 or more cigarettes daily). This holds true for all categories of workers

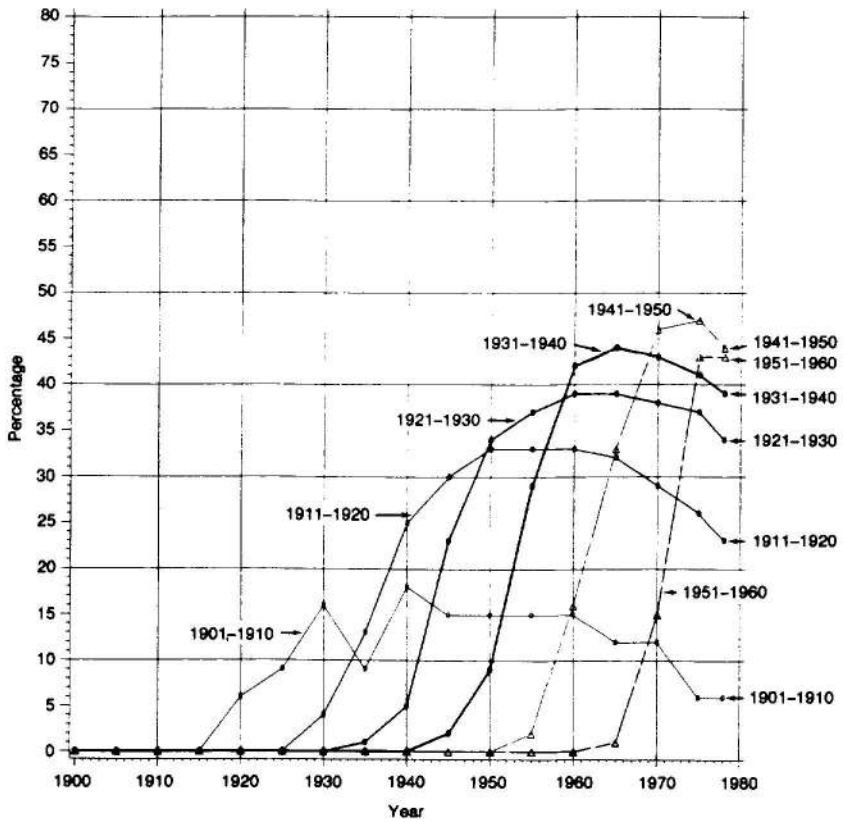


FIGURE 11.—Changes in the prevalence of cigarette smoking among successive birth cohorts of U.S. women employed in blue-collar occupations, 1900–1978

SOURCE: Data from National Center for Health Statistics, National Health Interview Surveys, 1978–1980 (combined).

and for men and women. Among white women and black men, blue-collar workers are somewhat more likely than others to be heavy smokers. The consumption differences between white workers and black workers are even more pronounced when the percentage of smokers smoking 40 or more cigarettes daily is examined. White men are about four times more likely than black men to smoke 40 or more cigarettes daily, regardless of occupation. Similarly, white women are about three times more likely than black women to smoke more than 40 cigarettes daily, regardless of occupational group.

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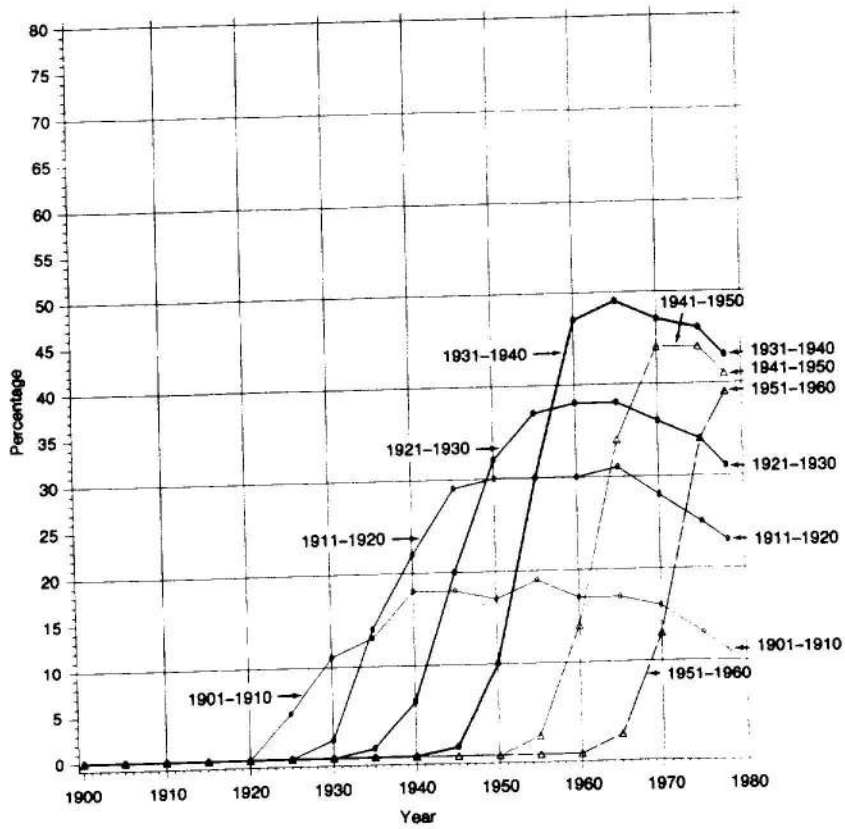


FIGURE 12.—Changes in the prevalence of cigarette smoking among successive birth cohorts of U.S. women employed in service occupations, 1900–1978

SOURCE: Data from National Center for Health Statistics, National Health Interview Surveys, 1978–1980 (combined).

Among women, there are minimal racial or occupational differences in the proportion of current smokers who have attempted to quit smoking. However, blue-collar, service, and not employed black men are somewhat less likely than all other groups to have attempted to quit. Among those who have ever smoked, white-collar male workers are the most likely to have quit smoking. Blue-collar and service workers generally have lower quit rates than white-collar workers, and this pattern holds true for white men and black men and white women. Black women have low quit rates regardless of occupational category. Additionally, black male blue-collar work-

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TABLE 16.—Estimates of occupational distribution by sex and race, aged 20 to 64 years, United States, 1978–1980

Classification	Men (percentage)		Women (percentage)	
	White	Black	White	Black
White-collar	40.8	23.0	41.8	31.1
Blue-collar	40.6	45.2	9.0	11.0
Service	5.5	11.5	9.4	22.8
Homemaking	—	—	42.6	34.7
Not employed	10.0	18.8	—	—

SOURCE: National Center for Health Statistics, National Health Interview Surveys, 1970 and 1978–1980 (combined). (See Technical Addendum.)

ers have a considerably lower quit rate (24.9 percent) than white male blue-collar workers (36.0 percent).

In summary, black workers are more likely than white workers to be cigarette smokers, with black male blue-collar workers having the highest smoking rate. In contrast, white workers are much more likely than black workers to be heavy smokers, regardless of occupational category. White workers are more likely to have quit smoking, with the exception of white female blue-collar workers. Black male blue-collar workers and all black female workers have low quit rates. Among black men and white men and white women, white-collar workers have both lower rates of current smoking and higher proportions of former smokers than blue-collar or service workers. The one group that deviates from this pattern is black women; white-collar workers have a higher rate of current smoking and a somewhat lower proportion of former smokers than blue-collar or service workers, and homemakers have a relatively high rate of current smoking.

Summary and Conclusions

1. Among men, a substantially higher percentage of blue-collar workers than white-collar workers currently smoke cigarettes. Operatives and kindred workers have the highest rate of current smoking (approaching 50 percent), with professional, technical, and kindred workers having the lowest rates of current smoking (approximately 26 percent).
2. Among women, blue-collar versus white-collar differences are less pronounced, but still show a higher percentage of current smokers among blue-collar workers. Occupational categories

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TABLE 17.—Estimates (percentages) of smoking prevalence, heavy smoking, and quitting behavior by race, sex, and occupation, aged 20 to 64 years, United States 1978–1980

Occupation	White		Black	
	Men	Women	Men	Women
Current smokers				
Total	40.1	33.3	47.7	34.6
White-collar	32.8	32.0	38.4	35.2
Blue-collar	46.5	39.6	52.1	33.4
Service	47.0	38.7	48.8	33.5
Homemaking	—	32.9	—	37.1
Not employed	43.6	—	47.6	—
Smoke ≥20 daily				
Total	74.5	62.8	43.7	27.6
White-collar	74.9	62.5	40.0	29.5
Blue-collar	75.4	66.0	45.9	31.8*
Service	72.1	60.9	42.5*	31.4
Homemaking	—	63.2	—	23.5
Not employed	73.4	—	42.1	—
Smoke ≥40 daily				
Total	20.7	12.4	5.4	4.0
White-collar	22.5	12.6	3.3	4.2
Blue-collar	20.0	12.0	6.0	5.2*
Service	19.0	13.9	2.3*	3.5
Homemaking	—	12.2	—	4.0
Not employed	19.9	—	8.4	—
Current smokers who have made a serious attempt to quit				
Total	61.2	59.4	53.6	60.0
White-collar	63.6	59.7	62.1	60.0
Blue-collar	59.1	58.5	53.3	59.9*
Service	57.2	57.5	50.0*	58.1
Homemaking	—	60.5	—	64.2
Not employed	64.6	—	49.5	—
Ever smoked who are former smokers				
Total	41.4	33.1	28.6	24.6
White-collar	48.8	34.6	34.4	23.6
Blue-collar	36.0	24.6	24.9	24.8
Service	32.6	26.6	30.8	25.3
Homemaking	—	34.3	—	24.4
Not employed	35.2	—	29.7	—

* < 100 cases in the denominator (unweighted sample).
SOURCE: National Center for Health Statistics, National Health Interview Surveys, 1978–1980 (combined). (See Technical Addendum.)

with the highest rates of current smoking include craftsmen and kindred workers (approximately 45 percent current smokers) and managers and administrators (38 percent), with the

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lowest rate of current smoking occurring among women employed in professional, technical, and kindred occupations (26 percent).

3. Occupational differences in daily cigarette consumption are generally modest. For both men and women, the highest daily consumption of cigarettes occurs among managers and administrators and craftsmen and kindred workers.
4. Blue-collar workers (both men and women) report an earlier onset of smoking than white-collar workers. A substantial fraction of smokers report initiation of smoking at ages coincident with their entry into the workforce.
5. Blue-collar occupations have a lower percentage of former smokers than white-collar occupations; this difference is most pronounced among men. Among women, the pattern for homemakers closely parallels that of white-collar women.
6. Black workers have higher smoking rates than white workers, with black male blue-collar workers exhibiting the highest smoking rate. Black workers also have lower quit rates than white workers. In contrast, white workers of both sexes are more likely to be heavy smokers regardless of occupational category.

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Technical Addendum: National Health Interview Survey Estimates

Estimates of current smoking reported in this chapter were obtained from the 1978, 1979, and 1980 National Health Interview Surveys (NHIS). A special data tape was prepared by the National Center for Health Statistics to allow linkages across surveys, thereby permitting analyses of the combined 1978–1980 NHIS. This increase in sample size provides greater statistical reliability in the estimates of population subgroups of interest to this Report.

The smoking items were completed by 12,105 respondents in 1978, 24,727 in 1979, and 10,649 in 1980, resulting in a combined sample of 47,481. Standard NHIS protocols were followed in each survey, including a random probability sample design of the noninstitutionalized adult U.S. population, and face-to-face interviews using U.S. Bureau of the Census interviewers. Response rates routinely exceeded 95 percent.

Given the large samples and exceptionally high response rates, the NHIS estimates are generally regarded as the best available estimates of national smoking patterns. Because the focus of this Report is on occupational differences in smoking, analysis of the 1978–1980 NHIS was restricted to respondents 20 to 64 years of age (n = 36,745).

The definition of a current smoker was obtained from the following question asked in the surveys: "Do you smoke cigarettes now?" This includes both regular and occasional smokers who are currently smoking. For estimates of average age of initiation and quitting behavior, the denominator includes both current and former smokers who describe themselves as having ever smoked "fairly regularly."

The 1978–1980 National Health Interview Surveys utilized the occupational coding scheme used in the 1970 U.S. Census. The occupational subgroups examined in this Report, along with their respective code numbers, are listed in Table 18.

Accompanying each NHIS public use data tape is an algorithm that weights the sample to the 1970 U.S. population. All estimates of smoking behavior reported here use this algorithm.

Data from the 1970 NHIS (reported in Tables 1, 11–15) were obtained from the 1970 NHIS public use tape, which contains data from 76,239 respondents who completed questions on their smoking behavior. Of these, 59,557 respondents were between the ages of 20 and 64. Because the occupational classifications were revised between the 1970 and the 1978–1980 NHIS, changes in smoking behavior could be reported only for the specific occupations whose classification did not change.

As a preliminary step in the analysis of the 1978–1980 NHIS, the equivalency of the three NHIS samples within occupational groups

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TABLE 18.—Occupational codes and categories used in the 1978–1980 National Health Interview Surveys

Occupation category	Occupations included	U.S. Census Bureau occupation codes[1]
Professional, technical, and kindred	Engineers and architects	002, 006–023
	Scientists	034–054, 091–096
	Health workers	061–085
	Teachers, including college	102–145
	Engineering, science technicians	150–162
	All other professional, technical, kindred workers	001, 003–005, 024–033, 055–060, 086–090, 097–101, 146–149, 163–199
Managers, admin., except farm		201–245
Sales workers		260–280
Clerical and kindred workers	Bookkeepers	305
	Office machine operators	341–355
	Mail handlers, postal clerks, telegraph messengers	331, 332, 361, 383
	Secretaries, stenographers, typists, receptionists	364–372, 276, 391
	All other clerical workers	301–304, 306–330, 333–340, 356–360, 362, 363, 373–375, 377–382, 384–390, 392–399
Craftsmen and kindred workers	Carpenters	415–416
	Other construction craftsmen	410–412, 421, 430, 431, 436, 440, 510–512, 520–523, 534, 550, 560
	Mechanics and repairmen	470–495
	Metal craftsmen, except mechanics	403, 404, 442, 446, 454, 461, 462, 502–504, 514, 533, 535–540, 561, 562
	All other craftsmen	401–402, 405–409, 413, 414, 417–421, 422-429, 432–435, 437–439, 441, 443–445, 447–453, 455–460, 463–469, 496–501, 505–509, 513, 515–519, 524–532, 541–549, 551–559, 563–580
Operatives and kindred workers	Operatives, except transport	601–695
	Transport equipment operatives	701–715
Laborers, except farm		740–785
Service workers	Cleaning service	901–903
	Food service	910–916
	Health and personal service	921–954
	Protective service	960–965
	Private household workers	980–984
Farm	Farmers and farm managers	801, 802
	Farm laborers and foremen	821–824

[1] White-collar occupations are designated by code values 001–399; blue-collar occupations are designated by code values 400-785.

was examined in regard to smoking prevalence and heavy smoking. These results showed a high degree of statistical equivalency across

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TABLE 19.—Estimates of the percentage of current smokers by sex, occupation, and NHIS sample (1978, 1979, 1980), aged 20 to 64 years

Occupation	Men				Women			
	1978	1979	1980	P value	1978	1979	1980	P value
White-collar total	32.5	33.4	33.1	NS[1]	32.9	32.4	30.8	NS
Professional, technical and kindred workers	28.1	24.6	24.3	NS	26.3	26.8	26.6	NS
Managers and administrators, except farm	36.1	37.9	34.6	NS	44.8	36.3	34.1	.03
Sales workers	36.8	39.0	45.9	NS	35.1	34.4	31.2	NS
Clerical and kindred workers	37.6	38.5	37.4	NS	33.1	34.3	32.3	NS
Blue-collar total	46.8	46.8	47.6	NS	41.9	36.2	36.2	NS
Craftsmen and kindred workers	45.7	45.3	47.2	NS	49.2	39.0	45.6	NS
Operatives and kindred workers	48.6	48.8	48.6	NS	41.1	35.5	33.9	NS
Laborers, except farm	46.4	47.0	46.4	NS	36.0	39.4	33.3	NS
Service	45.1	41.9	54.8	.005	39.9	36.0	36.2	NS
Farm	33.1	32.0	28.7	NS	*[2]	*	*	*
Usual activity, homemaking	—	—	—	—	33.9	33.4	31.6	NS

[1] Not statistically significant ($p > 0.05$).
[2] Not enough cases for valid chi-square test (the expected cell frequency for one or more cells was less than five).

samples. As is reported in Table 19, among men one difference was detected for smoking prevalence, but this difference showed an inconsistent pattern across samples. Among women employed as managers or administrators, there was a remarkable 10.7 percentage point decline in smoking prevalence between 1978 and 1980, which is over twice as large as the 10-year net decline between 1970 and 1980 (see Table 11).

One possible explanation for this large 3-year decline in smoking prevalence is random fluctuation in the survey estimate. However, if this short-term time trend for female managers and administrators is valid, it would be of considerable interest. Given that the 1970–1978 comparisons already show female managers and administrators to be quitting at a relatively high rate (when compared with other

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TABLE 20.—Estimates of the percentage of current smokers who smoke 40 or more cigarettes daily by sex, occupation, and NHIS sample (1978, 1979, 1980), aged 20 to 64 years

Occupation	Men				Women			
	1978	1979	1980	P value	1978	1979	1980	P value
White-collar total	23.6	21.0	19.3	NS[1]	10.1	11.4	14.0	NS
Professional, technical and kindred workers	20.9	17.0	14.2	NS	9.0	8.6	14.1	NS
Managers and administrators, except farm	25.8	23.9	24.6	NS	15.7	16.0	15.2	NS
Sales workers	31.0	21.2	20.5	NS	3.4	9.4	17.3	.05
Clerical and kindred workers	16.0	20.5	15.4	NS	9.8	11.8	13.1	NS
Blue-collar total	19.4	17.4	18.7	NS	11.3	11.7	10.5	NS
Craftsmen and kindred workers	22.7	19.1	22.2	NS	16.1	13.0	22.9	NS
Operatives and kindred workers	16.9	16.6	13.8	NS	11.0	11.1	7.1	NS
Laborers, except farm	13.9	13.6	18.9	NS	•[2]	•	•	•
Service	13.4	15.9	18.9	NS	11.1	10.5	11.4	NS
Farm	20.5	11.5	17.2	NS	•	•	•	•
Usual activity, homemaking	—	—	—	—	10.4	10.6	12.9	NS

[1] Not statistically significant ($p > 0.05$).
[2] Not enough cases for valid chi-square test (the expected cell frequency for one or more cells was less than five).

female occupational groups), it would seem prudent to closely monitor the smoking patterns of this occupational cohort of women.

In regard to heavy smoking (see Table 20), no sample differences were found for men. Among female salesworkers, there was a striking 500 percent proportionate increase between 1978 and 1980 in the percentage of smokers of 40-plus cigarettes a day, which again must be interpreted with caution. Overall, 50 separate chi-square tests were examined, and 3 were statistically significant at $p \leq 0.05$—which would be expected solely on the basis of chance.

Detailed presentations of NHIS estimates of smoking prevalence are provided in Table 21 (1978–1980) and Table 22 (1970–1980 net change) for all occupational codes with 100 or more cases in the

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combined 1978–1980 NHIS (unweighted sample). In Table 23 are provided a comprehensive list of all occupational codes with 100 or more cases in the 1978–1980 NHIS and the estimated percentage of men and women, aged 20 to 64 years, who are employed in each occupation. Figures 13 through 18 depict results from birth cohort analyses that were briefly summarized in the text, including male professional, technical, and kindred workers (Figure 13), managers and administrators (Figure 14), craftsman and kindred workers (Figure 15), and operatives and kindred workers (Figure 16), and female professional, technical, and kindred workers (Figure 17), and clerical and kindred workers (Figure 18).

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TABLE 21.—Estimates of the percentage of current smokers by selected occupations, aged 20 to 64 years, United States, 1978–1980

Occupation	Men	Women	Total
WHITE-COLLAR			
Professional, technical, and kindred workers			
Accountants (001)	26.8	30.4	28.2
Electrical and electronic engineers (012)	16.2	33.0[1]	16.4
Lawyers (031)	21.9	21.4[1]	21.8
Personnel and labor relations workers (056)	30.9[1]	37.9[1]	34.1
Physicians, medical and osteopathic (065)	18.1[1]	18.2[1]	18.1
Registered nurses (075)	46.4[1]	27.2	28.0
Social workers (100)	42.6[1]	37.3[1]	39.0
Elementary school teachers (142)	18.8[1]	19.8	19.6
Secondary school teachers (144)	24.9	24.8	24.9
Managers and administrators, except farm			
Bank officers and financial managers (202)	35.9	28.1[1]	32.9
Office managers n.e.c.[2] (220)	43.9[1]	25.4[1]	45.0
Officials and administrators, public administrators n.e.c.[2] (222)	22.2[1]	20.3[1]	21.6
Restaurant, cafeteria, and bar managers (230)	53.9[1]	52.4[1]	53.3
Sales managers and department heads, retail trade (231)	28.7[1]	33.8[1]	30.5
Managers and administrators n.e.c. (245)	36.2	38.0	36.6
Sales workers			
Insurance agents, brokers, and underwriters (265)	41.1[1]	41.0[1]	41.1
Real estate agents and brokers (270)	27.8	48.1[1]	36.4
Sales representatives, manufacturing industries (281)	43.2	32.9[1]	41.2
Sales representatives, wholesale trade (282)	48.1	45.8[1]	47.9
Sales clerks, retail trade (283)	39.6	30.5	33.7
Salesmen, retail trade (284)	42.8[1]	39.3[1]	42.4
Clerical and kindred workers			
Bank tellers (301)	0.0[1]	25.7	24.7
Bookkeepers (305)	42.9[1]	36.5	37.1
Cashiers (310)	43.4[1]	44.2	44.1
Estimators and investigators n.e.c. (321)	28.4[1]	35.9[1]	33.1
Expediters and production controllers (323)	44.9[1]	43.1[1]	44.3
Computer and peripheral equipment operators (343)	31.3[1]	44.7[1]	38.5
Postal clerks (361)	38.2[1]	24.9[1]	33.9
Receptionists (364)	56.5[1]	31.0	31.8
Secretaries n.e.c. (372)	61.7[1]	30.9	31.2
Stock clerks and storekeepers (381)	38.1	31.2[1]	35.3
Typists (391)	10.3[1]	33.0	31.7
Clerical workers, miscellaneous (394)	34.9[1]	33.3	33.6
Clerical workers, not specified (395)	33.5[1]	28.4[1]	29.1

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TABLE 21.—Continued

Occupation	Men	Women	Total
BLUE-COLLAR			
Craftsmen and kindred workers			
Carpenters (415)	50.8	70.4[1]	50.9
Electricians (430)	48.3	100.0[1]	48.5
Foremen n.e.c. (441)	42.7		44.2
Machinists (461)	43.4	53.0[1]	43.7
Automobile mechanics (473)	50.5	54.7[1]	50.5
Heavy equipment mechanics, incl. diesel (481)	47.4	49.5[1]	47.7
Painters, construction and maintenance (510)	55.1	61.4[1]	54.0
Plumbers and pipe fitters (522)	47.1	39.1[1]	47.1
Operatives, except transport			
Assemblers (602)	48.7	42.9	45.3
Checkers, examiners, and inspectors; manufacturing (610)	45.8	39.3	42.3
Packers and wrappers, except meat and produce (643)	47.2[1]	40.0	42.3
Sewers and stitchers (663)	26.9[1]	25.8	25.9
Welders and flame-cutters (680)	47.8	28.9[1]	46.8
Machine operatives, miscellaneous, specified (690)	43.7	41.0	42.7
Machine operatives, not specified (692)	42.9[1]	50.3[1]	44.7
Miscellaneous operatives (694)	43.3	40.1[1]	42.4
Transport operatives			
Bus drivers (703)	50.3[1]	35.2[1]	42.7
Deliverymen and routemen (705)	42.4	46.1[1]	42.7
Fork lift and tow motor operatives (706)	49.3[1]	35.4[1]	48.7
Truck drivers (715)	53.6	62.7[1]	53.7
Workers, except farm			
Construction laborers, except carpenters' helpers (751)	53.0	52.8[1]	53.0
Freight and material handlers (753)	42.5	34.6[1]	41.6
Gardeners and groundskeepers, except farm (755)	46.1	43.7[1]	45.9
Stock handlers (762)	37.4[1]	34.5[1]	36.6
Laborers, not specified (785)	38.0	46.3[1]	39.0
Farm workers			
Farmers (801)	28.1	29.9[1]	28.3
Farm laborers, wage workers (822)	39.0	25.6[1]	34.9

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TABLE 21.—Continued

Occupation	Men	Women	Total
Service workers			
Cleaners and charwomen (902)	49.8 [1]	30.5	38.0
Janitors and sextons (903)	49.8	39.0 [1]	47.1
Cooks, except private household (912)	45.0 [1]	31.1	35.9
Waiters (915)	44.7 [1]	51.1	50.4
Food service workers n.e.c. [2], except private household (916)	42.1 [1]	24.6	27.0
Nursing aides, orderlies, and attendants (925)	48.2 [1]	41.0	42.0
Practical nurses (926)	55.3 [1]	40.3	41.2
Child care workers, except private household (942)	0.0 [1]	28.9	28.4
Hairdressers and cosmetologists (944)	63.2 [1]	37.5	39.0
Guards and watchmen (962)	50.5	35.7 [1]	47.3
Policemen and detectives (964)	44.5	51.5 [1]	45.1
Maids and servants, private household (984)	55.0 [1]	32.1	33.1

[1] < 100 cases in the denominator (unweighted sample).

[2] Not elsewhere classified.

SOURCE: National Center for Health Statistics Health Interview Surveys, 1978–1980 (combined).

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TABLE 22.—Estimates of the net change in smoking prevalence by sex and selected occupations, age 20 to 64 years, United States, 1970–1980

Occupation	Men	Women	Total
WHITE-COLLAR			
Professional, technical, and kindred workers			
Accountants (001)/(000)	−6.8	−0.4	−4.6
Electrical and electronic engineers (012)/(083)	−4.0	−18.0[1]	−4.1
Personnel and labor relations workers (056)/(154)	−8.9	−8.2	−2.0
Physicians, medical and osteopathic (065)/(153,162)	−8.5[1]	−29.3[1]	−10.0
Registered nurses (075)/(150)	+10.2[1]	−12.3	−11.4
Social workers (100)/(171)	+3.8[1]	+11.0[1]	+7.7
Elementary school teachers (142)/(182)	−10.5[1]	−1.2	−2.6
Secondary school teachers (144)/(183)	−3.5	−1.3	−2.4
Managers and administrators, except farm			
Officials and administrators, public administrators n.e.c.[2] (222)/(270)	16.3[1]	7.3[1]	−15.4
Managers and administrators n.e.c. (245)/(290)	−8.1	−4.2	−7.3
Sales workers			
Insurance agents, brokers, and underwriters (265)/(385)	−9.8[1]	−22.6[1]	−11.3
Real estate agents and brokers (270)/(393)	14.6	+3.8[1]	−6.8
Clerical and kindred workers			
Bank tellers (301)/(305)	−45.7[1]	−9.0	−11.3
Bookkeepers (305)/(310)	−1.3[1]	−4.2	−3.9
Cashiers (310)/(312)	+2.6[1]	+3.7	+3.5
Postal clerks (361)/(340)	−1.0[1]	−15.7[1]	−5.7
Receptionists (364)/(341)	—	−10.6	−9.8
Secretaries n.e.c. (372)/(342)	−0.8[1]	−8.1	−8.0
Stock clerks and storekeepers (381)/(350)	−12.0	8.2[1]	−12.2
Typists (391)/(360)	−52.8[1]	4.9	−7.1
BLUE-COLLAR			
Craftsmen and kindred workers			
Carpenters (415)/(411)	−4.1	+50.3[1]	−3.7
Electricians (430)/(421)	+3.9	+33.4[1]	−3.9
Foremen n.e.c. (441)/(430)	−8.9	—	−8.9
Machinists (461)/(465)	−8.7	−7.3[1]	−8.5
Automobile mechanics (473)/(472)	−4.5	+22.3[1]	−4.3
Painters, construction and maintenance (510)/(495)	−17.1	+17.7[1]	−17.3
Plumbers and pipe fitters (522)/(510)	−4.1	—	−4.1

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TABLE 22.—Continued

Occupation	Men	Women	Total
Operatives, except transport			
Assemblers (602)/(631)	–7.0	–2.0	–4.6
Checkers, examiners, and inspectors, manufacturing (610)/(643)	–8.7	–0.3	–4.4
Packers and wrappers, except meat and produce (643)/(693)	–8.0 [1]	+2.6	–0.7
Sewers and stitchers (663)/(705)	–18.8 [1]	–0.5	–0.8
Welders and flame-cutters (680)/(721)	–3.5	–12.7 [1]	–3.9
Transport operatives			
Bus drivers (703)/(641)	+6.6 [1]	+11.2 [1]	+4.0
Deliverymen and routemen (705)/(650)	–11.6	+10.0 [1]	–10.9
Farm workers			
Farmers (801)/(200)	–4.4	+9.3 [1]	–3.4
Farm laborers, wage workers (822)/(902)	–14.5	–6.2 [1]	–14.8
Service workers			
Cleaners and charwomen (902)/(824)	–14.3 [1]	–2.3	–1.6
Cooks, except private household (912)/(825)	–19.2 [1]	–5.5	–9.4
Janitors and sextons (903)/(834)	–1.9	+10.4 [1]	–0.4
Waiters (915)/(875)	–2.9 [1]	–9.0	–8.7
Practical nurses (926)/(842)	–31.1 [1]	+4.3	+3.7
Hairdressers and cosmetologists (944)/(843)	–5.4 [1]	–7.4	–8.0
Guards and watchmen (962)/(851)	–5.5	+17.6 [1]	–6.9
Policemen and detectives (964)/(853)	–3.2	+24.4 [1]	–2.0

[1] < 100 cases in the denominator (unweighted sample).

[2] Not elsewhere classified.

SOURCE: National Center for Health Statistics Health Interview Surveys, 1978–1980 (combined).

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TABLE 23.—Estimates of percentage of U.S. population, aged 20 to 64 years, in selected occupations, 1978–1980

Occupation	Men	Women	Total
WHITE-COLLAR			
Professional, technical, and kindred workers			
Accountants (001)	1.2	0.7	1.0
Electrical and electronic engineers (012)	0.6	0.0	0.3
Lawyers (031)	0.7	0.1	0.4
Personnel and labor relations workers (056)	0.5	0.4	0.4
Physicians, medical and osteopathic (065)	0.5	0.1	0.3
Registered nurses (075)	0.1	2.0	1.1
Social workers (100)	0.2	0.4	0.3
Elementary school teachers (142)	0.5	2.1	1.3
Secondary school teachers (144)	1.0	1.0	1.0
Managers and administrators, except farm			
Bank officers and financial managers (202)	0.7	0.4	0.5
Office managers n.e.c.[1] (220)	0.1	0.3	0.2
Officials and administrators; public administrators n.e.c. (222)	0.4	0.2	0.3
Restaurant, cafeteria, and bar managers (230)	0.5	0.3	0.4
Sales managers and department heads, retail trade (231)	0.4	0.2	0.3
Managers and administrators n.e.c. (245)	9.4	2.4	5.8
Sales workers			
Insurance agents, brokers, and underwriters (265)	0.6	0.2	0.4
Real estate agents and brokers (270)	0.6	0.4	0.5
Sales representatives, manufacturing industries (281)	0.9	0.2	0.5
Sales representatives, wholesale trade (282)	0.9	0.1	0.5
Sales clerks, retail trade (283)	0.5	1.0	1.6
Salesmen, retail trade (284)	0.5	0.1	0.3
Clerical and kindred workers			
Bank tellers (301)	0.0	0.6	0.3
Bookkeepers (305)	0.3	2.7	1.5
Cashiers (310)	0.2	1.5	0.9
Estimators and investigators n.e.c. (321)	0.3	0.4	0.4
Expediters and production controllers (323)	0.4	0.2	0.3
Computer and peripheral equipment operators (343)	0.4	0.4	0.4
Postal clerks (361)	0.4	0.2	0.3
Receptionists (364)	0.0	0.6	0.3
Secretaries n.e.c. (372)	0.1	5.5	2.9
Stock clerks and storekeepers (381)	0.6	0.4	0.5
Typists (391)	0.1	1.1	0.6
Clerical workers, miscellaneous (394)	0.3	1.1	0.7
Clerical workers, not specified (395)	0.1	0.7	0.8

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TABLE 23.—Continued

Occupation	Men	Women	Total
BLUE-COLLAR			
Craftsmen and kindred workers			
Carpenters (415)	2.4	0.0	1.2
Electricians (430)	1.0	0.0	0.5
Foremen n.e.c. (441)	3.0	0.4	1.7
Machinists (461)	1.1	0.0	0.5
Automobile mechanics (473)	1.7	0.0	0.8
Heavy equipment mechanics, incl. diesel (481)	1.2	0.0	0.6
Painters, construction and maintenance (510)	0.7	0.1	0.4
Plumbers and pipe fitters (522)	0.8	0.0	0.4
Operatives, except transport			
Assemblers (602)	0.8	1.1	0.9
Checkers, examiners, and inspectors, manufacturing (610)	0.7	0.7	0.7
Packers and wrappers, except meat and produce (643)	0.3	0.6	0.5
Sewers and stitchers (663)	0.1	1.3	0.7
Welders and flame-cutters (680)	1.0	0.1	0.5
Machine operatives, miscellaneous, specified (690)	1.7	0.9	1.3
Machine operatives, not specified (692)	0.4	0.1	0.2
Miscellaneous operatives (694)	0.7	0.3	0.5
Transport operatives			
Bus drivers (703)	0.3	0.3	0.3
Deliverymen and routemen (705)	0.7	0.1	0.4
Fork lift and tow motor operatives (706)	0.6	0.0	0.3
Truck drivers (715)	3.0	0.0	1.5
Workers, except farm			
Construction laborers, except carpenters' helpers (751)	1.2	0.0	0.6
Freight and material handlers (753)	0.8	0.1	0.4
Gardeners and groundskeepers, except farm (755)	0.7	0.0	0.4
Stock handlers (762)	0.5	0.2	0.3
Not specified laborers (785)	0.7	0.1	0.4
Farm workers			
Farmers (801)	2.0	0.2	1.1
Farm laborers, wage workers (822)	0.7	0.3	0.5

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TABLE 23.—Continued

Occupation	Men	Women	Total
Service workers			
Cleaners and charwomen (902)	0.5	0.7	0.6
Janitors and sextons (903)	1.3	0.4	0.8
Cooks, except private household (912)	0.6	1.0	0.8
Waiters (915)	0.2	1.4	0.8
Food service workers n.e.c., except private household (916)	0.1	0.6	0.4
Nursing aides, orderlies, and attendants (925)	0.2	1.3	0.8
Practical nurses (926)	0.1	0.7	0.4
Child care workers, except private household (942)	0.0	0.6	0.3
Hairdressers and cosmetologists (944)	0.1	0.8	0.4
Guards and watchmen (962)	0.7	0.2	0.5
Policemen and detectives (964)	0.9	0.1	0.4
Maids and servants, private household (984)	0.0	0.7	0.4
All other occupations	30.2	15.9	22.7
Not in labor force	10.9	38.6	25.3

NOTE: Includes all occupational codes with at least 100 cases (aged 20 to 64) in the 1978–1980 HIS (unweighted sample).

[1] Not elsewhere classified.

SOURCE: National Center for Health Statistics Health Interview Surveys, 1978-1980 (combined).

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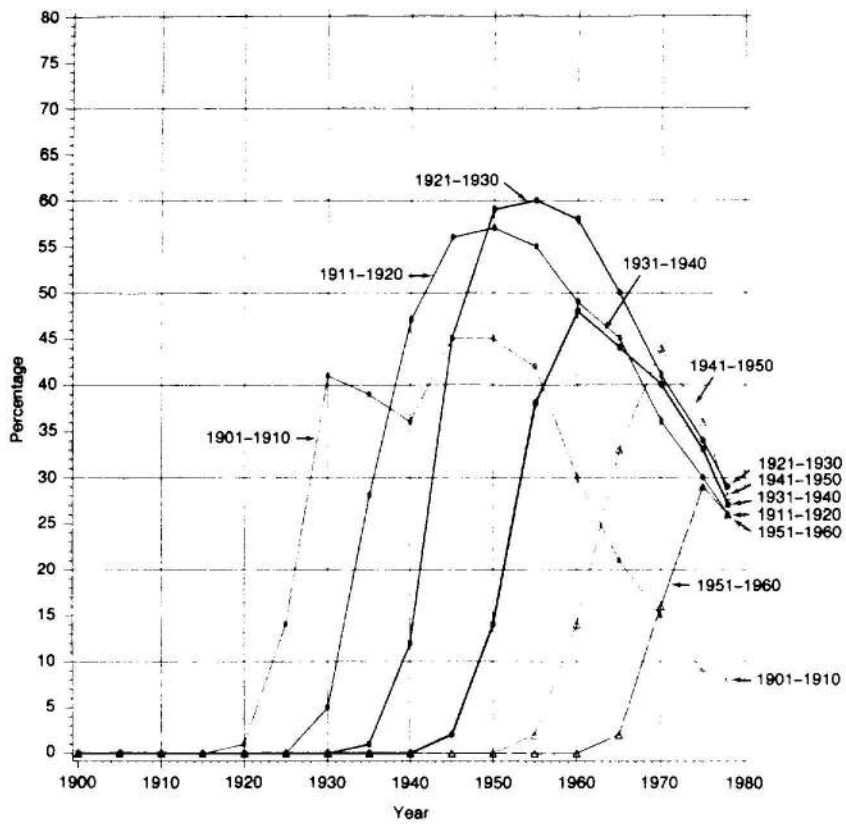


FIGURE 13.—Changes in the prevalence of cigarette smoking among successive birth cohorts of U.S. men employed in professional, technical, and kindred occupations, 1900–1978

SOURCE: Data from National Center for Health Statistics, National Health Interview Surveys, 1978–1980 (combined).

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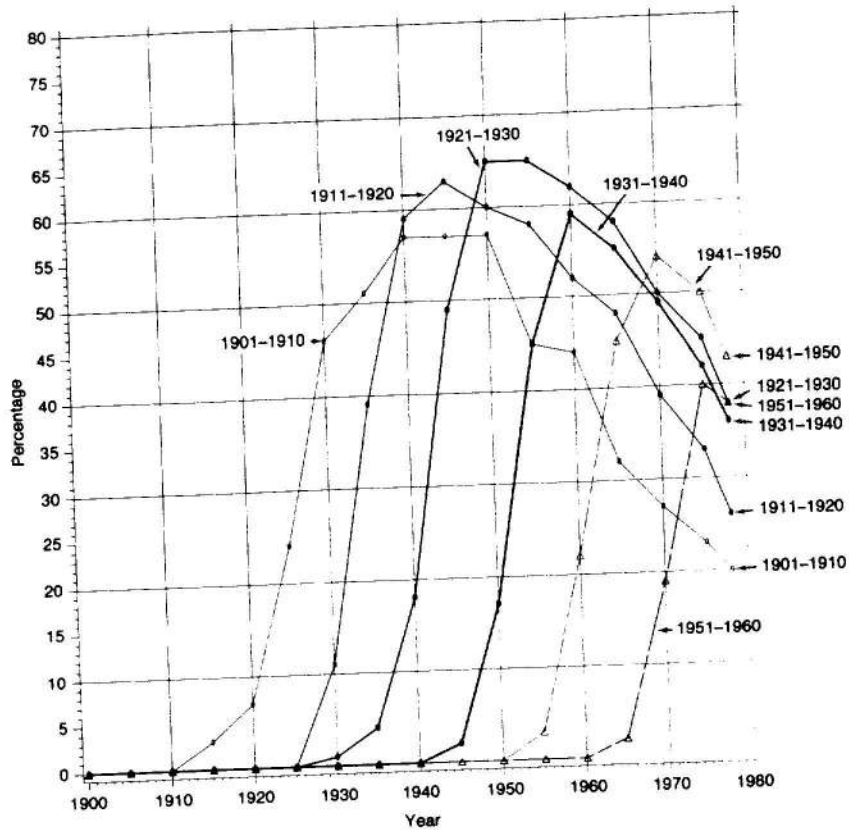


FIGURE 14.—Changes in the prevalence of cigarette smoking among successive birth cohorts of U.S. men employed as managers and administrators, 1900–1978

SOURCE: Data from National Center for Health Statistics, National Health Interview Surveys, 1978–1980 (combined).

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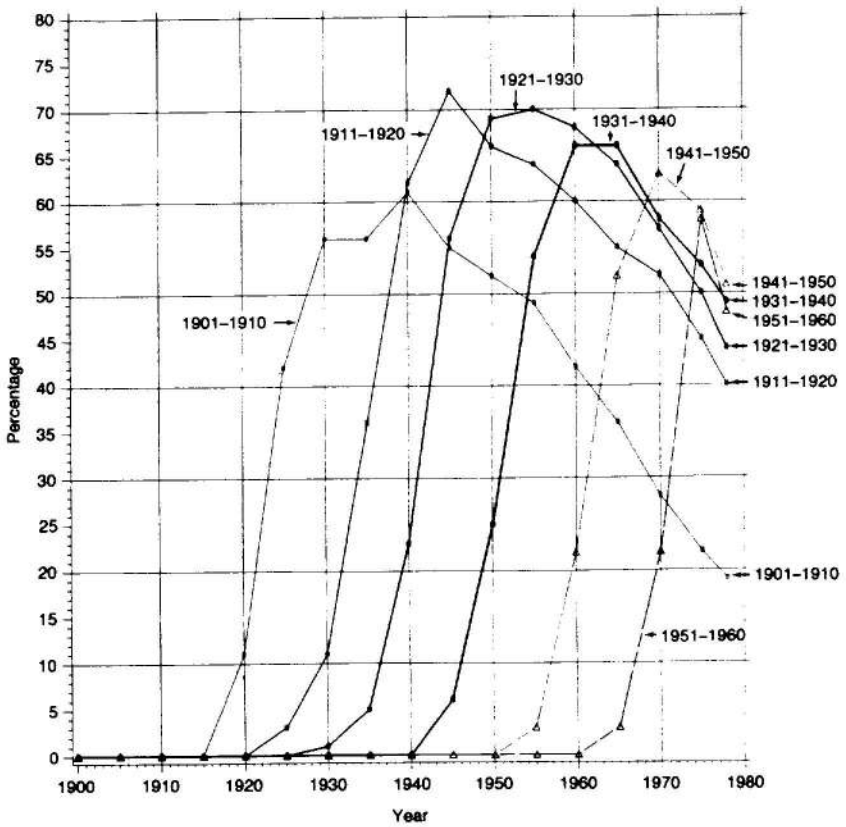


FIGURE 15.—Changes in the prevalence of cigarette smoking among successive birth cohorts of U.S. men employed as craftsmen or in kindred occupations, 1900–1978

SOURCE: Data from National Center for Health Statistics, National Health Interview Surveys, 1978–1980 (combined).

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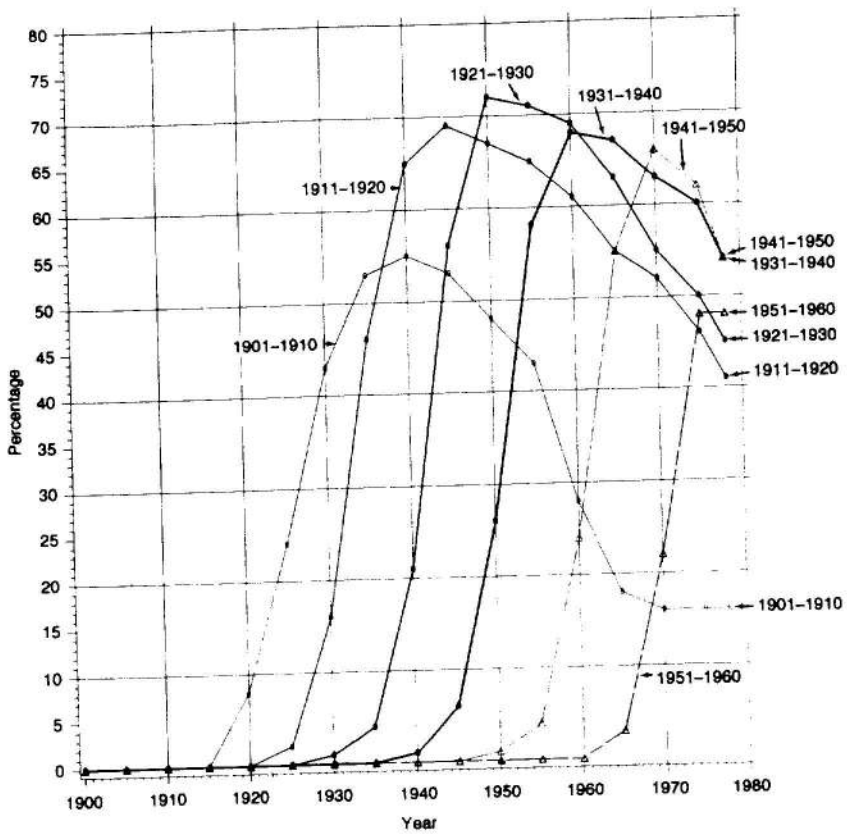


FIGURE 16.—Changes in the prevalence of cigarette smoking among successive birth cohorts of U.S. men employed as operatives or in kindred occupations, 1900–1978

SOURCE: Data from National Center for Health Statistics, National Health Interview Surveys, 1978–1980 (combined).

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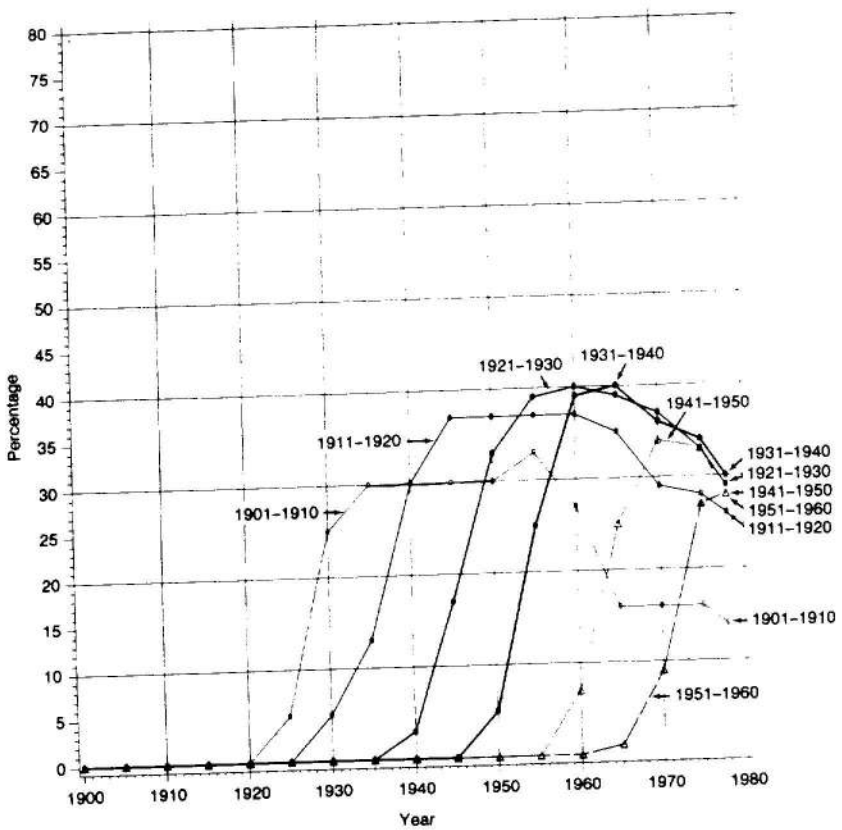


FIGURE 17.—Changes in the prevalence of cigarette smoking among successive birth cohorts of U.S. women employed in professional, technical, or kindred occupations, 1900–1978

SOURCE: Data from National Center for Health Statistics, National Health Interview Surveys, 1978–1980 (combined).

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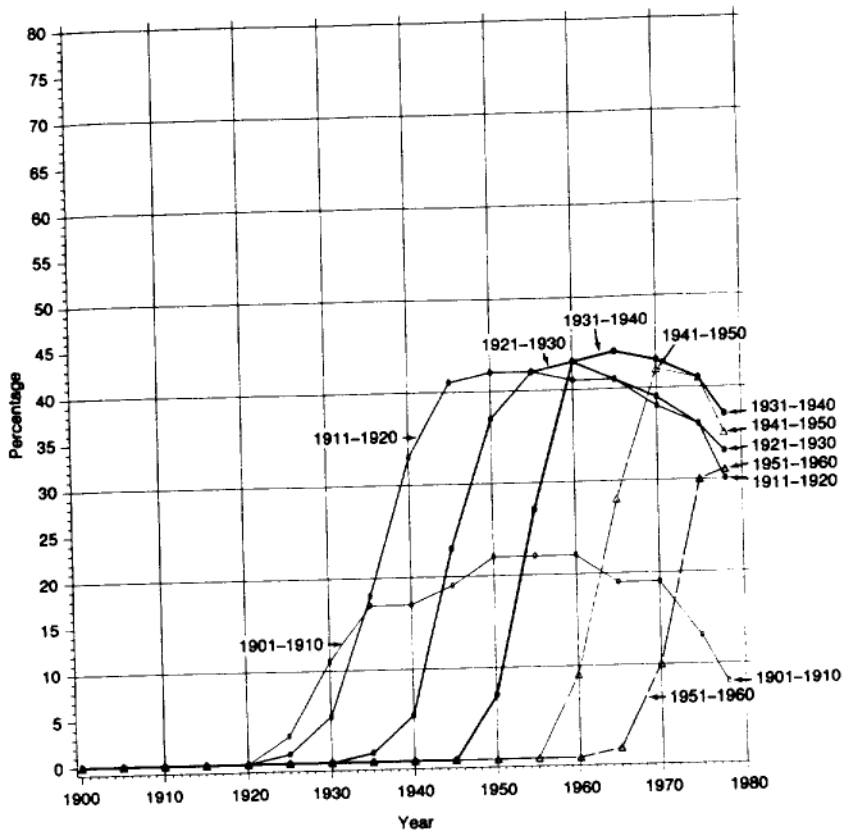


FIGURE 18.—Changes in the prevalence of cigarette smoking among successive birth cohorts of U.S. women employed in clerical or kindred occupations, 1900–1978

SOURCE: Data from National Center for Health Statistics, National Health Interview Surveys, 1978–1980 (combined).

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APPENDICES

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Appendix A

The two tables in appendix A describe the smoking habits of more than 18,000 employees from 16 components of the General Electric Company in various parts of the United States (personal communication, T. R. Casey and H. R. Richards, General Electric Company, June 1985). The data are presented to demonstrate the differences that can exist by payment category within the same workforce. The employees categorized as exempt are managers and specialists in various professions who are not bound by the provisions of the wage and hours law. Nonexempt personnel are generally clerical and secretarial workers, and hourly personnel are skilled and semi-skilled people who work in manufacturing. It is clear that substantial differences in smoking habits exist between men and women, between older and younger workers, and among employees in the three payment classifications.

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TABLE A1.—Sample of smoking habits of employees of 16 workforce components of the General Electric Company, May 1985

Category	Nonsmokers				Smokers				Ex-smokers				Total
	Women		Men		Women		Men		Women		Men		
	≤45	>45	≤45	>45	≤45	>45	≤45	>45	≤45	>45	≤45	>45	
Exempt													
≤20 cigs/day													
No. of employees	264	29	1,208	404	53	15	320	286	33	9	252	266	3,139
Years of smoking					721	485	5,172	9,979	232	205	2,050	5,106	
Average years					13.6	32.3	16.2	34.9	7.0	22.8	8.1	19.2	
>20 cigs/day													
No. of employees					9	4	122	140	6	3	75	163	522
Years of smoking					154	135	2,175	4,363	56	66	820	3,527	
Average years					17.1	33.8	17.8	31.2	9.3	22.0	10.9	21.6	
Nonexempt													
≤20 cigs/day													
No. of employees	370	135	528	94	188	79	273	83	75	29	131	91	2,076
Years of smoking					2,441	2,376	3,631	2,810	555	518	1,111	1,919	
Average years					13.0	30.1	13.3	33.9	7.4	17.9	8.5	21.1	
>20 cigs/day													
No. of employees					47	20	130	35	11	9	57	40	349
Years of smoking					863	666	2,021	1,220	161	226	761	1,092	
Average years					18.4	33.3	15.5	34.9	14.6	25.1	13.4	27.3	

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TABLE A1.—Continued

Category	Nonsmokers				Smokers				Ex-smokers				Total
	Women		Men		Women		Men		Women		Men		
	≤45	>45	≤45	>45	≤45	>45	≤45	>45	≤45	>45	≤45	>45	
Hourly													
≤20 cigs/day													
No. of employees	1,521	1,153	1,779	582	1,211	674	1,558	716	219	168	501	507	10,589
Years of smoking					17,247	21,786	22,287	25,942	2,036	3,682	4,579	11,986	
Average years					14.2	32.3	14.3	36.2	9.3	21.9	9.1	23.6	
>20 cigs/day													
No. of employees					155	91	405	259	35	34	144	233	1,356
Years of smoking					2,714	3,083	7,520	9,716	482	870	1,706	6,265	
Average years					17.5	33.9	18.6	37.5	13.8	25.6	11.8	26.9	
Total employees	2,155	1,317	3,515	1,080	1,663	883	2,808	1,519	379	252	1,160	1,300	18,031

SOURCE: General Electric Company Corporate Medical Operation (1985).

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TABLE A2.—Smoking habits of General Electric employees in various employment categories

Category	Men						Women					
	≤45 years old			>45 years old			≤45 years old			>45 years old		
	Never	Current	Former	Never	Current	Former	Never	Current	Former	Never	Current	Former
Exempt												
Total	61.1	22.4	16.5	32.1	35.1	34.1	72.3	17.0	10.7	48.3	31.7	20
<20 cigarettes/day		72.4	77.1		67.1	62.0		85.5	84.6		78.9	75
>20 cigarettes/day		27.6	22.9		32.9	38.0		14.5	15.4		21.1	25
Nonexempt												
Total	47.2	36.0	16.8	27.4	34.4	38.2	53.6	34.0	12.4	49.6	36.4	14.0
≤20 cigarettes/day		67.7	69.7		70.3	69.5		80.0	87.2		79.8	76.3
>20 cigarettes/day		32.3	30.3		29.7	30.5		20.0	12.8		20.2	23.7
Hourly												
Total	40.6	44.7	14.7	25.7	42.4	32.2	48.4	43.5	8.1	54.4	36.1	9.5
<20 cigarettes/day		79.4	77.7		73.4	68.5		88.7	86.2		88.1	83.2
>20 cigarettes/day		20.6	22.3		26.6	31.5		11.3	13.8		11.9	16.8

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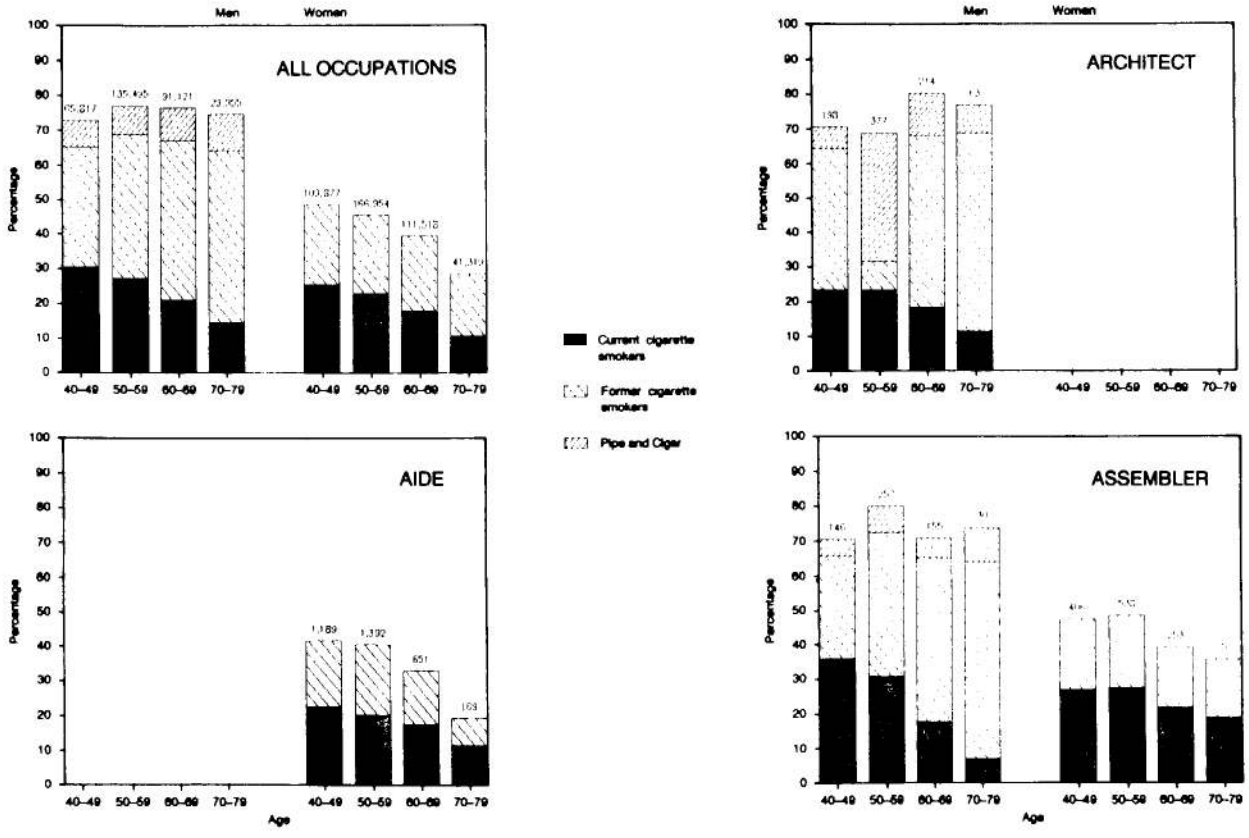
Appendix B

The data in appendix B, portrayed in bar graph format (personal communication, L. Garfinkel, October 1985), represent smoking characteristics by age, occupation, and sex of the more than 1.2 million men and women studied in the American Cancer Society's Cancer Prevention Study II. This study, initiated in 1982, is the largest known prospective study of its kind. The data on smoking and occupation were collected at the time of enrollment. Occupational categories were determined from answers to open-ended questions and, therefore, may not correspond to U.S. Department of Labor categories.

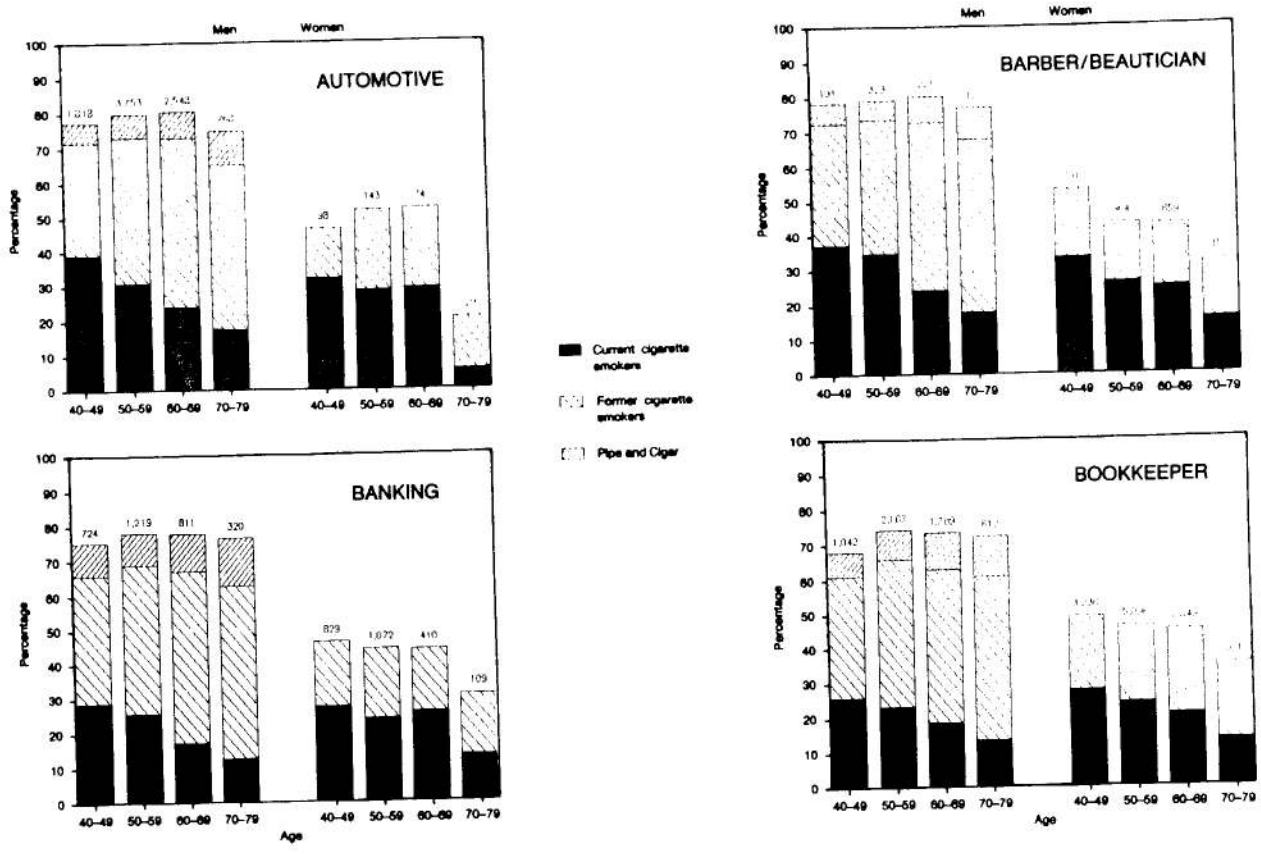
These data provide comparative information on smoking habits within occupational categories to demonstrate the variability that exists between the estimates derived from individual research designs and the national probability estimates derived from surveys. The number above each bar represents the total population for each age and occupational category. The first graph presents the percentages for all occupations; the occupational categories compared are the following.

Aide
Architect
Assembler
Automotive
Banking
Barber/Beautician
Bookkeeper
Civil Service
Clergy
Construction
Data Entry
Dentistry
Disabled
Doctor
Education
Electrician
Engineer
Executive
Factory Worker
Farmer
Fire Fighter
Food Preparation
Foreman
Heavy Equipment
Hospital Worker
Housewife
Law Enforcement
Lawyer
Machine Operator
Maid
Maintenance
Manager
Military
Miner
Nursing
Office Worker
Painter
Pharmacy
Photo and Printing
Plumber
Postal Service
Printing
Railroad Worker
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Sales
Social Worker
Steel Mill
Technician
Telephone Operator
Textile
Truck Driver
Unemployed
Waiter/Waitress
Welder
Woodworker

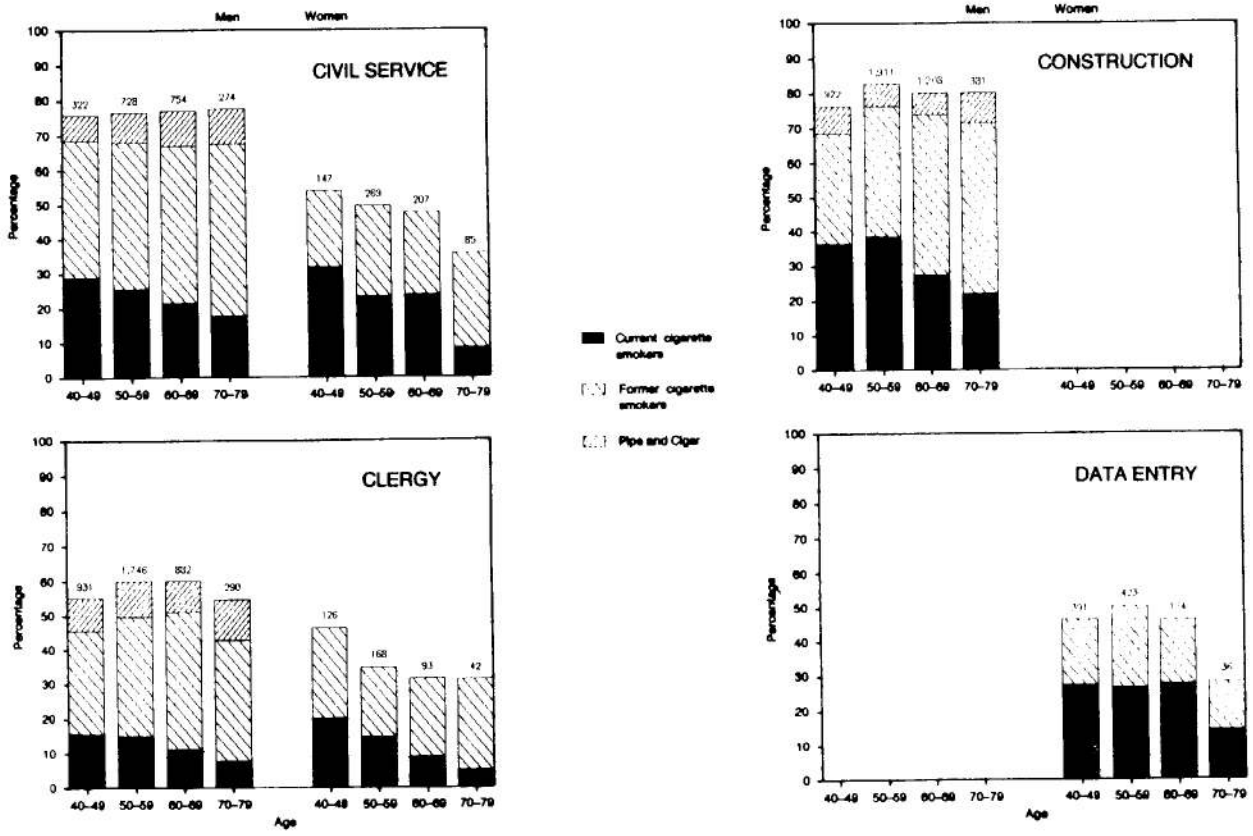
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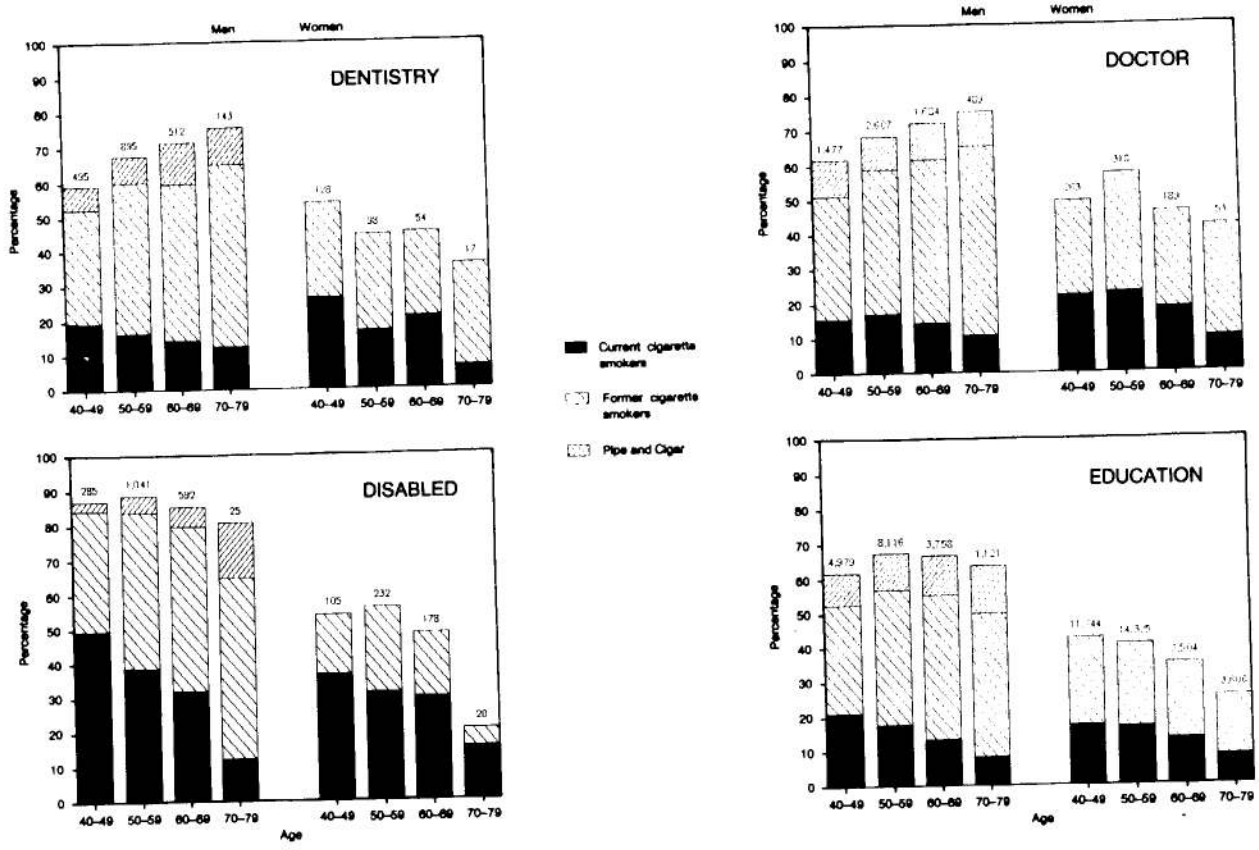
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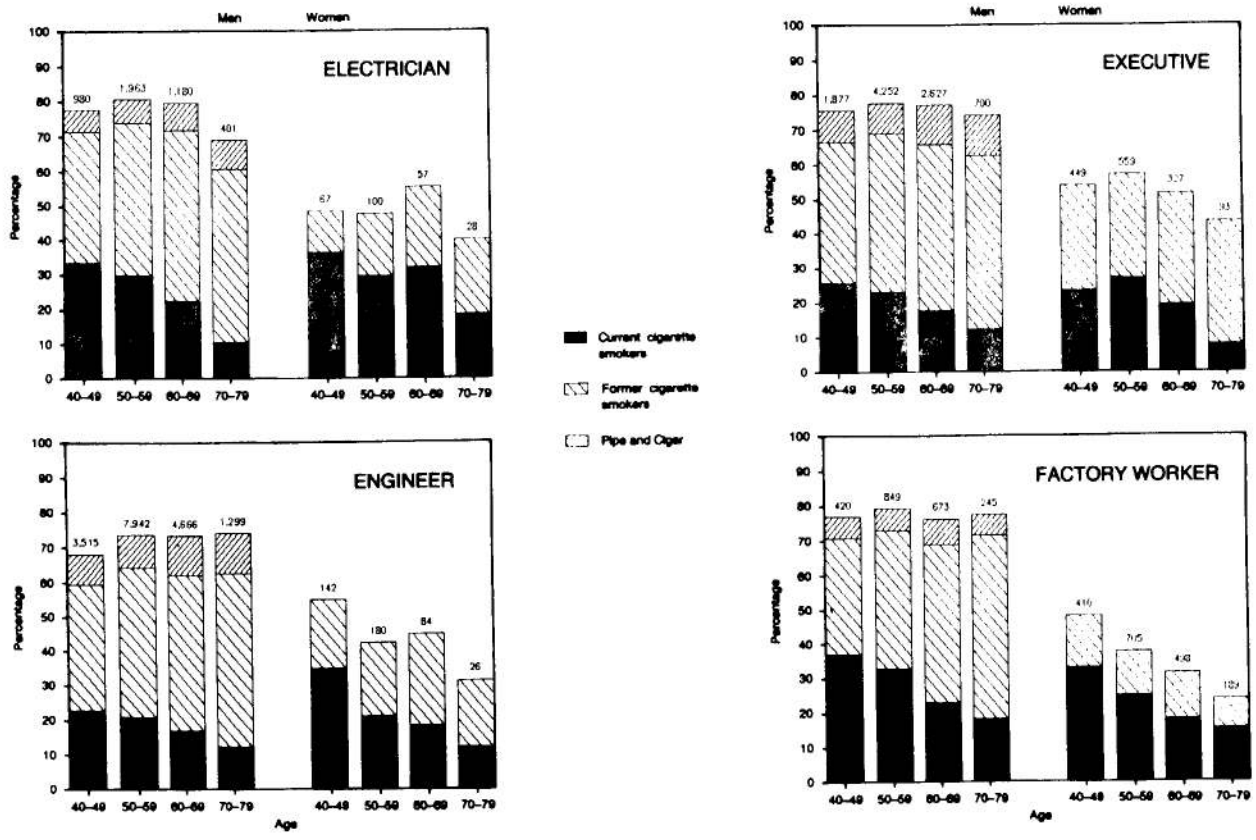
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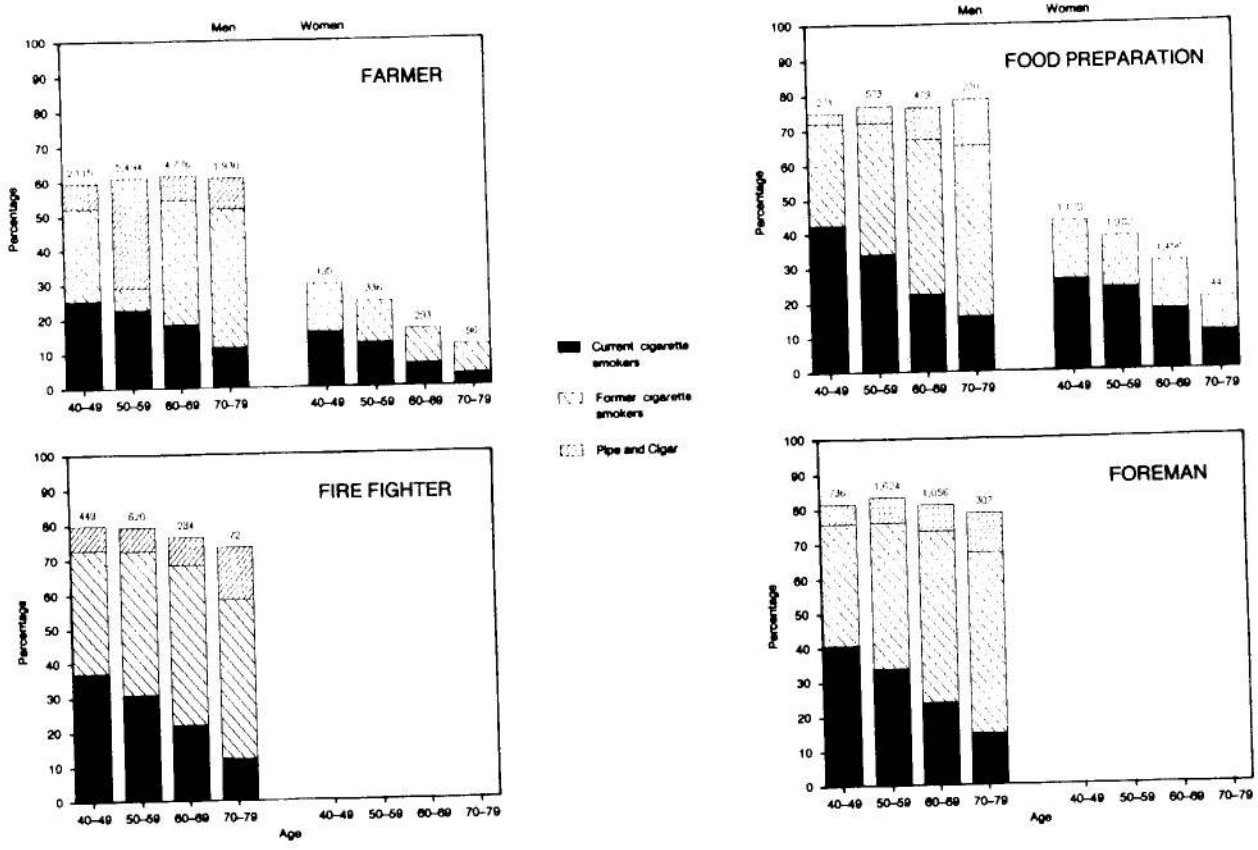
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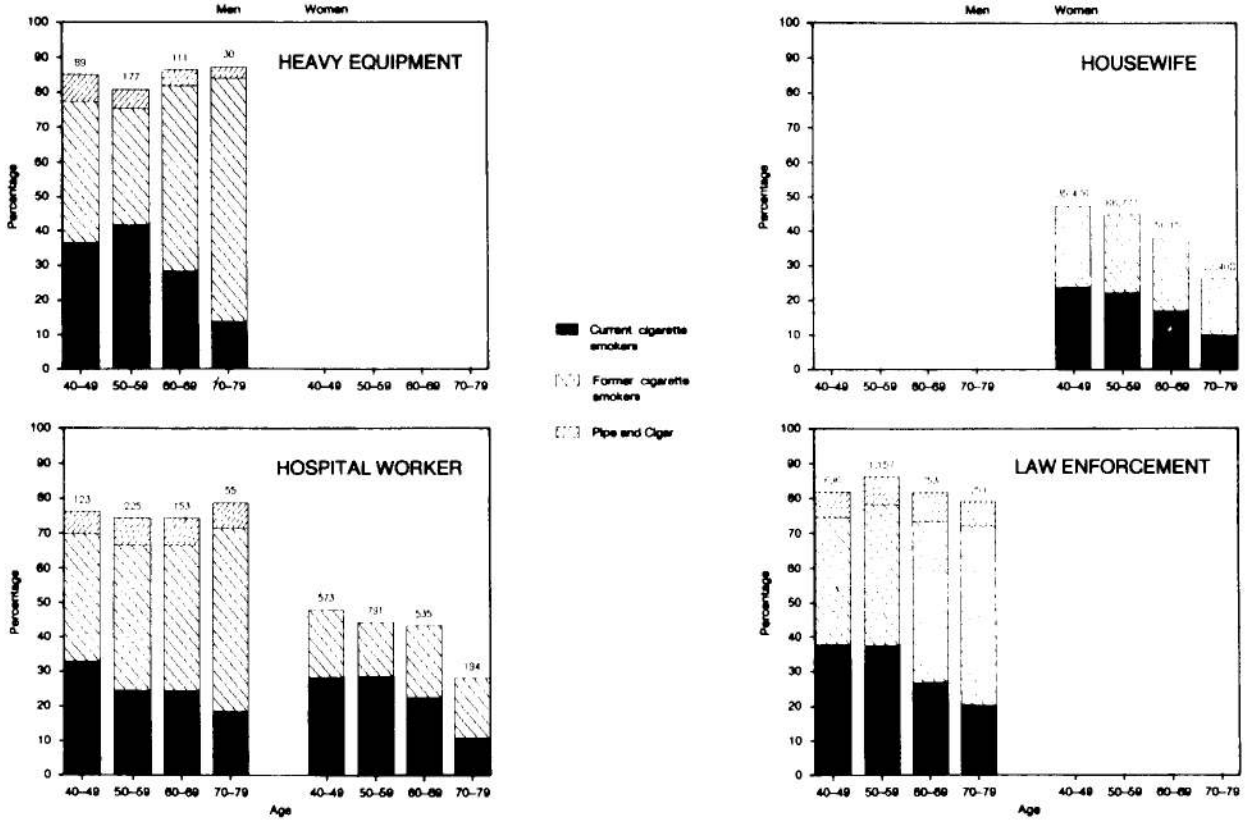
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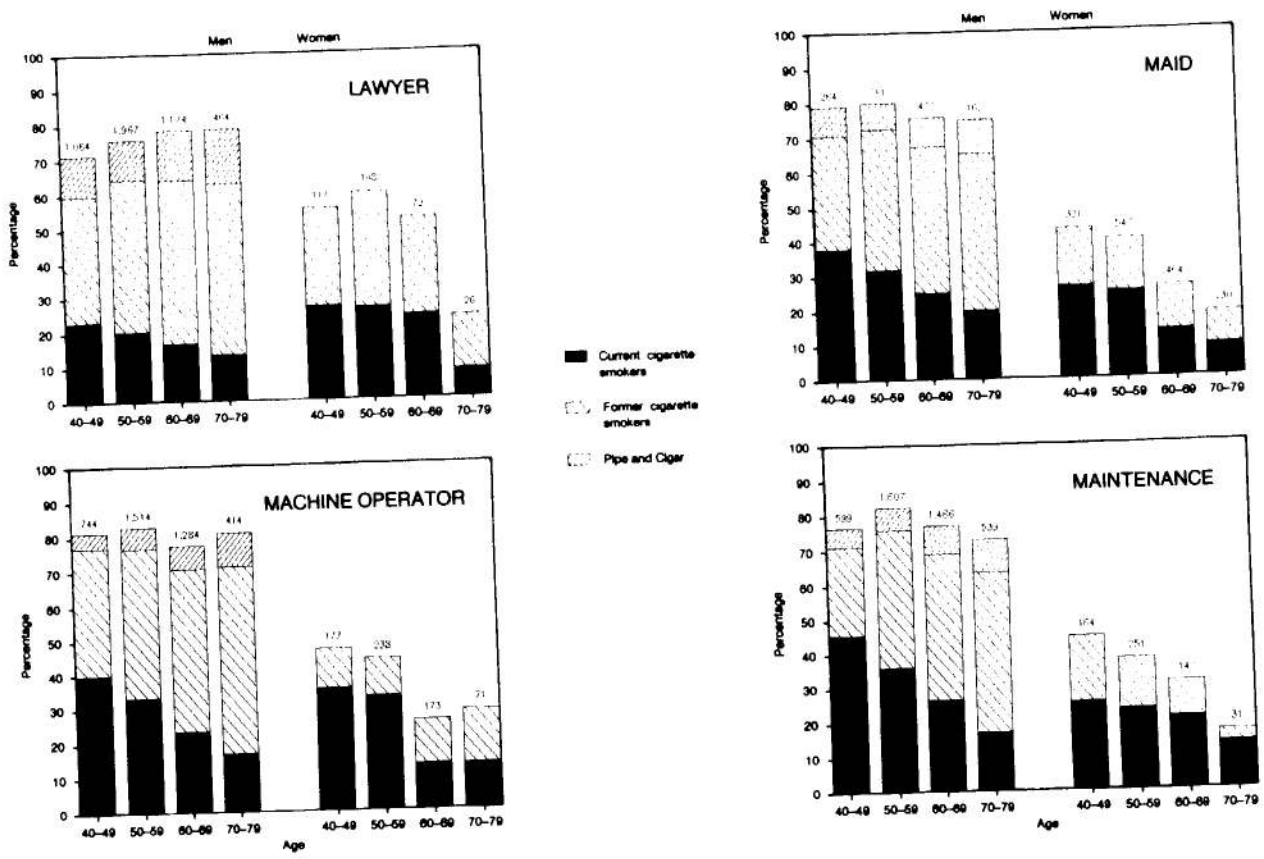
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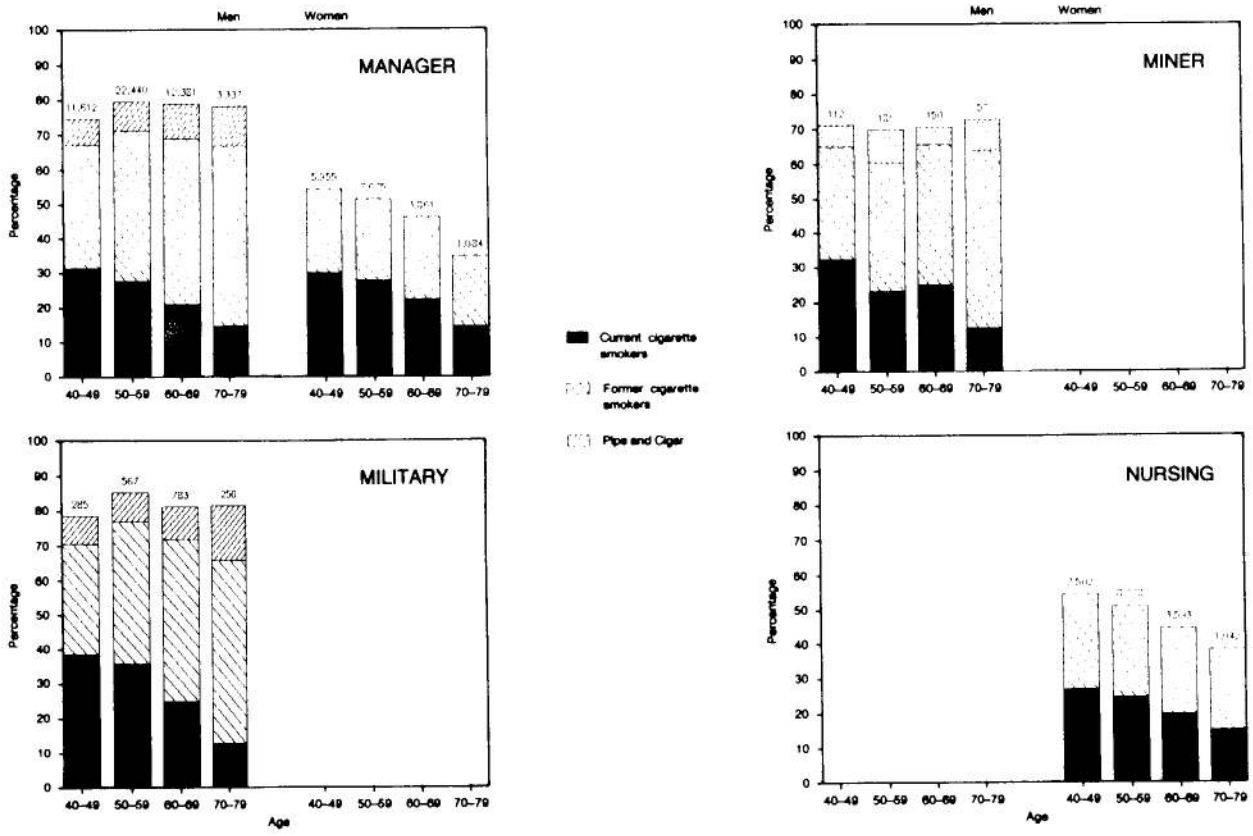
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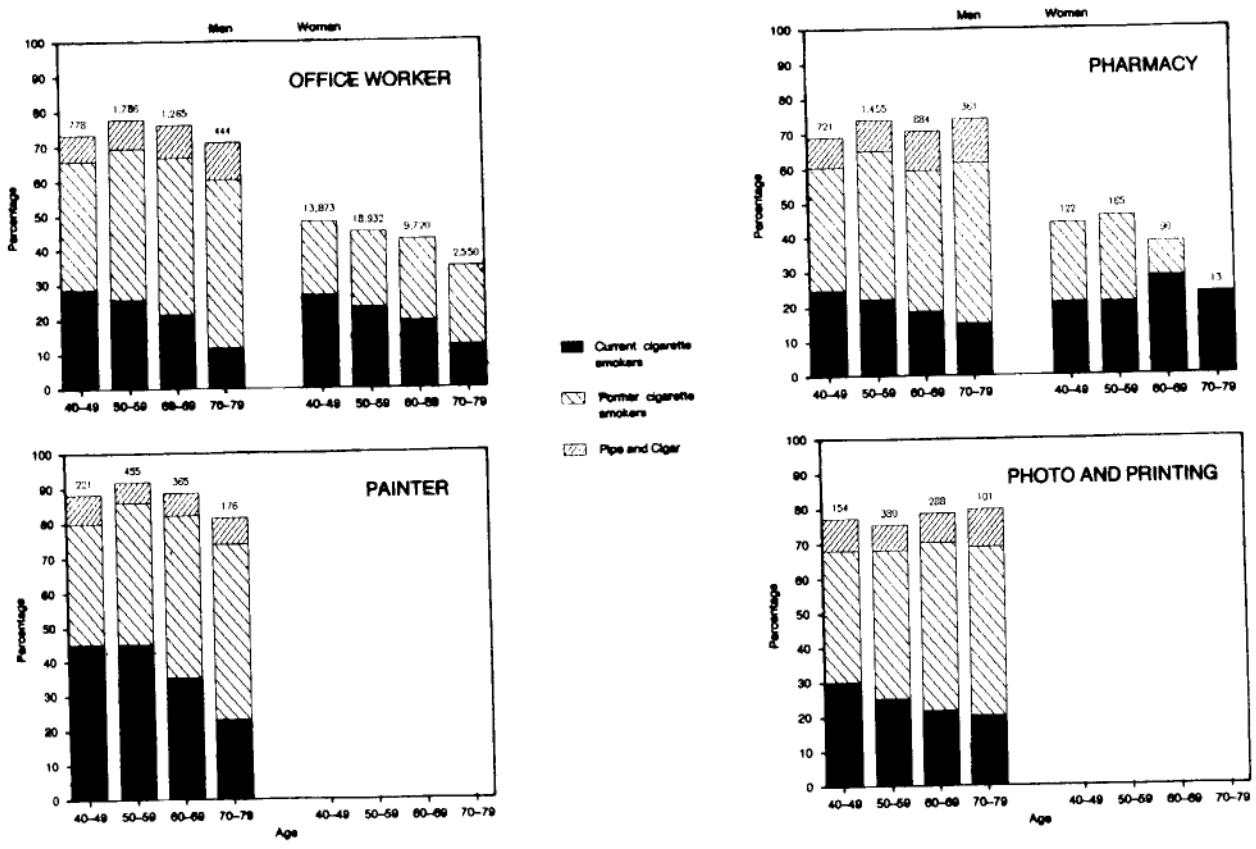
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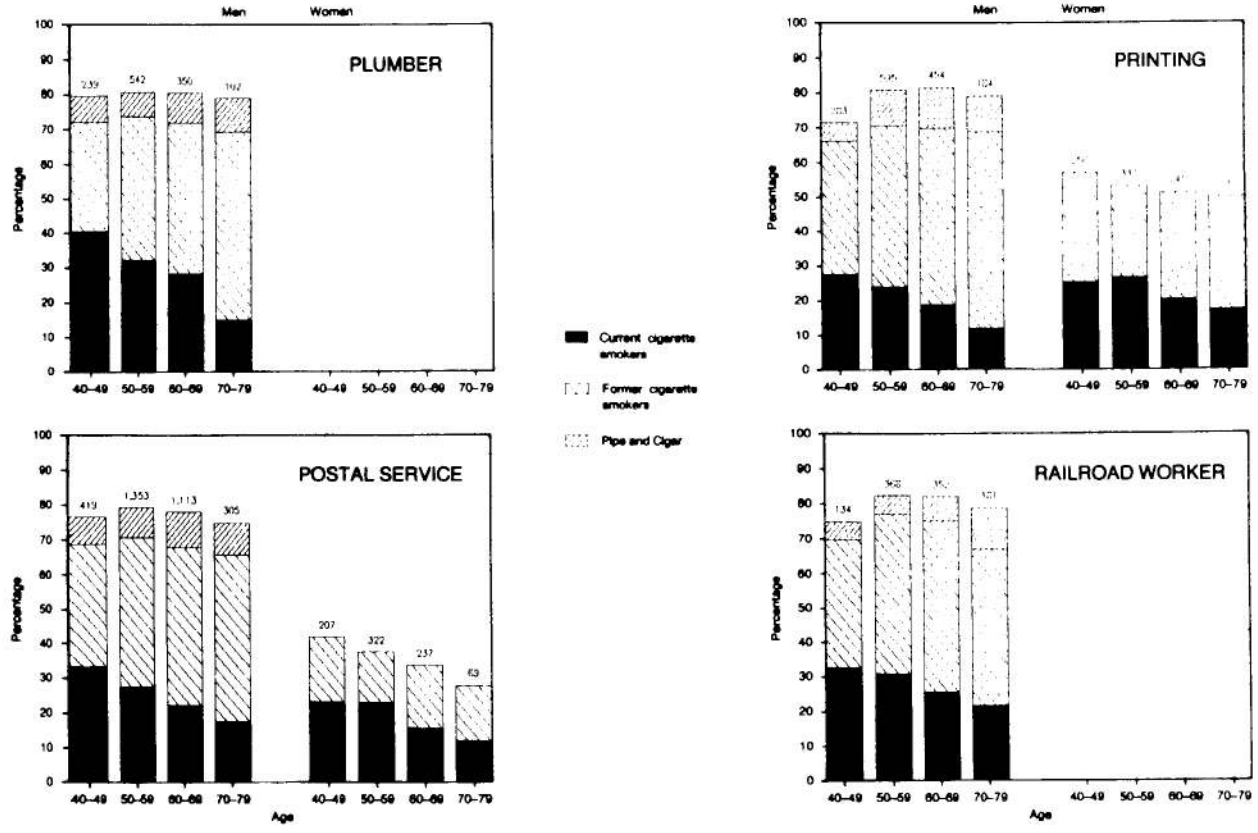
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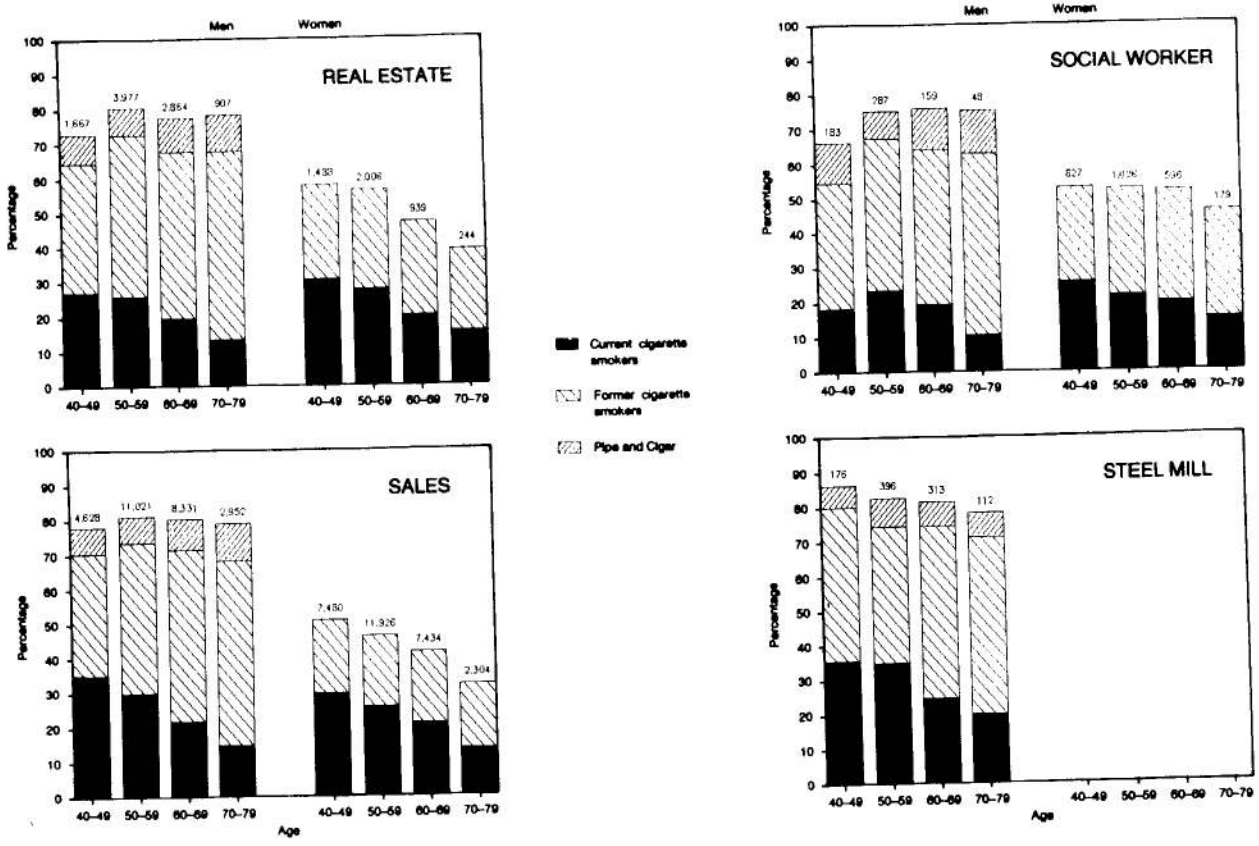
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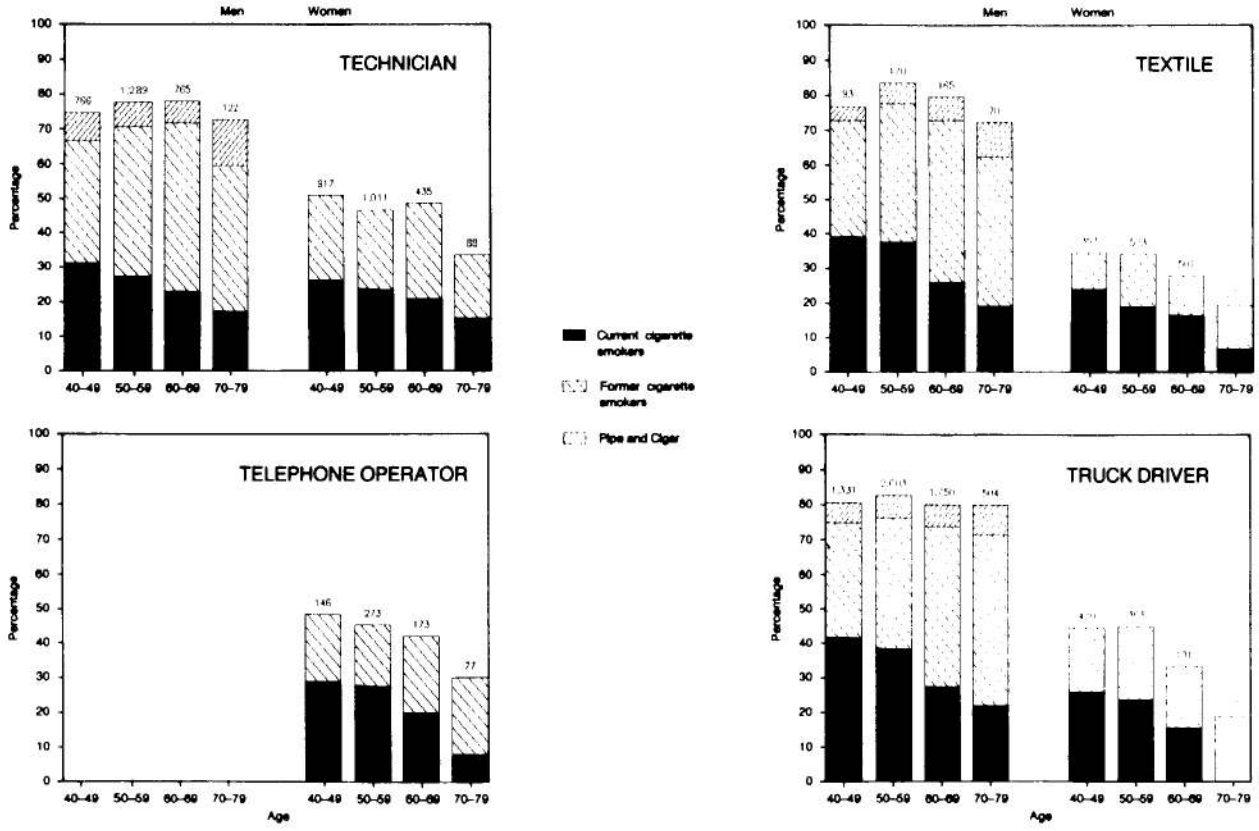
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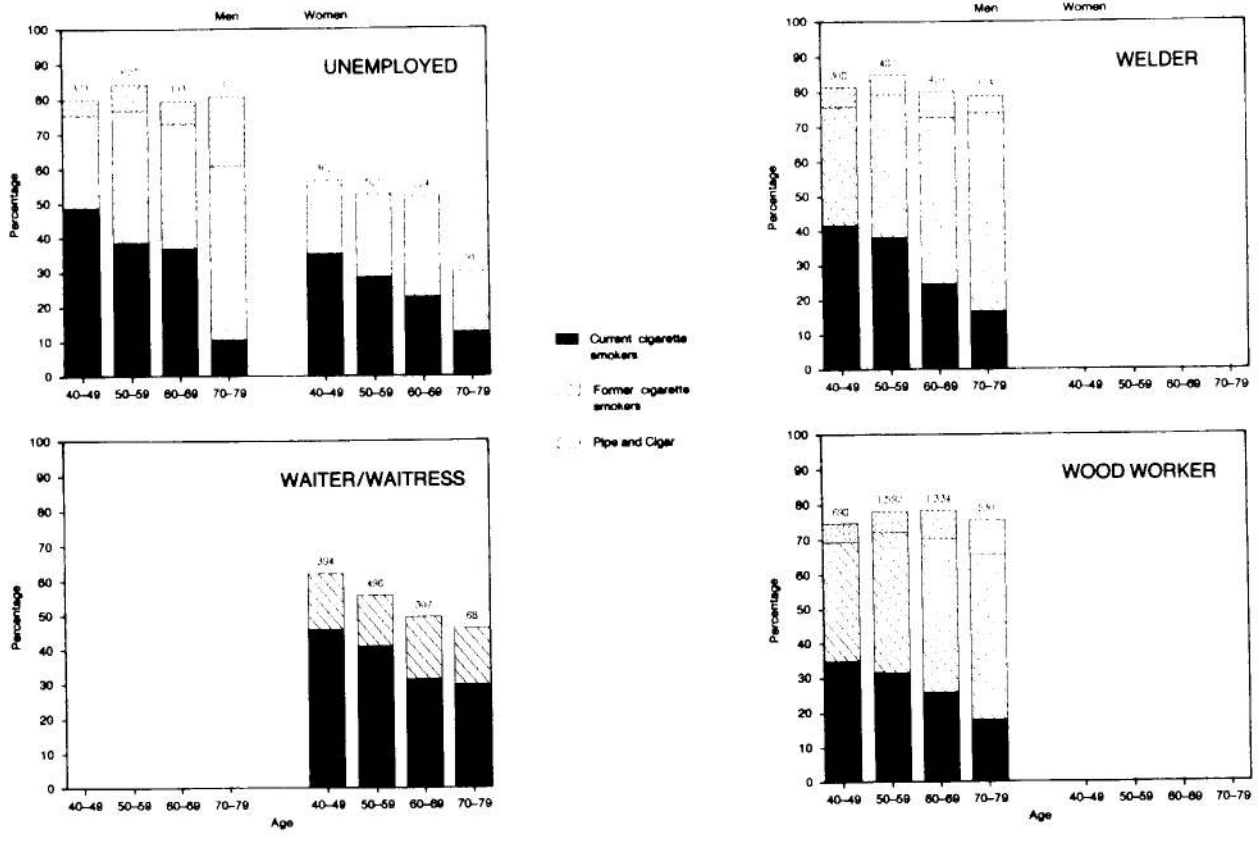
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CHAPTER 3

EVALUATION OF SMOKING-RELATED CANCERS IN THE WORKPLACE

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Introduction

Cigarette smoking is a major cause of cancer of the lung, larynx, oral cavity, and esophagus and is a contributory factor for cancer of the kidney, urinary bladder, and pancreas (US DHHS 1982). These cancers will cause 278,700 of the estimated 910,000 new cancer cases in the United States during 1985 (ACS 1985), or 30.6 percent of the cancers occurring in the United States other than skin cancer. Exposures to agents in the workplace other than cigarette smoke will also cause some of these new cancers, and a number of cancers will result from the combined effects of cigarette smoking and carcinogenic exposures in the workplace.

The role that cigarette smoking plays in causing these cancers is well established and extensively documented (US DHHS 1982). The role that occupational agents play in the development of these same cancers continues to emerge as the effects of more agents are examined both in the laboratory and in the workplace. However, cigarette smoking by exposed workers makes it difficult to separate the effects of smoking from the effects of occupational agents for cancers of sites causally linked to cigarette smoking. For some agents, such as asbestos, both the large numbers of people exposed and the magnitude of the increased cancer risk have allowed a careful examination of the relative contributions of cigarette smoking and the workplace exposure. For most agents, the data are more limited. Nevertheless, protection of workers requires that regulatory decisions be made about individual workplace exposures, even in the face of limited data. In assessing the effects of workplace exposures, consideration must be given to the interactions of smoking with agents that increase risk and to the bias introduced into studies of occupational groups by confounding effects of cigarette smoking. This chapter discusses the nature and measurement of interactions between smoking and occupational exposures and the sources and control of confounding of smoking and occupational exposures. It is not intended to be a comprehensive discussion of the epidemiologic methods used to evaluate workplace exposures, but rather a discussion of how smoking behavior in the workforce can effect the evaluation of occupational exposures. The data on smoking and specific occupational exposures are presented in later chapters of this Report. The discussion of these issues is intended to aid in the design and interpretation of studies of occupational exposure and not to criticize those studies in which smoking could not be completely addressed.

Lung Cancer Death Rates and Smoking

A detailed discussion of the causal relationship between cigarette smoking and the cancers is provided in an earlier Report in this

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series (US DHHS 1982) and is not repeated here. However, the relationship between smoking and lung cancer is briefly described, as a framework for the discussion of interaction and confounding in subsequent sections of this chapter. Lung cancer was chosen as an example because of its strong link to smoking and because it is the greatest cause of cancer death in both men and women (ACS 1985).

Lung cancer will cause an estimated 125,600 deaths in 1985 (ACS 1985): 87,000 men and 38,600 women. For men, this represents more than 8 percent of all deaths. Current U.S. age-specific lung cancer death rates increase with age into the late seventies age range and then decline. However, when death rates for any given birth cohort of men are examined (Figure 1), there is no decline in death rates at the older ages. This difference between the cross-sectional mortality statistics and the cohort data is generally attributed to differences in the smoking habits of successive birth cohorts of men (and women) during this century. This Report's chapter on smoking patterns in the U.S. population also carefully documents that cigarette smoking is not uniformly distributed in the U.S. population, but rather varies considerably with both age and occupation. This nonuniform distribution of smoking patterns introduces much of the difficulty in controlling for smoking in occupational studies.

The relationships among age, lung cancer death rates, and number of cigarettes smoked per day, derived from the mortality study of U.S. veterans (Kahn 1966), are presented in Figure 2. The risk associated with smoking is a function of both the intensity of smoking, as measured by number of cigarettes smoked per day and depth of inhalation, and the duration of smoking as measured by age and age of initiation.

The lung cancer mortality ratios derived from the American Cancer Society (ACS) study of 1 million men and women (Hammond 1966) for smokers compared with nonsmokers, stratified by age and by number of cigarettes smoked per day, depth of inhalation, and age of initiation are presented in Table 1. In general, the mortality ratios are greater in the older age groups and increase with increasing dosage measure within each age strata. The data demonstrate that within the broader category of smokers a substantial variation in risk (up to fivefold) occurs between the different levels of dose and duration of smoking. The variation in mortality ratios for each isolated measure in Table 1 almost certainly overestimates the independent contribution of that measure to the actual risk, owing to correlation among the measures of number of cigarettes smoked per day, depth of inhalation, and age of initiation. For example, those who begin to smoke at a young age also smoke more cigarettes per day (Shopland and Brown 1985). However, it is unlikely that this correlation among dosage and duration measures explains all of the variation in mortality ratios with the isolated measures; therefore, it

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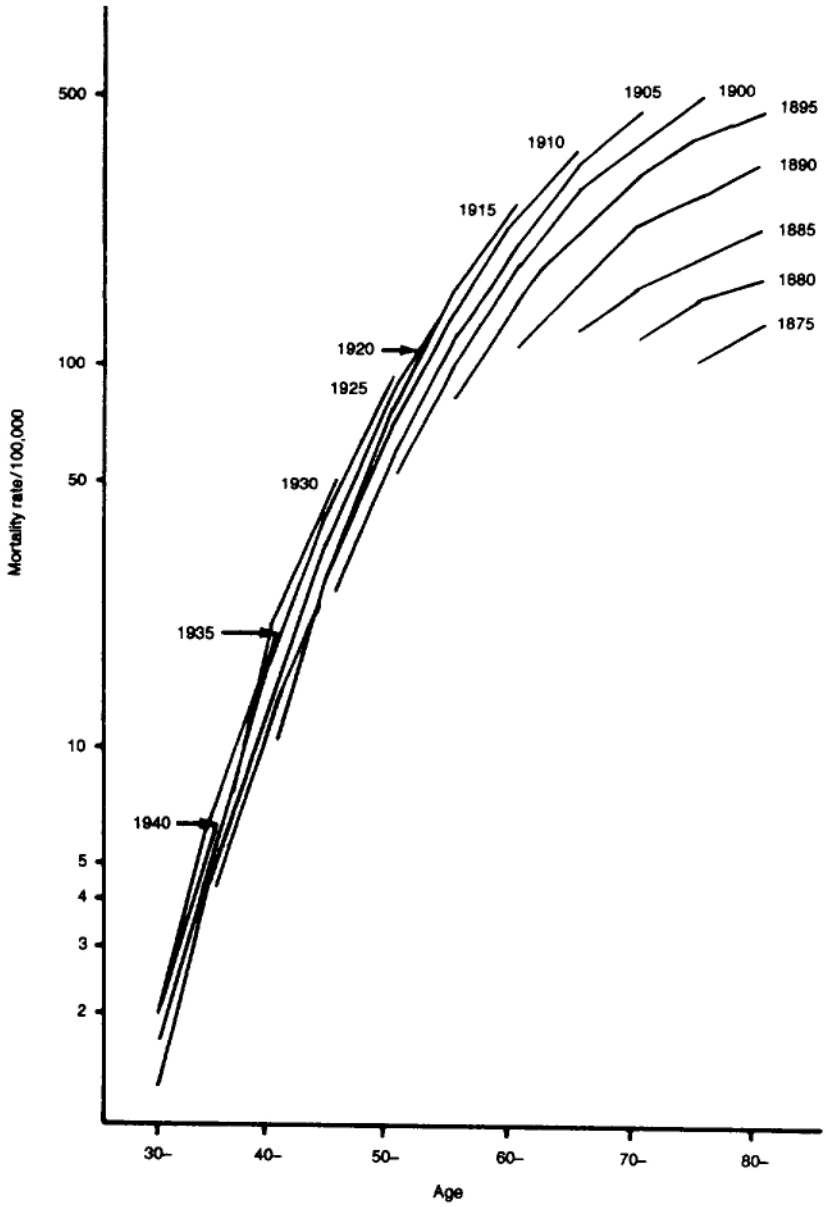


FIGURE 1.—Age-specific mortality rates for cancer of the bronchus and lung, by birth cohort and age at death, men, United States, 1950–1975

SOURCE: Data derived from McKay et al. (1982).

is reasonable to expect that the accuracy of lung cancer risk estimates for a population would improve with the inclusion of a

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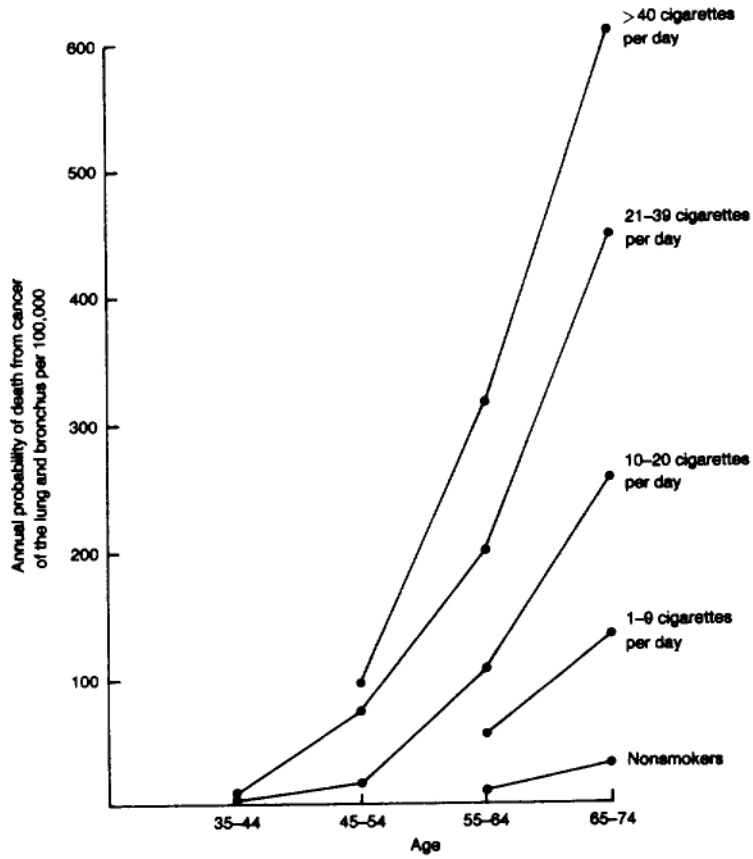


FIGURE 2.—Death rates from cancer of the lung and bronchus in nonsmokers and smokers of various numbers of cigarettes per day

SOURCE: Kahn (1966).

measure of smoking prevalence, a measure of smoking intensity, a measure of smoking duration, and a measure of the duration of cessation for former smokers.

Interactions Between Cigarette Smoking and Occupational Exposures

Interactions between cigarette smoking and occupational exposures may be examined in the context of a biological process, as a statistical phenomenon, or as a problem in public health and individual decisionmaking (Rothman et al. 1980; Saracci 1980; Siemiatycki and Thomas 1981). In each of these contexts the

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TABLE 1.—Number of lung cancer deaths (men), age-standardized death rates, and mortality ratios, by current number of cigarettes smoked per day, degree of inhalation, and age began smoking, by age at start of study

Smoking characteristics	Age 35–54			Age 55–69			Age 70–84			All ages, 35–84		
	Number of deaths	Death rate	Mortality ratios	Number of deaths	Death rate	Mortality ratios	Number of deaths	Death rate	Mortality ratios	Number of deaths	Death rate	Mortality ratios
Current number of cigarettes a day												
1–9	9	38	6.17	12	68	3.53	5	134	5.32	26	56	4.60
10–19	15	24	3.90	57	168	8.77	10	243	9.62	82	90	7.48
20–39	138	58	9.37	216	264	13.82	27	446	17.62	381	159	13.14
≥40	26	47	7.67	50	334	17.47	6	754	29.84	82	201	16.61
Degree of inhalation												
None or slight	19	29	4.75	87	203	10.60	14	193	7.65	120	102	8.42
Moderate	114	52	8.48	177	224	11.72	20	401	15.88	311	138	11.45
Deep	55	55	9.00	73	266	13.93	13	638	25.26	141	173	14.31
Age began cigarette smoking												
≥25	5	17	2.77	12	65	3.39	3	85	3.38	20	39	3.21
20–24	31	36	5.83	72	212	11.11	7	306	12.11	110	118	9.72
15–19	112	54	8.71	176	250	13.06	27	490	19.37	315	155	12.81
<15	35	79	12.80	57	302	15.81	9	424	16.76	101	183	15.10
Never smoked regularly	11	6		27	19		11	25		49	12	

NOTE: Mortality ratios are based on death rates carried out to one more significant figure than shown.
SOURCE: Hammond (1966).

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concepts are applied somewhat differently, and confusion results when a move from one context to another is attempted without consideration of these differences in application. Biological interaction refers to the presence of one agent influencing the form, availability, or effect of a second agent, and includes physical interaction such as the adsorption of carcinogens to particulates in inspired air, process interactions such as the induction by one agent of an enzyme system capable of converting a second agent into a carcinogenic metabolite, and outcome interactions such as the number of tumors produced by separate and combined exposures in an animal exposure system. Statistical interaction refers to a departure from the mathematical model used to assess the effects of the exposure variables. The model being tested may be additive, multiplicative, or some other form; the outcome of interest may be death rates, relative risks, or other outcome measures; the independent variables may be intensity of exposure, duration of exposure, a combination of intensity and duration (e.g., pack-years), or a logarithmic or other transformation of these measures. Public health interaction usually refers to the presence or level of one agent influencing the incidence, prevalence, or extent of disease produced by a second agent. An exposure to two agents that resulted in a multiplicative effect on lung cancer death rates might show no interaction using a multiplicative statistical model, but might show a profound interaction in terms of public health and a variety of interactions within the biologic system under consideration (i.e., human carcinogenesis).

Biologic Interactions

The transformation of normal lung tissue into a clinically manifest lung cancer is a complex, incompletely understood process that is generally assumed to require multiple inheritable changes within the cell (Armitage and Doll 1961; Day and Brown 1980). Although cellular changes are assumed to be requisite for carcinogenesis, phenomena taking place outside the cell may influence carcinogenesis. Cigarette smoke and occupational agents may potentially interact by influencing the fraction of inhaled carcinogen deposited and retained in the lung, the rate of metabolic activation of a procarcinogen into a carcinogenic metabolite, the transfer of agents across mucosal and cellular boundaries, the vulnerability of the cell to carcinogenic change (by increasing the rate of cell replication), or the transformation of the cellular DNA. In addition, cellular DNA repair, humoral or metabolic factors influencing tumor growth, and immunologic recognition or destruction of tumor cells are processes that may influence tumor manifestation and may be affected by occupational exposures and cigarette smoke. A detailed discussion of chemical carcinogenesis is beyond the scope of this chapter and is

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provided elsewhere (Weinstein 1985; Farber 1982); however, this chapter explores some potential sites of biological interaction between occupational exposure and cigarette smoke to illustrate the biologic interactions that may take place.

Cigarette smoking and occupational exposures may interact through effects of smoking on the dose of the carcinogen that reaches the cell. Long-term exposure to cigarette smoke impairs mucociliary clearance (US DHHS 1982) and could alter the dose of an occupational agent retained. Carcinogens may adsorb to particulates in smoke or to environmental dusts (Natusch et al. 1974; Mossman et al. 1983), resulting in a higher fractional retention or different distribution in the lung. The adsorption to dust may also facilitate or inhibit transport of carcinogens through the mucus layer. Cigarette smoke has been shown to increase epithelial permeability in the tracheobronchial tree (Simani et al. 1974); the effect may increase the exposure of the underlying cell to an occupational agent.

Another potential site of biologic interaction is the metabolic activation of a carcinogen. A number of agents, including the polycyclic aromatic hydrocarbons in cigarette smoke, undergo chemical transformation within the body to metabolites that are considered to be active carcinogens (Gelboin and Tso 1978a, b). The majority of known conversions occur through the mixed function oxygenase system predominately located in the microsomal fraction of the cell. A number of constituents of cigarette smoke have been shown to induce this enzyme system (US DHEW 1979), and its activation may increase the rate of biologic activation of procarcinogens in the worksite. Cigarette smoking also alters the cellular composition of the lung, increasing the number of neutrophils and activated macrophages in the lung (US DHHS 1984); these cells may also play a role in the metabolic transformation of occupational agents.

Much of the consideration of interactions between smoking and occupational exposures has centered on interactions that might influence the response of the cell rather than the "dose" of carcinogen (Siemiatycki and Thomas 1981; Rothman et al. 1980; Rothman 1974, 1978; Walter and Holford 1978). In a widely accepted conceptual model, the process of malignant transformation of a cell into a cancer is considered to be a multistage process requiring multiple inheritable changes (Armitage and Doll 1961; Day and Brown 1980). Individual agents may initiate or promote the process of carcinogenesis. Initiation is thought to be at least a two-stage process that requires cell division before becoming irreversible (Farber 1982). Promotion describes the process by which an agent encourages an initiated tissue to develop focal proliferation. A tumor initiator may exert its effect through a brief exposure, whereas a tumor promoter usually requires repetitive contact with initiated

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tissue to exert its effect. Cigarette smoke is known to contain a number of compounds that act as tumor initiators and promoters (US DHHS 1982); occupational exposures reflect a similar range of agents. Tumor promoters in smoke may influence the effects of exposure to tumor initiators in the workplace and thus increase the number of cancers that occur, and the presence of tumor initiators in smoke may allow the expression of a tumor promoter in the worksite.

The process of carcinogenesis is frequently modeled as a multistep process in which each succeeding step can occur only in those cells that have undergone the preceding step (Armitage and Doll 1961; Day and Brown 1980). In this model, agents may influence one (or more) of these steps, and therefore may have an effect early or late in the carcinogenic transition. Because the later steps in the process can occur only in cells that have undergone the changes of earlier steps, agents that act at separate steps may have multiplicative effects. For example, an agent that results in a fourfold increase in the rate of transition from a hypothetical step 1 to step 2 in the carcinogenic process would result in a fourfold increase in the number of malignant transformations by increasing the number of cells available for step 2 and subsequent steps. Similarly an agent that tripled the rate of transition from step 2 to step 3 would triple the number of malignant transformations. However, exposure to both agents would provide a fourfold (300 percent) increase in the number of cells available for transition from step 2 to step 3 as well as a threefold (200 percent) increase of the rate of transition from step 2 to step 3, with a resultant twelvefold (1,100 percent) increase in the number of malignant transformations. Therefore, the effect of the combined exposure on number of malignant transformations (1,100 percent) would be greater than the sum of the effects of independent exposures (300 percent plus 200 percent).

A similar phenomenon may occur with cigarette smoke and an agent that has an independent and additive effect as an initiator of carcinogenesis. The additive effects on tumor initiation may appear as a multiplicative effect on tumor occurrence because of the action of the tumor promoters in cigarette smoke. The tumor promoters in smoke may act on the cells initiated by an occupational agent, as well as on the cells initiated by smoke, to increase the number of the cells that become cancers. The number of tumors produced by a combined exposure could then be greater than the sum of the numbers of tumors produced by the individual exposures separately.

Two additional mechanisms by which cigarette smoking and occupational exposures may interact are by alterations in the immunologic surveillance for cancers and by increasing the frequency of cell division. Differences in the number, type, and function of cellular components of the immune system have been demonstrated

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between smokers and nonsmokers (US DHHS 1984) and among workers exposed to occupational agents (see other chapters of this Report). The potential for these differences to influence the rates of clinically manifest cancers (either positively or negatively) is an issue of considerable interest. The increase in cell turnover in the respiratory tract in response to the acute toxic and inflammatory effects of cigarette smoke, or of occupational exposures, may also influence cancer rates, as it is believed that cells are more vulnerable to carcinogenic changes during periods of replication.

This discussion is intended to illustrate the kinds of biologic interactions that might occur between smoking and occupational agents and not to be a complete description of either the carcinogenic process or the sites of potential interaction.

Statistical Interaction

Statistical interaction refers to departure from a mathematical model in assessing the main effects of independent variables; its presence is often evaluated by the addition of an interaction term to the independent variables (Siemiatycki and Thomas 1981; Blot and Day 1979; Saracci 1980). With this approach, the presence of interaction is dependent on the model being used (Rothman 1974; Kupper and Hogan 1978). For example, a multiplicative effect can be adequately modeled without an interaction term on a log scale, but requires an interaction term on an additive scale. In this section, an additive model for the effects of two exposures assumes that the combined exposure produces an effect equal to the background rate plus the sum of the increases from the background rate of the two exposures experienced separately. In a multiplicative model, combined exposure results in an effect equal to the product of the effects produced by the separate exposures.

The following example illustrates this terminology and demonstrates the dependence of statistical interaction on the selected model. Assuming that two agents independently increase the risk of lung cancer and that the separate exposures result in a fivefold and tenfold increase in risk, respectively, if exposure to both agents produces an eightfold increase in risk, there is negative interaction (protective effect) in the additive and the multiplicative models. A combined risk of 14 indicates no interaction in an additive model, but a negative interaction in a multiplicative model; a risk of 30 is a positive interaction with an additive model and negative with a multiplicative model; a risk of 50 is a positive interaction with an additive model and no interaction with a multiplicative model; and a risk of 60 is a positive interaction with both models.

This example illustrates the critical dependence of tests for interaction on the mathematical model that is selected. Ideally, the choice of a model is based on biological considerations and not on

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statistical convenience. For example, if the potential interaction of two initiators is being examined, an additive model should be used. The use of a multiplicative model may result in the demonstration of a negative interaction.

When applied to the multistage biologic model of carcinogenesis, independent actions at the same step would yield additive effects and actions at separate steps would yield multiplicative effects (Siemiatycki and Thomas 1981; Walter and Holford 1978). This progression from the biologic model to the statistical effect is easily defended; however, it is less clear that the reverse progression is valid, particularly in epidemiologic studies. The demonstration of an additive effect on lung cancer death rates does not necessarily imply that the two agents are acting at the same point in the carcinogenic process, nor does a multiplicative effect guarantee action at separate steps. As should be evident from the discussion of biologic interaction, cigarette smoke may interact with occupational agents at points external to the cell, and smoke consists of a variety of agents with different carcinogenic effects. The complex biologic processes that underlie the exposure–disease relationships evaluated in epidemiological studies limit the inference from the results of statistical modeling to biological mechanisms.

Rothman (1974) and Hogan and colleagues (1978) described methods of quantifying the magnitude of statistical interaction, and Kupper and Hogan (1978) described the detection of interaction in cohort and case–control studies. This Report's chapter on the evaluation of chronic lung disease also discusses the concepts of interaction and its measurement in studies of outcomes that are continuous (i.e., lung function measures) rather than binary (i.e., presence or absence of lung cancer).

In the simplest analytical problem, departure from additivity can be readily assessed when a population has two exposures, the rates in the presence of each individual exposure are known, and the rates in the presence and absence of both are known. If the relative risk (RR) in the absence of exposure is set equal to 1, then the ratio of the rate in the population with only one of the exposures to the rate in the population with neither exposure is the RR associated with the exposure. Correspondingly, the ratio of the rate in the population with both exposures over the rate in the population with neither exposure is the RR associated with combined exposure. The magnitude of the interaction can then be estimated by the ratio of the increase in rate with combined exposure (the RR of combined exposure minus 1) over the sum of the increases from the unexposed rate produced by the single exposures ($(RR_a-1)+(RR_b-1)$). The confidence interval around this estimate of interaction can also be estimated (Rothman 1974) as a measure of its statistical significance. More complicated estimates of the magnitude of interaction are

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necessary when the rate in the unexposed population is unknown, when the rate of the disease being measured is high in the general population, and when case–control analyses are being performed (Rothman 1974; Hogan et al. 1978). In general, the size of the population needed to test for interaction between two exposures is considerably larger than the size of the population needed to establish statistically significant effects for the separate exposures.

Both case–control and cohort data can be analyzed with approaches that involve stratification (Kleinbaum et al. 1982; Rothman and Boice 1979). The data are separated into strata defined by levels of the occupational exposure and of cigarette smoking. By combining the information within the separate strata, summary measures can then be calculated that estimate the independent effects of the variables and describe their interaction. Although stratified analysis can be readily performed, its application is frequently limited by the number of available subjects, both in the entire study and within specific strata. For example, if an investigator designates four levels of exposure to an occupational agent and classifies smokers as currently smoking, previously smoking, or never smoking, twelve separate exposure categories are created. If age, sex, and race must also be considered, stratified analysis may be feasible only if the number of subjects is extremely large.

Statistical modeling represents an alternative that is less compromised by smaller sample sizes and that provides greater flexibility for controlling confounding and for testing for interaction. Modeling refers to the specification of a particular mathematical relationship between the outcome variable, e.g., the occurrence of lung cancer, and the variables representing the exposures of interest, e.g., cigarette smoking and an occupational agent. Statistical methods describe the adequacy of the model for the data and provide estimates of the effects of the exposure variables. Modeling can be performed with the programs available in most conventional statistical packages, but some special applications may require customized software.

In analyzing data on the effects of occupational exposures in populations with a high prevalence of smoking, modeling facilitates the control of confounding by smoking; multiple variables that characterize smoking, such as duration, daily amount, and depth of inhalation, can be entered simultaneously into the model. Further, if the cumulative exposures to the occupational agent and to cigarette smoke are temporally correlated, modeling may more satisfactorily separate their effects, in comparison with stratified analysis.

A recent report by Whittemore and McMillan (1983) illustrates the application of modeling to occupational data. These investigators analyzed data collected in the U.S. Public Health Service study of Colorado Plateau uranium miners, a prospective cohort study of

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mortality in relationship to exposure to radon daughters in the mines. Their analysis assessed exposure to radon daughters and cigarette smoking as risk factors for lung cancer. To assess the joint effects of smoking and radiation, they developed and contrasted additive and multiplicative models. They found that the multiplicative model fit the data better than the additive. Of the alternative multiplicative models, giving the highest likelihood of the data was a linear function of the variables for smoking and radon daughter exposure. Whittemore and McMillan then used this multiplicative model to assess the effects of age and birth cohort. This analysis complemented the conventional cohort methods that had been applied previously to the data (Lundin et al. 1971; Archer et al. 1976).

Most conventional forms of modeling assume either an additive or a multiplicative relationship between the independent effects of the variables representing the exposures. Case–control data are most often analyzed with the multiple logistic model (Breslow and Day 1980; Schlesselman and Stolley 1982), although alternatives have been described (Walker and Rothman 1982; Breslow and Storer 1985). The multiple logistic model is multiplicative; the risk of disease from multiple exposures is obtained as the product of the risks from the individual exposures, in the absence of interaction among the exposures. A variety of approaches have been described for the modeling of data from cohort studies (Breslow et al. 1983; Breslow 1985). These models may be developed as additive or as multiplicative or on other scales.

In developing a model, confounding is controlled by introducing variables for the potentially confounding exposures. Statistical interaction among the variables is tested by entering terms formed as their product or by running the model within groups of subjects separated by their classification on one of the exposure variables. When a product term is entered into a model to test for interaction, the presence and extent of interaction is indicated by the coefficient calculated for the product term. Most modeling techniques also supply a test of statistical significance for the coefficient, under the null hypothesis that its value is zero. Such a test of statistical significance may not be very powerful (Greenland 1983), and the coefficient may suggest an interaction of potentially important magnitude, although it does not reach statistical significance at conventional levels.

The presence of statistical interaction between two variables demonstrates that their effects are interdependent, as assessed by the specific statistical model (Rothman et al. 1980). Statistical interaction does not necessarily imply biological interaction. In fact, the interpretation of interaction hinges on the scale on which it is measured; the choice of the statistical model may determine whether

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interaction is present or absent, synergestic or antagonistic (Greenland 1979; Rothman et al. 1980). If possible, the choice of model should be based on biological considerations. For malignancy, the results of modeling may be interpretable within the conceptual framework supplied by the theory that carcinogenesis is a multistep process (Armitage and Doll 1961; Day and Brown 1980).

Public Health Interactions

From a public health perspective, an interaction occurs when the number of individuals injured, or the extent of the injury, with combined exposure exceeds that expected from the sum of the background rate and the differences between the background rate and the rates with the individual exposures. Public health interactions can be considered a case of statistical interaction in which both the model being tested and the outcome measurement scale being used are defined by their ability to assess the contribution of a given agent to the disease burden in society. When a positive interaction occurs in this definition, the term "synergism" should be used. The model used to examine interactions is often further specified by the importance of considering the intensity and duration of exposure in the risk model being examined. Establishing a dose–response relationship for an exposure supports a causal association, and the slope of the exposure–response relationship allows an estimation of the reduction in disease burden that might occur with a reduction in the workplace exposure. Both of these issues are important in establishing safe levels of exposure in the working environment.

Estimation of the reduction in disease burden due to an occupational exposure with the lowering of exposure levels has three components: How much disease will be prevented in those workers who begin their work exposure at the new levels? How much disease will be prevented by reducing the exposure of workers previously exposed to higher levels to these levels? and How much disease can be prevented by altering the smoking habits of the exposed workers? For those exposures for which synergism between smoking and an occupational exposure exists, the sum of these three estimates may exceed the total amount of disease that occurs in the population (Samet and Lerchen 1984; Doll and Peto 1981). If a group of asbestos workers have a fiftyfold increased risk with combined exposure and a fivefold risk with exposure only to asbestos and a tenfold risk with exposure only to cigarettes, then elimination of smoking would eliminate 90 percent of the risk (from 50 to 5) and elimination of asbestos would eliminate 80 percent of the risk (from 50 to 10). The sum of these reductions is greater than 100 percent, and points out that for prevention efforts, the synergistic effect works to potentiate the effect of the intervention.

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Confounding of Occupational Exposures by Smoking Behavior

By the nature of the employing industries, most occupational exposures occur to a limited number of individuals who are often geographically clustered and who are not representative of the U.S. population. Prospective studies of cancer rates in populations that are representative of the U.S. population generally contain too few individuals with specific occupational exposures to allow analysis by occupational exposure. Therefore, most studies of occupational exposures involve populations selected on the basis of a specific exposure. Then either these selected populations of exposed workers are compared with a control group or individuals with high dose exposures are compared with individuals with low dose exposures. Validity depends upon the comparability of the groups being examined for variables that may influence cancer risk other than occupational exposure. Age is one such variable, as rates of most cancers increase with increasing age. For those cancers linked to smoking, the comparability of the smoking habits of the various exposed subjects is a second such variable. This variation may potentially confound an association between an occupational exposure and a cancer known to be associated with smoking, and control for this potential confounding may be critical for an unbiased evaluation of such an association.

Sources of Confounding

Confounding is the distortion of the apparent effect of an exposure on risk brought about by the association with other factors that can influence the outcome (Last 1983). Cigarette smoking can be a confounding factor in occupational studies through an association (either positive or negative) with the exposure in question. As described earlier in this chapter, the major determinants of smoking-related risk in a population include smoking prevalence, intensity of exposure, and duration of exposure. Each of these measures can potentially confound an occupational exposure.

Smoking Status

In occupational studies, cancer mortality in the occupational group is often compared with that in the entire population of a given geographic area. Age-specific death rates are available for the U.S. population on an annual basis and can be used to develop an age- and calendar-year-adjusted overall expected number of deaths, or a cause-specific expected number of deaths, for the population of workers being examined. The ratio of the actual number of deaths in the exposed population compared with the expected number in the general population, multiplied by 100, is referred to as a standardized mortality ratio (SMR) for the exposed population. The SMR may

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be based on national mortality data or on data from the geographic location of the exposure group. In addition to providing a control population, the use of SMRs also adjusts for differences in age distribution between the exposed population and the population on which the SMR is based.

Cigarette smoking behavior is not uniformly distributed throughout the U.S. population. As demonstrated in the preceding chapter, there are substantial differences in smoking behavior among men and women, blacks and whites, different age groups, and different occupations. It is not surprising, therefore, that the smoking behavior of selected populations of exposed workers might differ markedly from the average for the U.S. population, and these differences would be expected to influence the SMR for smoking-related cancers.

Axelson (1978) has suggested that the effect on the SMR of differences in smoking habits could be estimated by dividing the population being examined into various smoking categories, multiplying the proportion of the population in that smoking category by the relative risk of developing disease produced by that smoking category, and summing the resultant numbers. The ratio of this number, calculated for the exposed population and compared with the number for the population on which the SMR is based, is then a multiplier that can be used to evaluate the effect on the SMR of the smoking habits of the exposed population.

In its simplest form this calculation would use only the proportion of smokers and nonsmokers in the population and a single relative risk number for the smokers. The effect that differences in smoking habits might have on the SMR for three different relative risks due to smoking is shown in Table 2. These different relative risks correspond approximately to the different relative risks for different sites of cancer associated with smoking (US DHHS 1982). Blair and colleagues (1985) have compared the crude and smoking-adjusted SMRs for different job categories in the population of the U.S. veterans study. They used four categories: smoker, never smoked, ex-smoker, and other. In general, adjustment for smoking did not substantially alter the SMRs for lung cancer (R 0.88), and the differences were small for most job categories (the largest difference between crude and adjusted SMR, 68.0).

Measures of Smoking Intensity

The risks due to smoking increase with increasing number of cigarettes smoked per day and depth of inhalation (Table 1) (US DHHS 1982). A calculation, similar to the one in the preceding section, can be performed using separate risk estimates for light smokers and heavy smokers and for ex-smokers. The magnitude of the effect on the SMR for lung cancer of a range of different smoking

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TABLE 2.—Effect of differences in smoking prevalence on the relative risk of an occupational group compared with a control group

Assumed risk due to smoking	Proportion of smokers in control group	Proportion of smokers in exposed group				
		.1	.3	.5	.7	.9
2	.1	1.00	1.18	1.36	1.55	1.73
	.3	.85	1.00	1.15	1.31	1.46
	.5	.73	.87	1.00	1.13	1.27
	.7	.65	.76	.88	1.00	1.12
	.9	.58	.68	.79	.89	1.00
5	.1	1.00	1.57	2.14	2.71	3.29
	.3	.64	1.00	1.36	1.73	2.09
	.5	.47	.73	1.00	1.27	1.53
	.7	.37	.58	.79	1.00	1.21
	.9	.30	.48	.65	.83	1.00
10	.1	1.00	1.95	2.89	3.84	4.79
	.3	.51	1.00	1.49	1.97	2.46
	.5	.35	.67	1.00	1.33	1.65
	.7	.26	.51	.75	1.00	1.25
	.9	.21	.41	.60	.80	1.00

prevalences and dosages is shown in Table 3, calculated using a relative risk of 7 for smokers of less than one pack per day, 20 for smokers of over one pack per day, and 4 for ex-smokers. These relative risks were drawn from the major prospective mortality studies on smoking (US DHHS 1982). The proportions of smokers and ex-smokers in the population and the percentage of smokers who smoke more than 20 cigarettes per day were drawn from the data presented in the preceding chapter for the U.S. population between the ages of 20 and 64. On the basis of the data, the current differences in smoking patterns between blue-collar men and the total male population might be expected to result in a 10.2 percent elevation in the SMR for lung cancer. A hypothetical population with a prevalence of current smoking of 80 percent might have a 59.9 percent increase in the lung cancer SMR. Correspondingly, a population with a low smoking prevalence might have a 45.1 percent reduction in the SMR. These numbers are similar to those calculated for the Swedish population by Axelson (1978) as outer limits of the adjustment that might need to be made in lung cancer SMRs, secondary to differences in smoking patterns in an occupationally exposed population.

One of the basic assumptions made in the risk adjustment calculations described is that differences in smoking behavior (and the resultant risk) can be described by simple prevalence numbers (percentage of smokers, never smokers, and ex-smokers) or by using

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TABLE 3.—Effect of differences in smoking prevalence on the standardized mortality ratio for lung cancer

Group	Smoking status					SMR multiplier
	Total	Current		Former	Never	
		< 20	≥ 20			
U.S. population	40.9	29.4	70.6	40.0	19.1	1.0
White collar	39.9	27.8	72.2	40.8	19.7	0.994
Blue collar	47.1	28.2	71.8	34.8	18.1	1.102
Hypothetical low	20.0	29.4	70.6	20.0	60.0	0.549
Hypothetical high	80.0	29.4	70.6	10.0	10.0	1.599

a division of current smoking prevalence into heavy smokers or light smokers. Other characteristics of smoking behavior have also been shown to influence lung cancer risk, including depth of inhalation, age of initiation (duration), and tar and nicotine yield of the cigarette smoked (US DHHS 1981, 1982). The differences in lung cancer relative risks among male smokers in the ACS study of 1 million men and women resulting from differences in depth of inhalation and age of initiation are presented in Table 1. It is apparent that substantial differences in lung cancer mortality ratios (up to fivefold) can occur within the broad category of smokers because of differences in the various dosage measures. It also appears that, in general, the difference in mortality ratios between the highest and lowest exposure categories was greater in the older age group than in the younger age group.

When the SMR is based on the general population, in which smoking behavior is in the middle range of the dosage measures in Table 1, it is unlikely that differences in behaviors between an exposed population and the general population would equal the differences between the highest and lowest dosage categories. However, sizable differences may occur, and the values shown in Table 1 can be used to estimate the impact of these differences. If the lowest age of initiation (under 15 years) were used as the risk for the exposed population, and the risk for an age of initiation of age 20 to 24 were used for the control population, there would be a 30 percent increase (using one risk value for all current smokers) in the SMRs listed in Table 3. This would increase the SMR for the hypothetical high smoking prevalence population to 207.4. A corresponding adjustment for a difference in depth of inhalation could increase

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hese numbers even further. However, because there is almost ertainly some correlation among the various dosage measures smokers of higher numbers of cigarettes per day are more likely to nhale and to have begun smoking at an earlier age), it is not valid to reat these numbers as independent measures of risk. It does seem lear, however, that substantial variations can occur in the "expect-ed SMR" for a population, based on differences in smoking preva-ence, differences in number of cigarettes smoked per day, and probably differences in age of initiation. These adjustments suggest that SMRs in excess of 200 may occur owing to differences in smoking patterns and differences in depth of inhalation. The use of high tar and nicotine cigarettes might increase the SMR even further.

In the description of differences in smoking patterns by occupation presented in the preceding chapter, only modest differences between blue-collar workers and white-collar workers were found for age of initiation and number of cigarettes smoked per day. However, larger differences in these dosage measures are present among some of the subcategories of blue-collar and white-collar workers. Substantial variation from national norms in the various dosage measures may also occur because of sampling and selection bias in the small population samples that are often a real limitation in occupational studies. Even in larger studies, such as the study of 17,800 asbestos insulation workers (Hammond et al. 1979), substantial differences between the asbestos-exposed workers and the general population in number of cigarettes smoked per day are demonstrable (82.8 percent of the asbestos workers smoked more than 20 cigarettes per day in contrast with 68.5 percent of the men in the general population).

Failure to control for differences in smoking behavior may lead to a spurious impression of interaction. A spurious interaction produced by differences in smoke dose has a greater public health significance when the outcome is an apparent antagonism rather than a synergism. If the workers who smoke and are exposed to a given agent smoke fewer cigarettes per day, or began smoking later in life than the control population, an apparent protective effect (i.e., a less than additive effect) of the occupational exposure may result. In this setting, if the population of nonsmokers is too small to evaluate the effects of the occupational agent, only the biased estimate of the agent's effect on smokers will be available; the spurious antagonism may mask the effect of an occupational carcinogen by lowering the rate of lung cancer in the workers with combined exposure. A lower number of cigarettes smoked per day may be a relatively frequent confounder in worksites where smoking is not allowed during working hours, and a later age of initiation may exist in workforces with higher education levels. Thus, lack of information on smoking may lead to biased estimates of the effect of

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an occupational agent, and even to the impression that the agent has no effect. This potential for missing the effects of an occupational carcinogen makes the incorporation of dosage data a critical part of the consideration of statistical interactions.

This discussion has used examples in which differences in smoking dosage measures resulted in spurious interactions between smoking and occupational exposures. However, the same potential exists for differences in occupational exposure dose between smokers and nonsmokers in the exposed population. If the smokers in the exposed population have a greater exposure to an occupational carcinogen than the nonsmokers, then the effect of combined exposure might be expected to appear to be greater than additive.

A companion question of "dosage" measurement among the smokers in occupational studies is how to classify pipe and cigar smokers and former smokers. Pipe and cigar smokers have a lower risk of developing lung cancer (but not oral cancer) than cigarette smokers and are distributed differently by age, reflecting the greater use of pipes and cigars by older men (US DHEW 1979). To the extent that differences in the use of pipes and cigars exist among exposed groups and control populations, the effects of smoking may be confounded if pipe and cigar smokers are classified in the study as smokers. Pipe and cigar smokers should be either analyzed as a separate category, or if the number of subjects is too small for separate analysis, they may be combined with light smokers as part of a dose–response relationship. A similar problem arises with former smokers. The lung cancer risk in former smokers declines with the increasing duration of cessation. Few people begin to smoke after age 25, and the percentage of the population who have quit smoking increases with increasing age. Many occupational settings have been the focus of intensive cessation efforts, particularly those worksites where an increased lung cancer risk has been established or suspected. These efforts, as well as the other previously described reasons for differences in smoking patterns, may make the prevalence and age distribution of former smokers in an occupationally exposed population different from that in a control population; therefore, former smokers should not be included with current smokers in an analysis of occupational exposures but should be treated as a separate category.

One of the methods that has been used to control for the differences in smoking between control groups and exposed populations, or between cases and controls (Liddell et al. 1984), is to examine the dose–response relationships of smoking and occupational exposure for lung cancer. An example of such an analysis performed on a group of asbestos miners using a case–control approach is presented in Table 4. The risk of developing lung cancer is shown to increase with increasing cumulative asbestos exposure in

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TABLE 4.—Risks of lung cancer, by cigarette smoking and asbestos exposure, relative to all 223 cases and 715 referents for whom smoking histories were reliable; unmatched analysis

Pack-years[1]		Exposure accumulated up to 9 years before death of case (f/mL)•y			
		Low (<100)	Medium (<1,000)	High and very high (≥1,000)	All
0	Number of cases	6	7	10	23
	Number of referents	103	61	37	201
	Relative risk	0.19	0.37	0.87	0.37
1, <40	Number of cases	29	27	34	90
	Number of referents	123	93	63	279
	Relative risk	0.76	0.93	1.73	1.03
≥40	Number of cases	40	35	35	110
	Number of referents	117	79	39	235
	Relative risk	1.10	1.42	2.88	1.50
All	Number of cases	75	69	79	223
	Number of referents	343	233	139	715
	Relative risk	0.70	0.95	1.82	1.00

[1] Number of cigarettes a day/20 x duration in years.
SOURCE: Liddell et al. (1984).

all three categories of smoking dose. Stratification is useful for examining exposure–response relationships, an important element in establishing a causal association between a given exposure and lung cancer.

If stratification is used to control the confounding between smoking and an occupational exposure, careful consideration must be given to the relative magnitudes of the effects of smoking and occupational exposure on lung cancer risks when determining the number of smoking dose categories compared with the number of occupational exposure dose categories. As discussed elsewhere in this Report, the prevalence of smoking has been higher among men born between 1910 and 1930 than among men born in later decades. This cohort of men represents the older workers in many occupationally exposed populations, and it is these same workers who were previously exposed to levels of occupational agents that substantially exceeded the levels currently experienced. Thus, populations of older workers have had higher cumulative exposures to occupational agents than their younger peers at the same age, and have also had higher cumulative exposure to cigarette smoke than their younger peers at the same age. The result may be a residual confounding between cumulative occupational exposure and cumulative smoke exposure in assessing the effects of these two exposures. If the

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magnitude of the effect of smoking is large compared with the magnitude of the effect of the occupational exposure, and few broad categories of smoking status are used with a greater number of categories of occupational exposure, then higher levels of smoking dose may occur with increasing occupational exposure dose category, generating a spurious dose–response relationship. Correspondingly, too few occupational exposure categories may result in a spurious strengthening of the dose–response relationship present for smoking. The total number of categories that can be used in this kind of analysis is usually limited by the number of lung cancer patients available for analysis; therefore, the distribution of the dosage categories to smoking and to the occupational exposure should reflect the relative magnitude of the effects of the separate exposures on lung cancer risk.

Duration of Exposure

In models of lung cancer risk due to smoking behavior, separate terms for intensity of smoking and duration are commonly included. In a risk model developed by Doll and Peto (1978) for the study of British physicians, the term for intensity of exposure was raised to the second power and the term for duration of exposure was raised to the power of 4.5.

Confounding may arise because of correlation between age and duration of exposure. Because of the importance of duration of exposure (and its covariate age) on lung cancer risk, the majority of the lung cancer cases will develop in the older members of a population. Correspondingly it is the smoking prevalence and dosage among these older workers that will largely determine the lung cancer risk for the population. The mean prevalence or mean dosage measures for the population do not take into account the effect of duration of exposure on the lung cancer risk. In a comparison of populations with different age distributions of smoking prevalence, or of the prevalence of heavy smokers, the population with the higher prevalence in the older age ranges will have the higher risk.

A final source of concern in examining the relationship between occupational exposure and lung cancer in cigarette smokers is generated by the lag time between the exposure to a carcinogen and the clinical manifestation of lung cancer. This lag time is a combination of the induction period (the time from exposure to disease initiation) and the latent period (the time from disease initiation to clinical manifestation) (Rothman 1981). This lag period is not fixed, but rather has a broad distribution over perhaps 50 or more years (Nicholson et al. 1982).

Epidemiologically, the shortest lag times are identified by the interval between the age of onset of exposure and the age when an increased relative risk can first be demonstrated secondary to the

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exposure. For some exposures, once the exposure period has exceeded the shortest lag time, the relative risk often increases rapidly with increasing duration of exposure (Nicholson et al. 1982), resulting in a dramatic increase in disease rates with increasing age. It appears that the shortest lag period for smoking-induced lung cancers is in the range of 15 to 20 years, as demonstrated by the rise in lung cancer death rates that begins after age 30 to 35. The lag period for occupational carcinogens in lung cancer is not well characterized, but some agents have lag times similar to that found with smoking (Nicholson et al. 1982; Selikoff and Lee 1978). However, the onset of exposure to cigarettes and occupational carcinogens may occur at substantially different ages. Any such difference needs to be considered when examining the interactions of occupational exposures and smoking.

Ideally, the study of an occupationally exposed cohort would follow the entire cohort until the last survivor had died, so that late effects of exposures would not be missed. The reality of examining working populations and the need for timely assessment of existing risks makes the examination of workers at a variety of ages the norm in epidemiologic studies. In this setting, careful consideration of the differences in age of onset of smoking and of occupational exposures is necessary if the effects of occupational exposure are not to be missed or underestimated. For example, assuming that the average age of onset of smoking is 15 and the average age of onset of a particular occupational exposure is 25, the combined exposure effect is one of equal and additive risks of lung cancer and the lag time for both agents is 20 years. The lung cancer risk due to smoking would begin to increase at age 35, but because of the 10-year difference in age of onset of exposure, the risk due to the occupational exposure would not begin to be expressed until age 45, and even then would appear to be much smaller than the risk due to smoking because of the effects of the longer duration of exposure to cigarettes. If the cohort of workers with these two exposures is relatively young, with few older workers, then the effect of an occupational exposure may be missed or substantially underestimated. A similar concern exists when examining an agent that was introduced into the workplace 20 to 30 years ago. The cohort of exposed workers would represent a cross-section of ages, and therefore a cross-section of smoking habit durations. An additive risk effect of the occupational exposure would be small in comparison with the cumulative risk secondary to smoking in the older workers, and the number of cases of lung cancer in young workers (where the risk effects might be more equal) would be small. Again, the effect of an occupational carcinogen could easily be missed in this setting.

This discussion uses a simple statistical model of independent additive effects in concert with a biological concept of lag time.

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Interpretation based on this kind of biologic extrapolation of statistical concepts is hazardous at best; nevertheless, some consideration of the differences in the age of onset of exposure should be part of both the biologic and the statistical considerations of the interactions between smoking and occupational exposures.

Control of Confounding

The examination of the risk associated with an occupational exposure generally requires a comparison group. Prospective mortality studies of the general population generally have too few individuals with the exposures of interest to allow analysis. Therefore, cohort and case–control formats have commonly been used. The control groups in either of these formats may be external (i.e., separate population) or internal (i.e., workers with high exposure compared with workers with lower exposure). A variety of methods have been used to deal with the confounding of occupational exposure by cigarette smoking.

Comparisons Using External Control Populations

Common external control populations are the national or regional populations. Death rates in these populations can be used to generate age- and time-adjusted expected numbers of deaths for the exposed population, with the ratio of actual deaths to expected deaths as the SMR. The large numbers of deaths in these large control populations results in relatively stable death rates over time for the common causes of death, and the smoking habits of these populations are often available from national or regional survey data. However, the smoking habits of the population are not known in relation to the cause of death, which limits the use of this data to control the confounding of occupational exposure by smoking in occupational cohorts. If the smoking habits of the workforce are also known, then the magnitude of the effect that the differences in smoking habits might have on the SMR can be estimated by assigning risk values to the proportions of the populations in different smoking categories (as described in the section on sources of confounding) (Axelson 1978). This adjustment for differences in smoking prevalence ignores trends over time as well as a variety of other potential sources of confounding. However, when this approach is used, the smoking-adjusted SMR alters the expected value of the SMR from the value of 100 that was expected prior to adjustment for smoking.

An alternative approach is to use an external control population for whom the smoking habits are known in relation to the causes of death. The use of a control population with known smoking habits allows the direct comparison of populations of smokers and non-

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smokers with and without the exposure being investigated. These direct comparisons allow an examination of the risk of the occupational exposure in the absence of smoking (i.e., in never smokers) and also the examination of potential interactions between smoking and occupational exposures. A study may be constructed to prospectively or retrospectively examine the lung cancer death rates in a cohort of occupationally exposed workers compared with a control population, or a group of patients with lung cancer may be identified and matched with a set of controls without lung cancer in order to examine the frequency of a given occupational exposure in the two groups. In examining lung cancer risk, it is important that the control population be similar to the exposed population in age, ethnicity, socioeconomic status, and geographic location.

In general, studies are designed to be able to identify levels of lung cancer risk due to occupational carcinogens that are lower than the level of risk due to smoking. This potential difference in magnitude of effect needs to be assessed carefully when considering the level of detail with which the smoking data are obtained and examined.

The selection of a control group for an occupational study is often influenced by the ease with which data can be collected as well as by the comparability of the control group with the exposed workers. Control groups can be selected from unexposed workers in the same plant, from workers in different plants where no exposure occurred, from populations selected from the same geographic locations as the workers, and from populations being followed as part of other epidemiologic investigations. Some of these control groups may have substantial differences in smoking behavior from the exposed group. For example, if management and administrative employees are included in the control group, the prevalence of smoking in the control population or in comparison with a blue-collar exposed group may be reduced. Similarly, controls selected from different worksites may have different smoking patterns owing to differences in work rules, age of employees, or other demographic factors, or simply by chance. Populations drawn from other epidemiologic studies may also have different smoking patterns, and the mode of determination and definition of smoking status may be different from that used in the exposed group.

A common method of controlling for the confounding due to smoking is to separately examine smokers, nonsmokers, and former smokers. This allows examination of the independent effects as well as of the interactions; however, the examination of smoking patterns represents slightly different challenges in each of these groups.

Lung cancer risks may be examined in nonsmoking populations of occupationally exposed and nonexposed individuals for two separate reasons. First, such analyses can establish whether a risk due to occupational exposure occurs in the absence of cigarette smoking or

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whether exposure only modifies the effect of smoking. Second, nonsmokers represent the lowest dosage category in examining the dose–response relationship for smoking. The demonstration of an effect of an occupational exposure in the absence of cigarette smoking requires a population of lifelong nonsmokers who have neither smoked cigarettes or cigars or used a pipe. In contrast, when a dose–response relationship is being examined, it would not be unreasonable to combine never smokers with pipe and cigar smokers, or even with light smokers, as a low dose group for lung cancer risk (pipe and cigar smokers should not be included in the low dose group for oral cancer risk). For exposures with modest increases in lung cancer risk, the low prevalence of never smoking status, coupled with the low expected risk of lung cancer in this group, means that large populations of workers must be examined in order to define the risk of exposure in the absence of smoking. Most occupational studies are limited by the size of the workforce being examined, and therefore, it is often necessary to combine never smokers with low smoking risk groups in order to have an adequate sample size. Once this combination has taken place, the study can examine only the effect of low smoke exposure coupled with occupational exposure, rather than the effects of occupational exposure in the absence of smoke exposure.

The low prevalence in many current workforces of people who have never smoked and the low risk of lung cancer in this group generally means that only a very few lung cancer deaths occur in this group, limiting the number of deaths for which to perform an analysis of the effects of an occupational exposure in the absence of smoking. For example, in the large study of asbestos insulation workers (Hammond et al. 1979), only 5 lung cancer deaths were recorded in nonsmokers out of more than 8,000 asbestos-exposed workers (smokers and nonsmokers included) whose smoking habits were known. Drawing inferences from small numbers of lung cancer cases is necessary in occupational studies, but two important caveats should be considered. First, it is essential that lung cancer patients placed in the never smoking category are actually individuals who have never smoked. The inclusion of even modest numbers of misclassified smokers or light smokers may increase the number of lung cancers over that expected on the basis of the risks in the never smoker, nonexposed control population. For this reason it is critical that the data on smoking habits be accurate and obtained in the same way in the exposed population as in the control population. When the level of monetary compensation for occupational disability may be influenced by smoking status, workers may be motivated to define themselves as never having smoked, regardless of their actual smoking status. In many studies the determination of smoking status is made for the living subjects by questionnaire or interview

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TABLE 5.—Comparison of smoking habit data obtained during life and after death

Smoking habit data obtained during life, 1971	Number	Smoking habit data obtained at death			
		Never smoked	Formerly smoked	Smoked	Smoked at some time
Never smoker	12	8	2	2	0
Ex-smoker	26	2	15	2	7
Smoker	76	1	12	33	30

SOURCE: Berry et al. (1985).

and for those who have died (which would include most individuals with lung cancer) by questioning next of kin or checking hospital records. Berry and colleagues (1985) examined the comparability of these data sources in a prospective evaluation of asbestos workers in which smoking data were accumulated both at the start of the study period (i.e., prospectively) and at the time of death from lung cancer (i.e., retrospectively). A comparison of the smoking status obtained by the two methods for the same individuals is shown in Table 5. In general, there was good agreement between the two methods, but both methods identified as never smokers individuals who were classified as smokers by the other method. No data were presented to allow determination of which method was more accurate.

The random misclassification of smoking status, of itself, should not introduce spurious associations for the population as a whole, or for the smokers in the population (Greenland 1980). However, when the question being asked is whether a risk exists in the absence of smoking and synergism between smoking and the occupational exposure is present, the misclassification of even small numbers of exposed smokers as nonsmokers can lead to the conclusion of increased risk of lung cancer due to an occupational exposure in the absence of cigarette smoking. The potential for misclassification exists and is of greatest concern when decisions are being made on small numbers of cases.

The second caveat that may need to be applied in the examination of the effects of occupational exposure among people who have never smoked is the potential effect of involuntary exposure to cigarette smoke. A number of studies have shown increased lung cancer risks in the nonsmoking wives of smokers, raising the question of a carcinogenic risk due to environmental tobacco smoke exposure (IARC, in press). If these studies can be extrapolated to the workplace, then the potential exists for environmental tobacco smoke in the worksite to act as an occupational carcinogen,

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particularly in those occupations in which there is a high prevalence of active smoking among workers.

The considerations raised by examination of smokers with workplace exposures are somewhat different from those raised by examination of nonsmokers. Comparisons of smokers with and without an occupational exposure require careful attention to the correlations among age, duration of exposure, and smoking dose. Age adjustment of the death rates in the exposed group and the control population is generally accepted as more useful than simply comparing the mean age of the two populations, because of the rapid rise in lung cancer death rates in the older age groups. It is less widely understood that age adjustment does not eliminate the effects of differences in the age distributions of smokers between the two populations. The smoking-related risk of developing lung cancer occurs disproportionately in older smokers compared with younger smokers. Therefore, in two populations with similar prevalences of smoking, but with different age distributions of that smoking prevalence, the population with the higher prevalence of smoking in the older age group will have the higher number of lung cancer deaths. This difference in number of lung cancers will persist after an age adjustment using the age distributions of the entire population (smoker and nonsmoker). Therefore, in considering the differences between occupationally exposed smokers and smokers who are not exposed, the lung cancer deaths should be adjusted for age on the basis of the age distribution of the smokers in the two populations rather than the age distribution of the entire population.

Several attempts have been made to combine the strengths of large population-based measurements with the detailed measurements of smoking status available in cohort studies. Hammond and colleagues (1979) used the American Cancer Society (ACS) study of 1 million men and women to develop a control group for a study of asbestos insulation workers. From the ACS study population, they extracted a group of more than 73,000 men who were white, not a farmer, had no more than high school education; did have a history of occupational exposure to dust, fumes, vapors, gases, chemicals, or radiation; and were alive at the time of the initiation of followup of the insulators. From this control group, they were able to develop age-specific and smoking-specific expected lung cancer death rates for comparison with the observed death rates in the insulation workers. There was a difference in the time period of followup between these two studies; therefore, the expected lung cancer death rates were adjusted upward on the basis of differences in the national lung cancer death rates during the years of differential followup. This approach allowed the expected rates to be calculated from a large enough population to provide stable rates in a number of separate age and smoking categories. The control group and the

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exposed populations were also matched for a number of those characteristics that raise questions about the comparability of national death rate data to populations of employed workers.

A somewhat different approach to the same problem was taken by Berry and colleagues (1985). They used data from a prospective mortality study of British physicians by smoking status (Doll and Peto 1978, 1981) to develop factors that related the risks of smokers, nonsmokers, and ex-smokers separately to the risk in the entire population of physicians. They calculated the expected number of deaths for the exposed workers in each smoking category, using national death rate data, and multiplied this expected number of deaths by the smoking factor to get a smoking-specific expected number of deaths for each category of exposed workers. They also adjusted the number of expected deaths for differences in geographic location by multiplying the expected deaths by the ratio of the local lung cancer SMR to the national lung cancer SMR. This approach is obviously quite sensitive to the method by which the smoking-specific factors are developed, and it is not clear that one set of factors can be applied to all ages.

When an explicit control population is being used, the differences in smoking behavior can be controlled through the use of a statistical model for lung cancer risk in the population. Models may include a variety of measures of cigarette smoking dosage and duration, and the mortality experienced by the exposed population can be examined by using the risk model developed in the control population. This approach allows the confounding due to smoking to be adjusted through the use of terms for intensity and duration of exposure.

Comparisons Using Internal Control Populations

The use of an internal control group drawn from the same workforce as the exposed population, but not exposed to the agent of interest, may produce a control group that is more closely matched to the exposed population than the total U.S. population would be (Breslow et al. 1983; Pasternack and Shore 1976; Redmond and Breslin 1975). Working populations tend to have a lower overall mortality than the U.S. population of the same ages (McMichael 1976; Enterline 1975; Fox and Collier 1976; Shindell et al. 1978; Vinni and Hakama 1980), at least in part because workers with illness tend to drop out of the working population. This lower mortality has been called the healthy worker effect and is one of the reasons the selection of an internal control population may be more appropriate than using SMRs for evaluating occupational exposure risks. External control groups, selected from populations geographically or demographically similar to the exposed population, may also provide a population more similar to the exposed workers than the general U.S. population.

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That the smoking behaviors of the exposed group and the control population are comparable must still be established. The selection of a control population based on its similarity in one variable (such as worksite) does not allow the assumption of comparability on other variables (such as smoking behaviors). It is possible for a control population to deviate from national measures of smoking behavior in one direction and for the exposed population to deviate in the opposite direction; thus it is important to actually examine the comparability of the smoking behaviors in the exposed group and the control population even when an internal control population is used.

The absence of an external control group means that the entire population has some exposure. Potential confounding of cumulative occupational exposure by cumulative smoking exposure can be reduced by stratification of the two exposures in question. The risk with increasing exposure to an occupational agent can then be examined within each strata of smoking exposure. Stratification of smoking by intensity only (cigarettes per day) would lead to a residual confounding of smoking and cumulative dust exposure, owing to the importance of duration of smoking for lung cancer risk and the association of age with both duration of smoking and cumulative dust exposure.

The reduction of residual confounding should also guide the selection of the number of strata selected for smoking and the occupational exposure. The larger the risk due to smoking in relation to the risk due to the occupational exposure, the larger the number of smoking strata needed to control the confounding. The use of too few strata may result in the residual confounding producing the appearance of a dose–response relationship with the occupational exposure.

A second method of controlling the confounding of occupational exposure by smoking behaviors is through the use of modeling techniques. By using a multiple logistic regression, a model of the smoking variables that contribute to lung cancer risk can be developed. The model should include measures of intensity and duration as well as a factor for cessation. Other factors that may contribute to the model are type of cigarette smoked, use of pipes or cigars, and age of initiation (as separate from duration). Once the model is established for smoking variables, a term or terms for the occupational exposure can be added to the risk prediction equation and tested to see whether the term improves the fit of the model to the observed data.

Case–control analyses can also be applied in the absence of an external control group by examining the distribution of exposures in cases of lung cancer and in a control group selected from the sample population of workers, but who have not died of lung cancer. Confounding due to cigarette smoking can then be controlled by

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stratification (Liddell et al. 1984) or by modeling (Whittemore and McMillan 1983; Pathak et al., in press). This approach is particularly useful when a case–control analysis can be nested within an ongoing study of a cohort of workers. In this setting, the smoking habits of the workforce are often known prior to the development of lung cancer, eliminating the potential for biased recall of smoking habits by the lung cancer patients (or their survivors) compared with the controls.

Examination of Occupational Exposures When Smoking Habits Are Not Known

In many occupational settings the smoking habits of the workforce are either unavailable or incompletely ascertained. In these cases, the death rates for these workers are compared with rates for a control population or with national mortality data (to generate an SMR). The potential for smoking pattern differences to influence the SMR is then evaluated by calculating the maximal distortion that would be produced, assuming that the exposed population had a very high smoking prevalence. The calculations used are similar to those used in generating Tables 2 and 3. As discussed earlier, extremes of differences in smoking prevalence and dosage could be expected to generate SMRs in excess of 200, and differences in age distribution and type of cigarette smoked may increase this number even more. Once an outer limit for smoking-related distortions of the SMR is estimated, it becomes the value that must be below (outside) the confidence interval surrounding the actual SMR for the exposed population in order to exclude a potential smoking effect. This approach may be useful in settings where smoking data are unobtainable, but should not be used as a substitute for collecting smoking information.

When the mortality in a control population is compared with the mortality of an exposed population in the absence of smoking data, the potential for differences between the smoking habits of the two populations may be larger than the differences when using SMRs. The control group and the exposed population may deviate in opposite directions from the mean smoking behaviors represented in the SMR, and correspondingly, the differences in cancer outcome may also be magnified.

One method of adjusting for differences in smoking patterns between populations when smoking data are not available, or would be too costly to obtain, is to survey a random sample of the two populations for smoking behavior. The limitation of this technique is that the sample size needed to obtain estimates of usable precision is large and may approximate the size of the two populations combined.

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An additional method of examining the effects of unknown differences in smoking habits on the rates of one smoking-related cancer is to look at the rates of other smoking-related cancers in the same population. The various smoking-associated cancers do not all have the same incidence rates, rate of change in incidence with time, ethnic distribution, cure rate, or age distribution. These differences make cross-comparison between rates of these cancers as a measure of differences in smoking patterns between populations a complex and uncertain exercise at best. This kind of comparison may be useful as a point of discussion, but probably offers little in the way of an estimate of the differences between populations in their smoking behavior.

Summary and Conclusions

1. Cigarette smoking and occupational exposures may interact biologically, within a given statistical model and in their public health consequences. The demonstration of an interaction at one of these levels does not always characterize the nature of the interaction at the other levels.
2. Information on smoking behaviors should be collected as part of the health screening of all workers and made a part of their permanent exposure record.
3. Examination of the smoking behavior of an exposed population should include measures of smoking prevalence, smoking dose, and duration of smoking.
4. Differences in age of onset of exposure to cigarette smoke and occupational exposures should be considered when evaluating studies of occupational exposure, particularly when the exposed population is relatively young or the exposure is of relatively recent onset.

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CHAPTER 4

EVALUATION OF CHRONIC LUNG DISEASE IN THE WORKPLACE

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Introduction

Exposure to harmful agents in the workplace is, and will probably continue to be, an important and avoidable cause of both acute and chronic lung diseases. The major chronic lung diseases associated with workplace exposures can be classified as the pneumoconioses (fibrotic diseases of the lung parenchyma secondary to dust inhalation), industrial bronchitis and other processes involving the lung's airways, and occupational asthma. Some of these diseases were recognized long before cigarette smoking became prevalent. During the 16th century, Agricola and Paracelsus described diseases of miners (Hunter 1978); early in the 18th century, Ramazzini (1940) reported further on the respiratory problems of miners and noted that the lungs of stonecutters were full of sand. Occupational lung disease in coal miners was recognized during the 1800s (Morgan 1984a).

In the 20th century, many chronic lung diseases caused by workplace exposures have been studied intensively using epidemiological, physiological, and clinical approaches. The resulting data have been essential for developing the standards that govern workplace exposures and for evaluating worker safety. In this century, however, assessment of the effects of occupational agents on the lung has been made difficult by the widespread smoking of cigarettes. This behavior has been particularly prevalent among those at high risk for occupational lung diseases—men employed in blue-collar jobs (US DHEW 1979b).

The degree of pulmonary impairment in any individual represents the summation of the effects of all harmful environmental factors, including cigarette smoking, occupational agents, and other exposures. Cigarette smoking, in the absence of other exposures, causes chronic bronchitis (cough and mucous hypersecretion), airway abnormalities, and emphysema (abnormal dilation of the distal airspaces with destruction of alveolar walls); together, the last two disease processes underlie the expiratory flow limitation found in chronic obstructive lung disease (COLD) (US DHHS 1984). Cigarette smoking may potentiate the effects of some occupational agents on the lung. This potentiation may occur through an effect of cigarette smoke on the mechanism of lung injury that results from a given occupational exposure, or it may result from a mechanism of lung injury due to cigarette smoke that is independent of the mechanism of occupational injury but produces a level of combined lung damage capable of potentiating the level of disability or the level of abnormality detected by pulmonary function tests, x rays, or symptoms. The term "synergism" is used in this chapter to refer to an effect of combined exposure to cigarette smoke and occupational agents that results in a level of abnormality (by whatever measure being used) that is significantly greater than the sum of the levels of abnormality

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produced by the agents separately. Such interactions are of importance not only for researchers but also for the exposed workers and their employers. Synergism between cigarette smoking and occupational agents may, at the individual level, markedly raise the risk of developing disease and, at the group level, greatly increase the burden of occupational disease in the workforce. Thus, in evaluating the effects of workplace exposures on the lung, consideration must be given not only to the independent effects of cigarette smoking and of the agent of interest but also to the possible interaction of these factors.

This chapter describes the techniques used to evaluate chronic lung disease in the workplace and addresses the methodological issues raised by cigarette smoking. The focus of the chapter is largely confined to the chronic, fixed lung injuries that result from these exposures rather than the acute reversible responses that characterize occupational asthma. This focus was adopted in the interest of clarity and brevity and does not suggest that the issues related to the evaluation of occupational asthma are either unimportant or unrelated to cigarette smoking. Emphasis is placed on methodological problems; specific exposures are reviewed in other chapters of this Report.

Chronic Lung Diseases

Sources of Information

Although cigarette smoking is the predominant cause of preventable morbidity and mortality from respiratory diseases in the United States (US DHHS 1984), occupational exposures also produce substantial disease. Because the occurrence of nonmalignant respiratory diseases is not directly monitored, its frequency must be estimated from diverse information sources such as the National Center for Health Statistics, the U.S. Bureau of Labor Statistics, the Social Security Administration, and epidemiologic surveys. The extent to which chronic lung diseases are ascertained by these sources is difficult to establish, but coverage is probably not comprehensive.

Vital statistics enumerate the numbers of deaths from specific causes. Chronic conditions, such as respiratory diseases, may be listed on the death certificate, but remain uncoded unless they led directly to death. For example, Rank and Bal (1984) reviewed death certificates and found that in comparison with its frequency as an underlying cause of death, emphysema was listed nearly twice as often as an uncoded "other" condition. Vital statistics data cannot readily be used for addressing questions related to the pulmonary effects of cigarette smoking and occupational exposures. Cigarette smoking is not included on the death certificate, and only usual

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TABLE 1.—Number of deaths in selected categories of the International Classification of Diseases (ICD), for three time periods, United States

Cause of death	Year (classification)		
	1960 (ICD)	1970 (ICD)	1980 (ICD)
COLD			
Chronic bronchitis	2,287 (502)	5,014 (491)	3,269 (491)
Emphysema	9,253 (527.1)	22,721 (492)	13,877 (492)
Chronic airways obstruction n.e.c.[1]	—	4,444 (519.3)	34,743 (496)
Occupational disorders			
Coal workers' pneumoconiosis	810 (523.1)	1,160 (515.1)	982 (500)
Asbestosis	21 (523.2)	26 (515.2)	101 (501)
Silicosis	550 (523.0)	355 (515.0)	207 (502)
Other inorganic dusts	—	13 (516.0)	8 (503)
Other dusts	62 (524)	7 (516.1)	3 (504)
Unspecified	210 (523.3)		281 (505)
Conditions due to chemical fumes/vapors	—	5 (516.2)	43 (506)
Chronic interstitial pneumonia	3,973 (525)	3,351 (517)	202 (516.3)

[1] Not elsewhere classified.
SOURCE: US DHEW (1963); National Center for Health Statistics (1974), unpublished data (1980).

occupation and industry are noted. Further, the occupational information is not routinely coded by States (Kaminski et al. 1981).

Cause of death is coded according to the International Classification of Diseases, currently in its ninth revision (WHO 1977). For the chronic respiratory diseases, separate categories cover the obstructive disorders, major pneumoconioses, and other interstitial diseases (Table 1). As the International Classification of Diseases has been modified from the seventh through the ninth revisions, major changes in the coding of chronic respiratory diseases have been made. The categories for occupational lung diseases have been expanded and their titles have been made more specific. With the eighth revision (US DHEW 1968), a category (519.3) was added for the diagnosis of chronic obstructive lung disease (COLD). These changes must be considered in examining time trends of mortality. For example, after the introduction of a category for COLD, the number of deaths assigned to this code increased and deaths attributed to emphysema decreased (Table 1).

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Estimates of disease occurrence based on vital statistics must be interpreted with caution. Some causes of death may be underreported, and mortality rates may not directly reflect incidence. The mortality rate for a particular disease approximates the incidence rate as the case–fatality rate approaches unity (Kleinbaum et al. 1982). Competing causes of death will also influence the relationship between incidence and mortality (Kleinbaum et al. 1982). For example, Berry (1981a) examined the mortality of 665 men certified as having asbestosis by medical boards in England and Wales. Of the 283 deaths, 39 percent were from lung cancer, 9 percent were from mesothelioma, and only 20 percent were from asbestosis. The distribution of competing causes of death should be different in smokers and nonsmokers; thus, even for non-smoking-related occupational lung diseases the relationship between incidence and mortality may vary with smoking practices.

For several respiratory diseases, vital statistics underestimate mortality. For COLD, Mitchell and colleagues (1971) compared cause of death, as reported on the death certificate, with clinical and autopsy-derived diagnoses. In 211 subjects who died of COLD, as determined by autopsy, another cause of death was listed on the death certificate for 51. For asbestosis, Hammond and colleagues (1979) used "the best available medical information" and identified 160 deaths from this pneumoconiosis in a cohort study of asbestos workers. Only 76 were similarly classified by the death certificate statement of cause of death.

State workmen's compensation claims are another source of information about the occurrence of occupational lung diseases. However, most workmen's compensation claims involve acute problems (Whorton 1983) and may more accurately measure conditions associated with irritant gas or vapor inhalation than with the pneumoconioses.

Under the Occupational Safety and Health Act, selected employers are required to maintain records of occupational injury and illness (US House of Representatives 1984). In an annual survey, the Bureau of Labor Statistics collects and reports the injury and illness data. During 1982, 2,000 reports for dust diseases of the lungs and 8,800 for respiratory conditions due to toxic agents were filed, but more specific diagnoses were unavailable (US DOL 1984). In the introduction to the 1982 survey, it was acknowledged that "to the extent that occupational illnesses are unrecognized and therefore unreported, the survey estimates understate their occurrence" (US DOL 1984, p. 3).

On a national level, the Social Security Administration operates a compensation program for people who have been disabled for at least 5 months (US DHHS 1983). People receiving compensation for chronic lung diseases must meet this criterion as well as stringent

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requirements for the extent of impairment on lung function testing (US DHEW 1979a). Data from the Social Security Administration probably underestimate the prevalence of most chronic lung diseases. For example, Epler and colleagues (1980) showed that approximately 9 percent of a series of clinically diagnosed patients with pneumoconiosis met the Social Security disability criteria.

Epidemiological surveys offer the most accurate estimates of disease frequency, though the surveyed populations are generally limited to employed workers and disease frequency may therefore be underestimated. Estimates of disease frequency from a particular survey should be generalized cautiously. Nonrandom selection of occupational groups for study as well as the nonrandom enrollment of workers within a particular workforce may introduce bias.

Occurrence of Chronic Lung Diseases

Although the available data sources have limitations, they can be used to document the relative frequencies of cigarette-related and occupation-related chronic lung diseases. Most indicate that the diseases associated with cigarette smoking are much more common in the general population than those resulting from occupational exposures.

In recent years, mortality from COLD has steadily increased; the number of deaths rose from 32,179 in 1970 to 51,889 in 1980 (Table 1). The 1984 Surgeon General's Report, *The Health Consequences of Smoking: Chronic Obstructive Lung Disease* (US DHHS 1984), offered the estimate that 60,000 people would die from COLD during that year. Examination of COLD mortality rates for smokers and nonsmokers suggests that 85 to 90 percent of COLD deaths in the United States can be attributed to cigarette smoking (US DHHS 1984).

As described in the 1984 Surgeon General's Report, numerous surveys provide estimates of the prevalence of COLD (US DHHS 1984). Representative recent data have been collected in Tucson, Arizona, in six other U.S. cities, and nationwide in the National Health Interview Survey (NHIS). Lebowitz and colleagues (1975) sampled 3,805 subjects in Tucson from 1972 through 1974. In men over 44 years of age, physician-diagnosed chronic bronchitis and emphysema were reported to be 10.2 and 13.3 percent, respectively. In women over 44 years of age, the percentage with chronic bronchitis was 9.0 percent and with emphysema, 4.3 percent. From 1974 through 1977, Ferris and colleagues (1978) surveyed 7,909 men and women in six U.S. cities; 5 percent of the men and 1.9 percent of the women had airway obstruction, defined as a ratio of forced expiratory volume in 1 second (FEV_1) to forced vital capacity (FVC) less than or equal to 60 percent. The 1970 NHIS included about 116,000 persons in a nationwide sample (NCHS 1974). Individuals 19

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years of age and older were asked whether they or other family members not present at the time of the interview had bronchitis or emphysema during the previous 12 months. On the basis of this survey, 3.4 million Americans over 45 years of age were projected as having chronic bronchitis or emphysema. In contrast, data from the Social Security Administration, not included in the 1984 Surgeon General's Report, showed only 20,246 new claimants for COLD receiving disability benefits in 1979 (US DHHS 1983).

The available data sources also probably do not comprehensively document the nationwide occurrence of occupational lung diseases. The number of deaths recorded as due to several occupational lung diseases was stable from 1960 to 1980 (Table 1), but it is unlikely that these death certificate data provide accurate estimates of the actual prevalence or severity of these disease processes in the U.S. population, owing to the inaccurate reporting of these diseases as cause of death. The Social Security Administration is also an ongoing source of information. In 1977, 820 persons were granted disability for pneumoconiosis; in 1979, the number had decreased to 389 (US DHHS 1983). Data from the 1970 NHIS provide an estimate of the prevalence of work-related chronic lung diseases across the Nation (NCHS 1974). Participants were queried concerning dust in the lungs, silicosis, or pneumoconiosis during the previous 12 months; their responses were used to estimate that 126,000 people nationwide had these conditions.

Numerous workforces in the United States and elsewhere have been surveyed to establish the prevalence of occupational and nonoccupational lung diseases. Representative recent surveys of workers in the United States are presented in Table 2, showing the prevalence of disease and of cigarette smoking. Various disease indicators were considered in these studies. Chronic bronchitis was diagnosed on the basis of persistent cough and phlegm as ascertained by questionnaire. For the pneumoconioses, the presence of disease was based on the presence of radiographic abnormality. Of note is the high prevalence of coal workers' pneumoconiosis reported by Morgan and colleagues (1973). A different group of readers subsequently reinterpreted the chest films reported in the Morgan and colleagues study and found a prevalence of only 12 percent; this lower prevalence suggests overinterpretation on the initial reading (Morring and Attfield 1984).

Regardless of the occupational group, cigarette smoking is common, even in workforces exposed to acknowledged respiratory hazards (Table 2). At the time the selected surveys of these workers were conducted, 1966 to 1977 for the asbestos workers (Weiss and Theodos 1978; Samet et al. 1979) and 1981 for the uranium miners (Samet et al. 1984), knowledge of the hazards of these occupations was widely disseminated and information concerning interaction

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TABLE 2.—Prevalence of cigarette smoking and occupational lung disease in selected survey populations

Study, location, years of study	Study population	Prevalence of smoking (per 100)	Prevalence of disease[1] (per 100)
Kibelstis et al. (1973), U.S., 1969	8,555 coal miners	Smokers 51 Ex-smokers 24 Nonsmokers 25	Chronic bronchitis Smokers 38 Ex-smokers 30 Nonsmokers 25 Airway obstruction[1] Smokers 18 Ex-smokers 14 Nonsmokers 6
Morgan et al. (1973), U.S., 1969	9,076 coal miners		Coal workers' pneumoconiosis Simple 30.0 Complicated 2.5
Weiss and Theodos (1978), U.S., 1975	88 workers from two asbestos manufacturing plants	Smokers 56 Ex-smokers 23 Nonsmokers 21	X-ray profusion ≥1/0 20
Samet et al. (1979), U.S., 1966–1977	409 workers from two asbestos manufacturing plants and two shipyards	Smokers 40–60 Ex-smokers 27–42 Nonsmokers 10–18	X-ray profusion ≥1/0 12–31 ≥2/1 5–13
Theriault et al. (1974), U.S., 1971	792 granite shed workers	Exposed workers Smokers 61 Ex-smokers 25 Nonsmokers 13	X-ray profusion 1/0 21 2/0 7 3/0 2
Samet et al. (1984), U.S., 1981	192 uranium miners	Smokers 43 Ex-smokers 39 Nonsmokers 19	X-ray profusion ≥1/0 8.0
			Chronic cough/phlegm <10 years mining 52 10–19 years mining 46 ≥20 years mining 59
Merchant et al. (1973), U.S., 1970–1971	787 male, 473 female cotton textile mill workers	M W Smokers 63 44 Ex-smokers 16 6 Nonsmokers 21 50	Byssinosis M W Current smokers 25 19 Never smokers 18 15
Do Pico et al. (1977), U.S., 1974	300 grain workers	Smokers 59 Ex-smokers 22 Nonsmokers 19	Chronic bronchitis Smokers 42 Nonsmokers 30
Gruchow et al. (1981), U.S.	1,510 farm workers	Smokers 15 Ex-smokers 27 Nonsmokers 57	Farmers lung disease 0.5

[1] Significant airway obstruction defined as an FEV_1/FVC ratio less than two standard deviations below predicted mean.

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with cigarette smoking was accumulating. Nevertheless, a large proportion of the participants in these surveys smoked cigarettes. The findings from these surveys with regard to the prevalence of smoking are supported by larger data sets collected from population samples (Friedman et al. 1973; Sterling and Weinkam 1976). Friedman and colleagues (1973) questioned 70,289 participants in the Kaiser-Permanente Multiphasic Health Checkups program and found a higher proportion of smokers in those reporting occupational exposure to asbestos, silica, or fumes. Similarly, Sterling and Weinkam (1976) examined smoking patterns by employment status in data from the 1970 NHIS and found the prevalence of smoking to be highest among blue-collar workers. Association between occupational group and cigarette smoking practices is addressed in detail elsewhere in this Report.

Thus, in research and clinical care related to chronic occupational lung diseases, consideration must be given not only to occupational exposures but also to cigarette smoking. The remainder of this chapter describes the general patterns of lung injury by cigarette smoking and occupational exposures and the methods used for evaluating workers who are exposed to both.

Patterns of Lung Injury

The sites of lung injury caused by cigarette smoke and occupational agents may be broadly categorized as the large airways, the small airways, and the parenchyma. The effects of cigarette smoke on these sites are summarized in Table 3. A comparison of injury patterns from cigarette smoke and from selected, but representative, occupational exposures follows.

Injury From Cigarette Smoke

The pattern of lung injury associated with cigarette smoking has been comprehensively described elsewhere (US DHHS 1984). In the large airways, cigarette smoke causes an increase in mucous gland size and in goblet cell number. These changes result in increased mucus production and the associated symptom of chronic bronchitis. Large airway injury may contribute to airflow obstruction, but the peripheral airways are the predominant site of the increased airflow resistance in COLD (US DHHS 1984).

Changes in the small airways are one of the earliest manifestations of cigarette smoking. Niewoehner and colleagues (1974) examined the lungs of 20 smokers and 19 nonsmokers who died suddenly at a mean age of 25 years. A pattern of small airways injury, termed "respiratory bronchiolitis," was readily identified, even in these young smokers. Clusters of brown pigmented macrophages were found in the respiratory bronchioles, which also displayed increased

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TABLE 3.—Pathologic changes and manifestations of lung injury by cigarette smoke

	Large airways	Small airways	Parenchyma
Pathologic changes	Mucous gland hyperplasia, inflammation and edema, ↑ bronchial smooth muscle	Goblet cell metaplasia, inflammation and fibrosis of the respiratory bronchiole	Emphysema, minimal interstital fibrosis
Manifestations			
Symptoms	Cough, phlegm	Cough, phlegm	Dyspnea
Physical signs	None	Crackles	Diminished breath sounds
X ray	None	? Linear opacities	? Linear opacities
Pulmonary function testing	? ↓ FEV_1	↓ FEV_1, ↓ FEV_1%, ↑ TLC, ↑ RV, ↓ DLCO	↓ FEV_1, ↓ FEV_1%, ↑ TLC, ↑ RV, ↓ DLCO
		Accelerated annual decline of FEV_1	Accelerated annual decline of FEV_1

numbers of inflammatory cells and denuded epithelium. To characterize the physiological consequences of small airways injury associated with smoking cigarettes, Cosio and colleagues (1978) correlated small airways morphology with lung function in 36 patients undergoing thoracotomy for a localized lesion. With increasing cumulative consumption, both inflammation and fibrosis of the respiratory bronchioles increased. Furthermore, airflow obstruction, as measured by the ratio of FEV_1 to FVC or by the maximum midexpiratory flow rate ($FEF_{25-75\%}$), progressively decreased and residual volume increased with the amount smoked. Physiological measures of airflow obstruction correlated with the severity of small airways abnormalities.

The major parenchymal injury associated with cigarette smoking is emphysema: "abnormal dilation of air spaces distal to the terminal bronchioles accompanied by destruction of air space walls" (US DHHS 1984, p. 119). Emphysema and small airways injury contribute to the physiological impairment found in COLD; in individual patients with COLD, either may be predominant, but both are probably important in most (US DHHS 1984). By itself, emphysema is accompanied by spirometric evidence of airflow obstruction, increased lung compliance, and increased total lung capacity (TLC) and residual volume (RV). The diffusing capacity for carbon monoxide varies inversely with the extent of emphysema (Park et al. 1970; Cotes 1979). Emphysema is also associated with abnormalities of gas exchange.

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Cigarette smoking, through its effects on the small airways and lung parenchyma, produces the clinical syndrome of expiratory flow limitation with dyspnea. The chronic airflow obstruction found in COLD develops progressively and insidiously in most cases through a sustained excessive decline of ventilatory function (US DHHS 1984). In COLD, spirometry shows reduced FEV_1 and a reduced FEV_1 to FVC ratio; FVC may also be diminished. The airflow obstruction is accompanied by increases in RV and TLC (Boushy et al. 1971; Cotes 1979).

Injury From Occupational Exposures

For occupational exposures in the absence of cigarette smoking, the patterns of lung injury vary among the agents, presumably on the basis of differences in their physical and chemical properties. Although the clinical and physiological manifestations of occupational lung injury may be distinct from those of cigarette smoking, overlap occurs for some exposures.

As with cigarette smoke, chronic irritation of the large airways by dusts and gases is associated with mucous gland enlargement and mucus hypersecretion (Morgan 1978, 1984b). This pattern of injury has been well documented clinically and pathologically for coal and cotton dust (Douglas et al. 1982; Edwards et al. 1975; Kibelstis et al. 1973; Merchant et al. 1972). Gold miners and grain workers also develop chronic bronchitis attributable to occupational dust exposure (Irwig and Rocks 1978; Dosman et al. 1980).

Industrial bronchitis may be associated with airflow obstruction. Hankinson and colleagues (1977) studied approximately 9,000 coal miners from 1973 to 1974. Among the nonsmoking miners with dust-induced bronchitis, decreased airflow at high lung volumes was demonstrated, a finding suggestive of changes in the larger airways.

Abnormalities of the small airways seem to be one of the earliest responses to mineral dust exposure (Churg et al. 1985). In a recent study of hard-rock miners and people employed in the asbestos, construction, and shipyard industries, Churg and colleagues (1985) showed that the abnormalities of the respiratory bronchioles associated with mineral dust are accompanied by airflow abnormalities. The lesions consisted of fibrosis and pigmentation in the small airways and were considered by these researchers to represent a nonspecific response to dust.

Involvement of the small airways has also been demonstrated in workers with specific exposures. For example, the coal macule is characterized by the deposition of alveolar macrophages loaded with coal dust in the respiratory bronchioles (Morgan 1984a). Subsequently, the involved respiratory bronchioles dilate, a change termed "focal emphysema" (Morgan 1984a). At this stage, individuals usually are asymptomatic and have no physical findings. The chest x

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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,

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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

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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

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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,

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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

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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.

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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).

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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). Epidemiclogists 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

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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

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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.

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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.

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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,

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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

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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

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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.

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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

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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

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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.

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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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CHAPTER 5

CHRONIC BRONCHITIS: INTERACTION OF SMOKING AND OCCUPATION

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Introduction

Occupational bronchitis is defined as the occurrence of bronchitis caused by worksite chemical or physical agents, whether encountered as gases, fumes, vapors, or dusts. Having derived from a crowded field of overlapping and confusing terms, the term "occupational bronchitis" has inherited a certain inexactitude and has been applied with ambiguity. To complicate the issues further, some industrial substances that cause bronchitis also frequently cause other lung diseases, especially the pneumoconioses and asthma, the symptoms of which may mimic those of occupational bronchitis. Studies of these occupational lung diseases have not always differentiated clearly between the development of bronchitis and the development of other lung disorders. Hence, this review begins by briefly applying the customary distinctions in terminology to the area of occupationally derived bronchitis.

Whether caused by cigarette smoking, industrial agents, or otherwise, "chronic simple bronchitis" denotes the presence of persistent cough with phlegm production not attributable to a specific pulmonary disease such as bronchiectasis or tuberculosis (Ciba 1959; American Thoracic Society 1962). The operational definition of this form of bronchitis provided by consensus groups of American and British investigators 20 years ago has been widely used in industrial and nonindustrial studies: cough and sputum production on most days for at least 3 months annually for 2 consecutive years (Ciba 1959). Fletcher and coworkers (1976) subsequently demonstrated that this hypersecretory disorder among cigarette smokers can occur independent of airway obstruction and does not of itself lead to an obstructive disorder. Brinkman and colleagues (1972) confirmed these findings in an occupational setting in a more abbreviated study. Mucus production causes morbidity in that it may lead to increased pulmonary infections, but it does not cause significant dyspnea or potentially disabling obstructive disease.

"Chronic obstructive bronchitis" often included in the generic term "chronic obstructive pulmonary disease" (COPD), is defined by the presence of airflow obstruction as measured in most occupational studies by the reduction in the ratio of forced expiratory volume in 1 second to forced vital capacity (FEV_1/FVC). More recently, flow rates at low lung volumes obtained from the same forced expiratory maneuver have been used to detect dysfunction of the small airways. In contrast to the mere production of cough and phlegm, the presence of obstruction may have important impact on morbidity and mortality (Fletcher et al. 1976). This subject is reviewed more fully elsewhere in this Report.

The term "occupational bronchitis" has been used more often to refer to simple bronchitis than to the airflow obstructive disorder

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because of the widespread notion that many airborne occupational contaminants produce chronic cough and phlegm, but relatively few agents have been found to lead to measurable airflow obstruction or to clinically significant COPD (Parkes 1982; Casey 1983; Kilburn 1980; Morgan and Seaton 1984).

Two related criteria have commonly been used to demonstrate the existence of occupational bronchitis in the presence of a specific exposure or in a specific workplace. First, occupational bronchitis is favored if excessive rates of respiratory symptoms are found in workers who have never smoked. The obvious advantage of such a criterion is the elimination of cigarette smoking, which is a major confounding variable in bronchitis. Unfortunately, this approach could fail to incriminate an occupational agent that produces no respiratory effects by itself but causes higher rates of bronchitis among workers who smoke than are attributable to cigarette smoking alone. Second, the entire exposed population—smokers, former smokers, and nonsmokers—may experience higher rates of chronic cough and phlegm production than a similarly constituted unexposed control population. If the population of exposed nonsmokers is small, however, only the interactive effects of smoking and the occupational agent of interest may be evaluated.

This chapter describes the impact of smoking and occupational exposures on the prevalence of simple bronchitis. Examining the interaction between smoking and hazardous substances, however, requires documenting the ability of industrial agents alone to produce chronic respiratory disease. The additional or multiplicative effects of cigarette smoking can then be described. Emphasis is placed on evaluating the nature and quality of data rather than on compiling a complete list of agents putatively associated with bronchitis.

Coal

The role of coal dust in the development of chronic simple bronchitis has been examined (Morgan and Seaton 1984; Parkes 1982), and respiratory disease in coal miners is discussed more fully in a separate chapter of this Report. The specific issue of bronchitis and occupational exposure to coal is reviewed briefly in this section.

Evidence supports an independent causal relationship for both cigarette smoking and coal dust in chronic cough and phlegm production (Higgins et al. 1959; Saric and Palaic 1971; Higgins 1972; Lowe and Khosla 1972; Kibelstis et al. 1973). In a series of community-based studies in England and in the United States during the 1950s and 1960s, Higgins and colleagues (Higgins et al. 1959; Higgins 1972) found an increased prevalence of chronic simple

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bronchitis in miners and ex-miners, ranging from 1.2 to 6.4 times the rates in nonminer controls.

Lowe and Khosla (1972) studied chronic bronchitis among more than 12,000 Welsh steelworkers, about one-fourth of whom were former coal miners. In the absence of cigarette smoking, previous exposure to coal dust increased the rate of chronic cough and phlegm production from 5.7 percent in nonsmoking nonminers to 13.6 percent in nonsmoking ex-miners. Cigarette smoking was somewhat more important than previous exposure to coal in producing chronic simple bronchitis; 16.6 percent of the nonminers who smoked and 25.5 percent of the ex-miners who smoked had chronic bronchitis. Differences in age among the various subgroups did not account for the varying prevalence of symptoms, which appeared to be additive.

Saric and Palaic (1971) compared 904 Yugoslav coal miners with 342 control workers of similar socioeconomic status without occupational exposure to dusts, and found that cigarette smoking and coal dust exposure were multiplicative in the production of chronic simple bronchitis. Of the miners who smoked, 32 percent reported chronic cough and phlegm production, compared with 10 percent of the controls who smoked, 8 percent of the nonsmoking miners, and 2 percent of the nonsmoking controls. However, the rates of chronic simple bronchitis for each exposure subgroup, except the workers who smoked, were below other published rates.

Increasing coal dust exposure increased the prevalence of chronic simple bronchitis in both smokers and nonsmokers in the studies by Kibelstis and colleagues (1973) and Rae and colleagues (1971). Neither study included groups not exposed to coal dust. Both studies reported a larger effect of cigarette smoking than of coal dust exposure in causing chronic simple bronchitis, but did demonstrate a substantial coal dust exposure effect. One-third to one-half of the nonsmoking American coal miners over the age of 50 reported chronic cough and phlegm production (Kibelstis et al. 1973). Somewhat lower proportions (20 to 40 percent) of the nonsmoking British coal miners with the highest levels of dust exposure suffered symptoms of chronic cough and phlegm production (Rae et al. 1971).

In summary, coal dust exposure causes chronic simple bronchitis independent of cigarette smoking. Although the effects are additive, the effect of smoking is somewhat greater than the effect of coal dust exposure in producing symptoms of chronic bronchitis.

Silica

Early studies showed no relationship between silica exposure and chronic cough and phlegm production. In 1959, Higgins and colleagues (1959) found no increase in chronic simple bronchitis in British foundry workers and former foundry workers, regardless of

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duration of employment, compared with community controls without dust exposure. In a cross-sectional study, Brinkman and Coates (1962) found no difference in cough and phlegm production in long-term American foundry workers with normal chest roentgenograms and control workers with no dust exposures. More recently, Glover and colleagues (1980) examined 725 Welsh slate workers and former workers and noted no relation between duration of exposure to slate and presence of chronic simple bronchitis independent of pneumoconiosis.

On the other hand, studies of South African gold miners showed an association between silica and simple bronchitis among smoking miners. White miners were compared with age-matched white nonminers in an area where gold mines had a 50 to 70 percent free silica content (Sluis-Cremer et al. 1967). Nonsmoking miners reported an 8.2 percent rate of chronic simple bronchitis, which did not differ from the 6.7 percent rate found among nonsmoking nonminers. However, 50.5 percent of the miners who smoked had chronic cough and phelgm production, almost twice the 28.0 percent found among the nonminers who smoked. Hence, silica dust alone appeared not to cause symptoms of simple bronchitis, but magnified the effects of smoking.

Wiles and Faure (1977) also studied white South African gold miners and found that they had an increased prevalence of bronchitic symptoms in the absence of cigarette smoking and that there was an additive effect among the workers who did smoke cigarettes. Among the nonsmokers with the lowest dust exposure, no workers had chronic cough with phlegm, but 15 to 20 percent of workers with the highest dust exposures had these symptoms. Twenty-five percent of smokers in the low dust category reported bronchitic symptoms. Among the miners who smoked, 50.5 percent suffered from chronic cough and phlegm production, demonstrating a simple additive effect.

A cross-sectional study of 931 Swedish long-term foundry workers with varying exposures to silica was published in 1976 (Karava et al. 1976). Less than 4 percent of the study population had evidence of silicosis on chest x ray. Two percent of the nonsmokers exposed to lesser amounts of dust reported simple chronic bronchitis compared with 9 percent of the nonsmokers with high dust exposure, but the difference was not significant ($p > 0.10$). However, 16 percent of the smokers exposed to slight or moderate levels of dust had chronic cough and phlegm production, significantly less than the 30 percent of smokers with high dust exposure ($p < 0.01$). Foundry dust may have potentiated the effect of cigarette smoking.

In summary, silica exposure appears to interact with cigarette smoking to increase the prevalence of chronic bronchitis, at least in white South African gold miners.

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Cement

A cross-sectional survey of 847 cement workers and 460 controls not exposed to occupational hazards found that 19.0 percent of the cement workers had chronic simple bronchitis, compared with 9.62 percent of the control group, using the Medical Research Council (MRC) (*British Medical Journal* 1966) criteria for bronchitis (Kalacic 1973a, b, 1974). However, the study group had more current smokers and was somewhat older than the control group (Kalacic 1973a). The nonsmoking cement workers had significantly more chronic simple bronchitis than the nonsmoking control subjects: 11.7 and 2.2 percent, respectively ($p < .001$). The cement workers who smoked cigarettes reported a 21.2 percent rate of chronic simple bronchitis, twice the rate of the nonsmoking cement workers.

An investigation of the relationship between chronic bronchitis and occupation among 14,154 persons in numerous occupations, including 344 cement workers (Deutsche Forschungsgemeinschaft 1978), revealed a positive association between the symptoms of chronic bronchitis and exposure to cement dust only in heavy smokers and younger nonsmokers.

In summary, cement dust exposure may cause chronic simple bronchitis independent of cigarette smoking. The interaction between the two exposures is likely to be additive.

Grain

Although for several decades cereal grain dust has been known to affect human lungs (Williams et al. 1964; Kleinfeld et al. 1968), the nature of grain-related chronic lung disease and its relationship to cigarette smoking has been elucidated only in recent years. Complicating factors have included the variety and overlap of the lung diseases associated with grain dust (asthma, allergic alveolitis, grain fever, and chronic obstructive lung disease) and the multitude of potentially toxic materials found in grain dust (various cereal grains, fungi, mites, insects, and pesticides) (Dosman et al. 1979).

Dosman and colleagues (1980) compared 90 lifetime nonsmoking grain workers with 90 lifetime nonsmoking control subjects selected randomly from a hospital service plan in the same Canadian Province. Study subjects and controls were individually matched for age, resulting in a mean age of 30.8 years for both groups. Using modified MRC criteria for the diagnosis of chronic bronchitis, the investigators found that 23.1 percent of the grain workers had cough and phlegm production compared with 3.1 percent of the control subjects, an eightfold difference. Among the grain workers, the rate of chronic bronchitis rose with duration of employment from 14.3 percent of the workers with less than 5 years of employment to 35.7

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percent of the workers with over 20 years' tenure, an increment not seen with increasing age among the control workers.

Other studies of smaller groups of nonsmoking grain handlers have been less impressive. Broder and colleagues (1979) compared two groups of Canadian grain workers (26 and 39 workers, respectively) with 40 civic workers: all three groups had never smoked. Mean duration of employment was at least 9 years. Symptoms of chronic simple bronchitis occurred in 12 and 8 percent of the grain handlers, respectively, and in 3 percent in the control workers. Do Pico and colleagues (1977) reported that 30 percent of 57 grain workers who did not smoke met the MRC criteria for chronic bronchitis. No control group was studied.

Comparison of 610 grain elevator workers in British Columbia with 136 civic workers and 187 noncedar sawmill workers (Chan-Yeung et al. 1980) showed no significant differences in prevalence of cough or phlegm production among the nonsmokers. However, the two control groups had higher rates of symptoms than the control groups from other studies.

Dosman, Cotton, and their colleagues (Cotton et al. 1983; Dosman et al. 1984) updated their 1980 study with reports of larger cross-sectional studies in 1983 and 1984. Rates of chronic bronchitis in 195 lifetime nonsmoking grain workers (approximately 15 percent) versus 195 age-matched lifetime nonsmoking control workers (about 3 percent) were similar to those found in the previous study (Dosman et al. 1980).

The interaction between smoking and grain dust exposure has received some attention. Dosman and others presented data relevant to chronic simple bronchitis in an editorial (Dosman et al. 1979). Rates of chronic cough with phlegm production in the four exposure groups are shown in Table 1. Smoking had a somewhat greater effect than grain dust on the prevalence of symptoms of chronic bronchitis. The combination of exposures reflected an additive effect of the individual exposures. A later study by Dosman's group (Cotton et al. 1983) yielded very similar results, with an additive interaction between smoking and grain exposure, albeit each group experienced lower rates of chronic bronchitis than in the 1979 study.

Other studies are less definitive about the nature of the interaction between cigarette smoking and grain exposure on the prevalence of chronic simple bronchitis, either because they lacked a nonexposed control group (Do Pico et al. 1977) or because smoking or grain exposure did not show significant independent effects on rates of chronic bronchitis (Chan-Yeung et al. 1980; Broder et al. 1979). The results of these studies suggest at most an additive effect between smoking and grain exposure.

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TABLE 1.—Prevalence of chronic bronchitis in grain-exposed workers and controls

Exposure group	Percent with chronic bronchitis	Morbidity ratio
Nonsmoking controls	3.5	1
Nonsmoking grain-exposed workers	16.5	4.7
Smoking controls	25.0	7.1
Smoking grain-exposed workers	36.5	10.4

SOURCE: Modified from Dosman et al. (1979).

Polyvinyl Chloride and Vinyl Chloride

Polyvinyl chloride (PVC) and related compounds, including vinyl chloride monomer and products of decomposition, have been implicated in asthma (Bardana et al. 1980), lung cancer (Wagoner 1983), and pulmonary fibrosis (Mastrangelo et al. 1979; Cordasco et al. 1980; Lilis 1980).

In a series of studies in the mid-1970s, Miller and Lilis and colleagues (Miller et al. 1975; Lilis et al. 1976; Miller 1975, 1980) evaluated approximately 900 active or retired polyvinyl chloride production workers exposed to a variety of levels of PVC dust and vinyl chloride gas in three separate facilities. Rates of chronic cough and phlegm production were 20.4 and 16.0 percent, respectively, among the workers in two of the plants, most of whom were smokers. Nonsmokers were not analyzed separately for symptoms, and no control group was studied. The authors (Miller et al. 1975) stated that the prevalence of chronic simple bronchitis in PVC production workers was similar to that found in studies of industrial and nonindustrial populations.

Gamble and colleagues (1976) studied 327 either active or retired PVC and vinyl chloride workers at one plant and found a smoking-adjusted prevalence of chronic simple bronchitis of 2.5 percent.

Soutar and colleagues (1980) performed a cross-sectional study of 818 Scottish PVC manufacturing workers, most of whom were actively working. Airborne dust levels were used to calculate a dust index. The authors found no relation between dust exposure index and prevalence of chronic cough and phlegm production.

In conclusion, the studies of the effects of PVC dust and vinyl chloride gas have not shown an association with symptoms of chronic simple bronchitis.

Welding

Welding entails a variety of methods, materials, and potentially hazardous exposures (Challen 1974; Parkes 1982). Welders may be

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exposed to irritants such as nitrogen dioxide, ozone, and phosgene, to metal fumes such as cadmium, zinc, and iron, and to dusts including free silica and asbestos (Parkes 1982). Hence, the task of elucidating welders' respiratory disorders independent of cigarette smoking, if any, and tying these disorders to specific exposures has been difficult (Parkes 1982; Morgan and Seaton 1984).

In an early study, Hunnicutt and colleagues (1964) compared 100 electric arc welders with over 10 years of welding experience in a shipbuilding plant with 100 other workers in the same plant. Smoking and welding had equivalent effects on rates of cough and phlegm production and the effects were additive.

Fogh and colleagues (1969) examined 156 welders, mostly electric arc welders, and 152 control workers from shipyards and engine- and tank-producing facilities. The groups had similar smoking habits and similar rates of chronic simple bronchitis.

Peters and colleagues (1973) compared the pulmonary status of 61 welders, 63 pipefitters, and 61 pipecoverers from the same shipyard. Age (mean, 50 years) and smoking habits of the three groups were similar. No welders had radiographic evidence of siderosis. No differences between groups in rates of chronic cough were observed.

In a Roumanian study (Barhad et al. 1975), 173 shipyard welders were compared with 100 shipyard workers of other trades, but with similar age and smoking habits, and no significant difference in rates of chronic simple bronchitis were observed.

Antti-Poika and colleagues (1977) investigated symptoms in 157 electric arc welders without siderosis on chest x ray and 108 control workers from engineering shops, matched for age, smoking, and social class. The study workers and the control workers were relatively young, with mean ages of 36.1 and 36.8 years, respectively. Under the modified MRC criteria, chronic simple bronchitis was reported in 24 percent of the welders versus 14 percent of the controls ($p < .01$). Nonsmokers and smokers were not analyzed separately.

Oxhoj and colleagues (1979) studied 119 electric arc welders and 90 clerks from a shipyard. The nonsmoking welders and the ex-smoking welders had higher rates of chronic cough and expectoration than the comparable controls (31 and 11 percent, respectively). The welders who smoked experienced the highest rates of symptoms (77 percent) compared with the controls who smoked (43 percent). Hence, smoking and welding had an approximately equivalent ability to produce chronic simple bronchitis and the effects were additive.

In conclusion, chronic simple bronchitis has been related to welding apart from smoking habits in some of the studies reviewed. Smoking and welding have produced additive rates of respiratory symptoms in those studies that have shown an effect.

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Sulfur Dioxide

Archer and Gillam (1978) compared 953 copper smelter workers and 252 control workers drawn from a nearby copper mine maintenance shop. With the smokers and nonsmokers combined, symptoms of chronic simple bronchitis were noted in 15.8 percent of the smelter workers compared with 9.5 percent of the control workers ($p < .05$); the smelter workers smoked slightly more than the control workers. Smoking was more important than the sulfur dioxide exposure in causing symptoms of cough and phlegm production, and the effects of the two factors appeared to be additive.

Other Exposures

Rubber curing workers had a 25.8 percent rate of chronic cough and phlegm production versus 14.3 percent for the controls ($p < .01$) (Fine and Peters 1976). The difference between nonsmokers was not significant (5.9 and 12.0 percent in controls and workers, respectively). However, the difference between smokers was significant (17.4 and 29.2 percent in controls and curing workers, respectively; $p = .03$).

In a comparison of 312 coke ovensmen with 464 other coke workers of similar ages (Walker et al. 1971), chronic simple bronchitis was reported in 32 percent of the smoking ovensmen versus 23 percent of the other coke workers who smoked ($p < .02$). Among the nonsmokers, 9 percent of the ovensmen noted these symptoms compared with 6 percent of the other coke workers, an insignificant difference. Hence, coke oven exposure potentiated the bronchitic effect of smoking.

Summary and Conclusions

1. Chronic simple bronchitis has been associated with occupational exposures in both nonsmoking exposed workers and populations of exposed smokers in excess of rates predicted from the smoking habit alone. Among these exposures are coal, grain, silica, the welding environment, and to a lesser extent, sulfur dioxide and cement.
2. The evidence indicates that the effects of smoking and those occupational agents that cause bronchitis are frequently additive in producing symptoms of chronic cough and expectoration. Smoking has commonly been demonstrated to be the more important factor in producing these symptoms.

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CHAPTER 6

ASBESTOS-EXPOSED WORKERS

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Introduction

Cigarette smoke and asbestos are agents with well-documented risks associated with exposure. Large numbers of individuals have had exposure to either or both of these agents sufficient to generate significant excess death and disability. The focus of this review is the effects of combined exposure to asbestos and cigarette smoke. The literature that establishes the causal nature of the risks associated with each of these exposures and the nature and extent of the disease that can occur is extensive, and has been reviewed in detail elsewhere (US PHS 1964; US DHEW 1979; US DHHS 1980, 1981, 1982, 1983, 1984; Selikoff and Lee 1978; Ontario, Royal Commission 1984; NRC 1984). However, populations with asbestos exposure commonly have coincident cigarette smoke exposure, and the magnitude of the risk of lung cancer and chronic lung injury produced by smoking necessitates a careful examination of the smoking habits of asbestos-exposed workers in order to define the risks of isolated and combined exposures.

A number of conditions or diseases known to be associated with smoking, asbestos, or both, including mesothelioma, heart disease, pleural plaques, adverse reproductive outcomes, and cancers other than lung, are not discussed here; the focus of this chapter is lung cancer and chronic lung disease, the disease processes for which the largest amount of data on the effects of combined exposure is available.

Asbestos-Exposed Populations

Some exposure to both cigarette smoke and asbestos appears to be an inescapable consequence of living in the urban U.S. environment. The relatively omnipresent nature of cigarette smoking as a social phenomenon makes at least incidental exposure to cigarette smoke a universal experience, and the digestion of lung tissue from individuals with no known asbestos exposure commonly reveals low concentrations of asbestos bodies and asbestos fibers (Churg and Warnock 1977, 1980). It is technically extremely difficult to establish the presence or absence of an effect in populations who have had no exposure to asbestos other than the levels in ambient air or who have not had repetitive exposure to smoke through active or involuntary smoking. However, it is generally accepted that these extremely low dose exposures do not substantially alter the occurrence of lung cancer or chronic lung disease in the general population (Ontario, Royal Commission 1984).

The same statement cannot be made for individuals with repetitive low dose or indirect exposures to either of these agents, however. Evidence continues to accumulate that shows that nonsmoker exposure to environmental tobacco smoke may carry with it an

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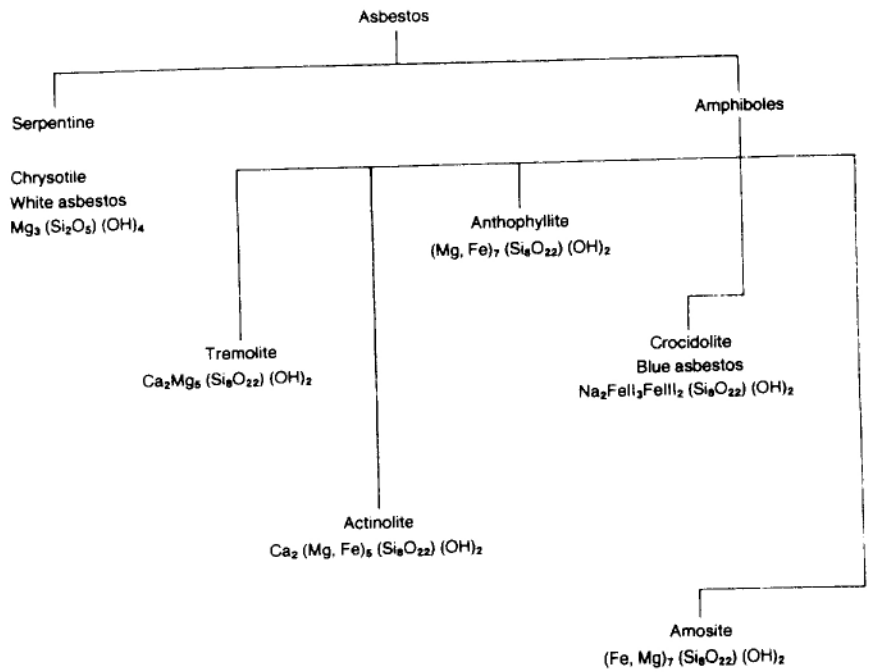


FIGURE 1.—Principal varieties of asbestos
SOURCE: Chatfield (1981).

increased risk of lung cancer (IARC, in press). The exposure of the wives and children of asbestos workers to asbestos on work clothing and in the home environment is thought to be associated with an increased risk for mesothelioma and possibly other diseases (Selikoff and Lee 1978). The risk from these low dose exposures is smaller than the risk for individuals directly exposed to these agents (active cigarette smokers and workers occupationally exposed to asbestos dust).

"Asbestos" refers to a specific group of fibrous silicates, the principle varieties of which are listed in Figure 1. Commercial use of asbestos stems from its qualities of resistance to heat and acid and its ability to be woven into fabric (Zoltai and Wylie 1979). Commercial products known as asbestos differ in the configurations and dimensions of their fibers as well as in their chemical makeup and crystalline structure. These properties determine, in part, the deposition patterns of fibers in the respiratory tract and the mechanisms whereby the fibers interact with the cells of the lung.

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The asbestos minerals are classified according to structural features into two groups, serpentine and amphibole. Chrysotile, a serpentine (white asbestos), comprises pliable, curly fibers that are formed individually from fibrillar subunits. Layers of linked silica tetrahedra alternate with layers of magnesium hydroxide octahedra to form long, hollow, scroll-like structures. Chrysotile accounts for approximately 95 percent of the world usage of asbestos today. The major producers are the Soviet Union and Canada.

The amphibole types of asbestos (crocidolite, amosite, tremolite, actinolite, and anthophyllite) are generally made up of straight, needle-like fibers consisting of strips of silica tetrahedra linked by one or more cations (calcium, sodium, magnesium, and iron). The mineral names are often distinguished by adding the modifier asbestos after the name for those minerals that may occur both as a fiber and not as a fiber. In this text, crocidolite refers to asbestiform richterite and amosite refers to asbestiform grunerite. In the United States, amosite and, to a lesser extent, crocidolite were widely used in the past, but their commercial importance has decreased dramatically in the last two decades (Craighead and Mossman 1982). The amphiboles tremolite, actinolite, and anthophyllite are minor contaminants of some chrysotile and industrial talc products, are present in both asbestiform and nonabestiform types, and are not produced for commercial use.

The occupations and industries in which the major mortality studies of asbestos-exposed workers have been conducted are presented in Table 1. Groups not described in this table, but for whom there is considerable concern about substantial asbestos exposure, include workers in the building and demolition trades and maintenance workers.

The number of workers exposed to asbestos in the United States has been variously calculated, but a detailed review by Nicholson and colleagues (1982) estimated that 18.8 million workers have had more than 2 months of exposure in occupations where significant asbestos exposure may have occurred.

An earlier chapter of this Report documents that age and occupation are associated with substantial differences in smoking behavior. These differences would be expected to substantially confound lung cancer and chronic lung disease mortality; therefore, a careful examination of the smoking habits of asbestos-exposed populations is needed in order to interpret the data on mortality and disease incidence and prevalence reported in the literature. Table 2 presents the smoking habits of asbestos workers from a number of studies of asbestos-exposed populations. In most of the studies of asbestos-exposed populations, approximately 70 to 80 percent of male asbestos workers smoked. In some subsets of workers, well over 90 percent of the individuals were current smokers or had smoked in the past. Li

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TABLE 1.—Mortality from asbestos-related diseases in various cohort studies

Type of activity	Study	Place	Fiber type	Percent smoking	Number in cohort	Total deaths	Meso-thelioma	Asbestosis (pneumo-coniosis)	Lung cancer		SMR
									Observed	Expected	
Mining	McDonald et al. (1980)	Quebec	Chrysotile		10,939	3,291	10	42	230	184	125
	Nicholson et al. (1979)	Quebec	Chrysotile		544	178	1	26	28	11.1	252
	Rubino et al. (1979)	Italy	Chrysotile		952	332	0	9	11[1]	10.4	106
	Hobbs et al. (1980)	Western Australia	Crocidolite		6,200	526	17[2]	14	60	38.2	157
	Meurman et al. (1974)	Finland	Anthophyllite	66.7	1,092	248	0	13	21	12.6	167
Friction materials	Berry and Newhouse (1983)	England	Chrysotile		M 9,113	1,640	8	NS	143[3]	139.5	103
			Crocidolite[4]		W 4,347	346	2	NS	6[3]	11.3	53
	McDonald et al. (1984)	Connecticut	Chrysotile Crocidolite[4] Anthophyllite[4]		3,641	1,267	0	12[5]	73	49.1	148.7
General manufacturing	Henderson and Enterline (1979)	United States	Chrysotile Crocidolite Amosite	81	1,075	781	5	31	63[6]	23.3	270.4
	Newhouse and Berry (1979)	England	Chrysotile		M 2,887	545	46	NS	103[3]	43.2	238
			Crocidolite		W 693	200	21	NS	27[3]	3.2	844
			Amosite								

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TABLE 1.—Continued

Type of activity	Study	Place	Fiber type	Percent smoking	Number in cohort	Total deaths	Meso-thelioma	Asbestosis (pneumo-coniosis)	Lung cancer		SMR
									Observed	Expected	
Textiles	Peto et al. (1977)	England	Chrysotile Crocidolite (?)		1,106	317	10	NS	51[3]	23.8	214
	Peto (1980)	England	Chrysotile Crocidolite (?)		679	239	7	10	40	23.3	172
	Dement et al. (1982)	South Carolina	Chrysotile Crocidolite[4]	52.4	768	191	1	15	26	7.5	348
	McDonald et al. (1983a)	South Carolina	Chrysotile Crocidolite[4]	89[5]	2,643	857	1	21	59	29.6	199.5
	McDonald et al. (1983b)	Pennsylvania	Chrysotile Amosite Crocidolite[4]	75[6]	4,137	1,392	14	74	53	50.5	105
	Robinson et al. (1979)	Pennsylvania	Chrysotile		M 2,722	912	13	NS	49	36.1	136
			Amosite		W 554	128	4	NS	14	1.7	824
			Crocidolite[4]								
Cement products	Weill et al. (1979)	New Orleans	Chrysotile Crocidolite Amosite[4]		5,645	601	0[7]	NS	51	49.2	104
	Finkelstein (1983)	Scarborough	Chrysotile Crocidolite		535	138	19	NS	26	5.4	480
	Thomas et al. (1982)	Cardiff	Chrysotile Crocidolite[4]		1,592	351	2	NS	28	33.0	85
Gas mask manufacturing	Jones et al. (1980)	England	Crocidolite		578	166	17	NS	12	6.3	190
Insulation products	Seidman et al. (1979)	New Jersey	Amosite		820	528	14	30	93	22.8	408

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TABLE 1.—Continued

Type of activity	Study	Place	Fiber type	Percent smoking	Number in cohort	Total deaths	Meso-thelioma	Asbestosis (pneumo-coniosis)	Lung cancer		SMR
									Observed	Expected	
Insulators	Newhouse and Berry (1979)	England	Chrysotile Amosite		1,368	83	10	NS	21[3]	5.6	375
	Selikoff et al. (1979)	United States and Canada	Chrysotile Amosite	82.3	17,800	2,271	175	168	486	105.6	480
	Selikoff, Seidman et al. (1980)	New York and New Jersey	Chrysotile Amosite		632	478	38	41	93	13.3	699
Shipyard workers	Rossiter and Coles (1980)	England	Chrysotile Crocidolite Amosite	66.8	6,076	1,043	31	9	84	119.7	70

NOTE: NS, not stated; M, men; W, women.

[1] Includes one suspected case of mesothelioma.

[2] According to the mortality study, which was restricted to deaths before January 1, 1978. The text of this study also noted 26 cases of mesothelioma diagnosed to January 1, 1979.

[3] Pleural mesotheliomas included in lung cancer total given by the authors but taken out of the lung cancer total for the purpose of this Table.

[4] Minimal usage.

[5] Authors stated that none of the cases were clearly attributable to asbestos exposure.

[6] Male eversmokers, 1910–1919 birth cohort.

[7] Two cases did not meet criteria for entry into the cohort.

[8] Includes mesotheliomas.

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and colleagues (1983) showed lower rates of smoking among shipyard workers in South Carolina. Only 42.9 percent reported that they were current smokers, and 24.8 percent had ceased smoking. This decline in smoking found in the United States is not evident in studies of asbestos workers in Great Britain.

Lung Cancer

Cigarette smoking is the major cause of lung cancer in the U.S. population considered as a whole (US DHHS 1982). Among U.S. men aged 50 to 70 (the group most commonly examined in occupational mortality studies), over 10 percent of the deaths were due to lung cancer in 1977 (McKay et al. 1982). The prevalence of smoking and the percentage of deaths due to lung cancer vary substantially in the studies of asbestos-exposed populations reported in the literature, but in the largest study (Hammond et al. 1979) of heavily exposed workers with a high smoking prevalence (82.3 percent), 21.4 percent of the deaths were due to lung cancer.

The high incidence of lung cancer in both asbestos-exposed workers and the U.S. population, together with the potency of cigarette smoking in determining lung cancer risk, makes the determination of the smoking habits of asbestos-exposed populations essential to any evaluation of lung cancer. The prevalence of smoking varies markedly among men born in different years of this century, between blue-collar and white-collar workers (see the chapter on smoking patterns), and among the populations of asbestos workers studied in the literature. In particular, men born between 1910 and 1930 have a higher prevalence of smoking than men born earlier; men born after 1930 have had lower prevalences of smoking at any given age than the men born between 1910 and 1930. Levels of asbestos exposure have also not been constant with time. Since the recognition of the hazards of asbestos exposure, improved control of asbestos dust has reduce the levels of asbestos in mines and manufacturing plants and, more recently, in other areas where asbestos exposure may also occur. These temporal trends of smoking prevalence and asbestos dust levels result in complex relationships between cumulative asbestos dust exposure and cumulative smoking exposure. The oldest workers (those born before 1910) may have higher cumulative asbestos dust exposure at any given age than younger workers, but will have a lower smoking prevalence. Workers born between 1910 and 1930 are likely to have both a higher smoking prevalence and a higher cumulative asbestos exposure at any given age than workers born after 1930. Therefore, in many studies of currently employed asbestos workers, cumulative asbestos exposure will be somewhat correlated with smoking prevalence, and biased estimates of dose–response relationships with

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TABLE 2.—Smoking characteristics of asbestos-exposed workers

Study	Number and type of population		Smoking characteristics (percent)				Comments
Selikoff et al. (1968)	370 union local members, aged 45–74, New Jersey		SM/EX 76.5	NR* 13	Pipe/cigar 10.5		*Never smoked regularly
Hammond et al. (1979)	17,800 union local members, New Jersey		SM* 54.2	EX 22.2	NS 10.8	Pipe/cigar 5.9	*82.9% smoked >20 cigs/day
Langlands et al. (1971)	252 insulation workers, Belfast	Age <40 years >40 years	69* 74				*19% smoked >25 cigs/day
Ferris et al. (1971)	183 shipyard workers		SM 54.6	NS/EX 45.4			
Murphy et al. (1971)	101 shipyard pipecoverers, New England		SM 66.4	EX 26.8	NS 6.9		
Harries et al. (1972)	2,443 male dockyard workers, Great Britain		64.7	2.2	33.1		
Harries and Lumley (1977)	945 royal naval dockyard workers, Great Britain		67.2	16.2	16.6		
McMillan et al. (1979)	719 royal naval shipyard workers, Great Britain		48.7	28.7	22.7		

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TABLE 2.—Continued

Study	Number and type of population	Smoking characteristics (percent)				Comments
Kolonel et al. (1980)	Male shipyard workers, Hawaii	Asbestos-exposed workers Nonexposed workers General population	63.8 62.5 58.8			
Pearle (1982)	131 male shipyard workers		75.6			
Li et al. (1983)	3,991 shipyard workers, South Carolina		SM 42.9	EX 24.8	NS 32.3	
Becklake et al. (1972)	Asbestos workers, Canada		SM* 85.3	NS 14.7		*Smokers = ever smoked 1 cig/day for ≥1 yr.; includes pipe and cigar
Meurman et al. (1973, 1974)	Anthophyllite mine workers, 1936–1967		SM* 66.7			*28.1% smoked >15 cigs/day
Liddell et al. (1982)	515 asbestos workers, Quebec			NS 33.8		
Berry et al. (1972)	1,203 male asbestos workers		SM 74.5	EX 19.5	NS 6	
Meurman et al. (1979)	Asbestos workers, Finland	Cohort survivors Deceased workers	66.7 79.8			

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TABLE 2.—Continued

Study	Number and type of population	Smoking characteristics (percent)				Comments
Weill et al. (1975) and Selikoff et al. (1979)	859 asbestos cement mfg. workers, New Orleans	SM 51	EX 26	NS 23		
Greenberg et al. (1976)	890 asbestos workers, Texas	84				
Weiss and Theodos (1978)	40 asbestos workers	55.7*	22.7	21.6		*22.7% smoked >1 pack/day
Berry et al. (1979)	Asbestos textile factory workers, Great Britain	SM 69.2	EX 13.8	NS 17		
Selikoff, Seidman, et al. (1980)	933 amosite asbestos workers, examined 20 yrs. from employment start date	SM 61.7	EX 12.1	NS 13.4	Other 12.6	
Skerfving et al. (1980)	241 asbestos workers, Sweden	64.3				
Weiss et al. (1981)	45 asbestos workers, aged ≥40, reexamined	SM 42.2	EX 31.1	NS 26.7		

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TABLE 2.—Continued

Study	Number and type of population		Smoking characteristics (percent)				Comments
				SM	EX	NS	
McDermott et al. (1982)	Two groups of asbestos workers, Swaziland	1	Group	38	10		
		2	Group	33	4		
Acheson et al. (1984)	Amosite asbestos workers, Great Britain			77	5	19	
Berry et al. (1985)	1,253 male and 423 female asbestos factory workers		Men	74.5	19.6	5.9	
			Women	49.4	22.7	27.9	

NOTE: SM = Smoker; EX = Ex-smoker; NS = Nonsmoker.

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asbestos may result. These associations between asbestos exposure and smoking must be considered when examining the literature and are particularly important when drawing conclusions from studies that either do not control for smoking or control for smoking inadequately. For these reasons, this discussion is limited largely to those studies that have provided data on the smoking habits of their populations.

Examination of the relationships among smoking, asbestos exposure, and lung cancer includes consideration of a series of separate questions. Does asbestos exposure exert an effect in the absence of active smoking exposure? What are the effects of combined exposure? Is there a threshold of exposure below which no effect occurs? What happens to the risk following smoking cessation and after cessation of new asbestos exposure?

Lung Cancer in Nonsmoking Asbestos Workers

The most direct way to demonstrate that asbestos exposure results in an increased lung cancer risk independent of cigarette smoking is to monitor disease occurrence in asbestos-exposed individuals who have never smoked cigarettes regularly. However, because lung cancer is a relatively rare phenomenon in people who have never smoked cigarettes, even among asbestos-exposed populations, a large population of nonsmokers is required before a statistically significant number of cases would be expected. The relatively high prevalence of smoking in asbestos-exposed populations decreases even further the number of nonsmoking asbestos-exposed workers available for study, making the evaluation of risks for the nonsmokers difficult. For example, no lung cancer deaths were identified among the nonsmokers in the original cohort of asbestos insulation workers reported by Selikoff and colleagues (1968).

Some authors have attempted to increase subject numbers in the nonsmoker category by combining ex-smokers or light smokers with never smokers (Blot et al. 1980). However, the risk of developing lung cancer remains elevated in ex-smokers compared with nonsmokers for at least 10 to 15 years after cessation, and the excess risk is proportionate to the amount smoked (US DHHS 1982). Smokers of less than 10 cigarettes per day have less risk than heavy smokers, but the relative risk for lung cancer in these light smokers compared with individuals who have never smoked regularly still varied from 2.3 to 9.5 in the major prospective studies on smoking mortality (US DHHS 1982). Thus, combining people who have never smoked with ex-smokers and light smokers is inappropriate and may introduce bias when the effects of asbestos exposure alone are being assessed.

Several studies have examined populations large enough to address the question of the risk of asbestos exposure in individuals who have never smoked regularly. Hammond and colleagues (1979)

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examined the mortality experience of the 17,800 members of the International Association of Heat and Frost Insulators and Asbestos Workers who were alive on January 1, 1967. This group was followed to December 1976, and the mortality of the 12,051 workers more than 20 years after onset of exposure was analyzed. Of this group, smoking histories were available for 8,220, of whom 6,841 (83.2 percent) had been regular smokers at some point and 891 (10.8 percent) had never smoked regularly. Of the 891 workers who had never smoked regularly, death certificates indicated that 4 died of lung cancer. The expected number of deaths was calculated from the mortality experience of a population of blue-collar workers who had never smoked regularly, drawn from the American Cancer Society (ACS) prospective mortality study of 1 million men and women. The resulting expected number of lung cancer deaths of 0.7 and the observed number of 4 yielded a relative risk for asbestos exposure of 5.33. When the deaths were classified according to the best estimate of the cause of death from all available data, rather than from the death certificate alone, one additional case of lung cancer was identified in a worker who had never smoked regularly.

Selikoff, Seidman, and Hammond (1980) reported the mortality of 933 men who began working in an amosite asbestos factory between June 1941 and December 1945. Of these men, 78 (8.4 percent) were known to have never smoked regularly; the death certificates of 5 of this group listed lung cancer as the cause of death. When the best estimate of cause of death was used, only three men were believed to have died of lung cancer. The expected number of deaths was 0.2, based on the ACS mortality study. This led to a relative risk of 25 (5/0.2) for workers who had never smoked regularly.

McDonald and colleagues (1980) examined the mortality experience of Quebec asbestos miners and millers and reported a dose–response relationship between cumulative asbestos exposure and lung cancer in nonsmokers. They compared the standardized mortality ratio (SMR) for lung cancer in miners who had never smoked, using the mortality rates for the Province of Quebec, which are based on both smokers and nonsmokers. The SMR increased from 0.18 among nonsmoking miners with less than 30 million particles per cubic foot times years (mppcf•y) of exposure to 0.36 in miners with 30 to 299 mppcf•y of exposure and 1.24 in nonsmoking miners with more than 300 mppcf•y of exposure. There were 19 lung cancer deaths among nonsmoking asbestos miners. These authors (McDonald et al. 1980) also performed a case–control study of the 245 miners who had died of lung cancer. The distribution of cumulative asbestos exposure among the 20 nonsmoking miners with lung cancer and 20 nonsmoking control miners matched for year of birth and smoking status was examined, and the relative risk for lung cancer was found

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to have increased from 1 in nonsmoking miners with less than 30 mppcf•y to 10 in nonsmoking miners with more than 1,600 mppcf•y.

Liddell and colleagues (1984) reexamined the same population of Quebec asbestos miners after recording their smoking history by pack-years of exposure. They identified 223 cases of lung cancer in men who worked in the asbestos mines and mills of Quebec for a month or more before January 1967 and who were followed to the end of 1975. The controls were selected from men in the same cohort, born in the same years as the lung cancer cases, but still living. Never smokers represented 23 of the 223 lung cancer cases and 201 of the 715 controls. The relative risks (RR) were calculated on the basis of the mortality experience of the entire asbestos-exposed population (whole population RR, 1.0), and the risk in even the most heavily exposed nonsmokers was still lower than the risk in the entire population, which included both smokers and nonsmokers. The RR for lung cancer increased from 0.19 in the nonsmoking miners who had experienced a cumulative exposure of less than 100 fibers per milliliter times years ((f/mL)y) to 0.37 for those with 101 to 1,000 (f/mL)y and 0.87 for those nonsmoking miners with over 1,000 (f/mL)y, thus demonstrating a dose–response relationship with cumulative asbestos exposure for lung cancer in the workers who had never smoked regularly.

Berry and colleagues (1972) conducted a retrospective study of the lung cancer mortality in more than 1,300 male and 480 female asbestos factory workers over a 10-year period and compared their mortality with the national lung cancer rates (Table 3). The national lung cancer rates were converted to smoking-specific rates by multiplying them by factors from the study of mortality of British physicians by smoking status (Doll and Hill 1964) in order to develop smoking-specific expected numbers of deaths. No lung cancer deaths were recorded among the men who had never smoked, and only one lung cancer death was recorded among the women who had never smoked. The expected number of deaths was also very low, and so even a single death was greater than expected, and it occurred in the group of women with heavy asbestos exposure. The women in the highest asbestos exposure category who had never smoked had 3.5 times the number of subject years at risk when compared with men in the same exposure category (1,404 to 399) owing to the higher prevalence of never-smoker status among women in the study. This difference in number of individuals at risk may have contributed to the demonstration of a lung cancer death among nonsmoking women but not among men. Subsequently, Berry and colleagues (1985) followed prospectively 1,253 male and 423 female asbestos factory workers from the same plants. Smoking habits were determined in 1971 at the start of the study, and the population was followed through 1980. The expected number of lung cancer deaths was

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calculated from the death rates for England and Wales multiplied by the lung cancer SMR for greater London, and an adjustment for smoking status was made using the data from the mortality study of British physicians. Observed and expected numbers of lung cancer deaths by smoking status and level of asbestos exposure are presented in Table 4. One lung cancer death occurred among the men who had never smoked (0.1 expected) and three lung cancer deaths occurred among the nonsmoking women (0.2 expected).

Meurman and colleagues (1979) reported 1 lung cancer death (of 23 total lung cancer deaths), a nonsmoking male anthophyllite miner. Acheson and colleagues (1984) also reported 1 death from lung cancer among the nonsmokers employed in an amosite manufacturing factory, with an expected number of 1.1. However, the expected number was calculated from age-specific population rates that included both smokers and nonsmokers rather than from the rates for a population of nonsmokers. Each of these studies supports an increased risk for lung cancer in nonsmoking asbestos workers, but the conclusions are based on a single death in a population.

In summary, the evidence that asbestos exposure results in an increased lung cancer risk in the absence of cigarette smoking is based on a small number of cases, but has been confirmed in several different populations of asbestos workers. The high smoking prevalence in asbestos workers introduces the possibility that environmental tobacco smoke may increase the risk of lung cancer among the nonsmokers, particularly if the synergism demonstrated between active smoking and asbestos exposure pertains to environmental tobacco smoke as well. In spite of these concerns, the available evidence supports the conclusion that nonsmokers with substantial occupational asbestos exposure are at increased risk of developing lung cancer and that the risk increases with increasing cumulative asbestos exposure.

Lung Cancer in Cigarette-Smoking Asbestos Workers

The risk of lung cancer in cigarette smokers has been examined in a number of asbestos-exposed populations, and the increased risk of lung cancer in smokers, coupled with the high prevalence of smoking in many of these populations, has generated substantial numbers of lung cancer deaths for analysis. These populations differ in smoking habits, type of asbestos and duration and intensity of exposure, type of activity that resulted in exposure, and duration of the followup of the population.

A number of authors have compared the lung cancer rates in asbestos-exposed populations with the rates in control populations (Table 1). This approach can establish an excess mortality in a population, but may not identify the causes of that excess. To establish a causal link between an exposure and lung cancer, specific

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TABLE 3.—Comparison of number of observed and expected deaths from cancers of the lung

Smoking habits on January 1, 1960	Number of subjects	Subject-years at risk (adjusted)	Observed deaths (all causes)	Observed lung cancer deaths (ICD 162, 163)	Adjusted observed lung cancer deaths	Expected lung cancer deaths
Men						
Low/moderate asbestos exposure						
Never smoked	44	376	2	0	0	0.0
Ex-smokers	38	335	1	0	0	0.1
Smokers	509	4,423	32	8(2)[1]	4.6	6.2
Not known	219	2,122	20	0	3.4	2.0
Severe asbestos exposure						
Never smoked	41	399	11	0	0	0.0
Ex-smokers	39	415	3	2	1.6	0.2
Smokers	663	6,920	82	32(5)	25.5	9.9
Not known	281	2,722	29	4	10.9	2.4
Women						
Low/moderate asbestos exposure						
Never smoked	25	271	8	0	0	0.0
Smokers	45	577	6	1	1	0.3
Not known	19	195	0	0	0	0.1
Severe asbestos exposure						
Never smoked	120	1,404	23	2(1)	1.7	0.2
Smokers	292	3,474	52	18(4)	15.5	1.4
Not known	157	1,547	9	0	2.8	0.4

[1] Figures in parentheses indicate number of pleuralmesotheliomas.

SOURCE: Berry et al. (1972).

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TABLE 4.—Observed and expected deaths from cancer of the lung during 1971–1980

Smoking habits in 1971	Number of subjects	Subject-years at risk	Total deaths	Lung cancer deaths	
				Observed	Expected [1]
Men					
Low/moderate asbestos exposure					
Never smoked	45	396	6	1	0.10
Ex-smokers	123	1,092	18	3	1.07
Smokers	441	3,557	84	17	11.29
Severe asbestos exposure					
Never smoked	29	273	2	0	0.06
Ex-smokers	123	1,003	38	8	1.25
Smokers	522	4,394	135	35	14.63
Women					
Low/moderate asbestos exposure					
Never smoked	17	128	5	0	0.04
Ex-smokers	12	93	3	0	0.09
Smokers	27	220	4	0	0.32
Severe asbestos exposure					
Never smoked	101	799	26	3	0.20
Ex-smokers	84	659	24	2	0.50
Smokers	182	1,413	52	10	2.02

[1] Calculated after allowing for the effect of smoking, sex, age, period, and region.

SOURCE: Berry et al. (1985).

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criteria must be applied to the entire body of information available on the exposure. This approach has been carefully and comprehensively followed for both cigarette smoking (US DHHS 1982) and asbestos exposure (Selikoff and Lee 1978), and the evidence is sufficient to establish a causal role for both of these agents in producing lung cancer. This section confines itself to an examination of their interaction.

Selikoff and colleagues (1968) were the first to demonstrate increased lung cancer risk among asbestos workers in an investigation that assessed smoking habits. In a group of 370 asbestos insulation workers, none of the 48 workers who had never smoked regularly or of the 39 workers who smoked only pipes or cigars developed lung cancer. Of the 283 cigarette-smoking workers, 24 died of lung cancer during the 4 years and 4 months of the followup period, although only 2.98 lung cancer deaths were expected on the basis of smoking-specific death rates.

A more extensive evaluation of the risk of cigarette smoking for asbestos insulation workers was provided (Hammond et al. 1979) by a prospective evaluation of the 17,800 members of the International Association of Heat and Frost Insulators and Asbestos Workers discussed earlier. Of this population, 8,220 workers were more than 20 years beyond their onset of asbestos exposure and had a known smoking status. Fifty-four percent of this group were cigarette smokers at the start of the study. The comparison group was drawn from the ACS study of 1 million men and women, and consisted of 73,763 white men with no more than a high school education and not employed as farmers, but with a history of occupational exposure to dust, fumes, vapors, gases, chemicals, or radiation, who were living on January 1, 1967, and were traced thereafter. The control group was followed only until September 30, 1972, and the asbestos workers were followed through 1976; therefore, the lung cancer death rates in the control group were adjusted upward to reflect changes in the U.S. national mortality experience for lung cancer during the time period of differential followup.

There were 1,332 deaths among workers more than 20 years after onset of exposure whose smoking habits were known; 314 (23.6 percent) deaths were due to lung cancer, using the best estimate of cause of death. Death certificate data indicated 272 lung cancer deaths. Figure 2 portrays the mortality ratios for smokers and nonsmokers in the control and the asbestos-exposed populations, with the mortality ratio of nonsmokers in the control group set at 1. The lung cancer death rates increased from 11.3 per 100,000 among nonsmokers in the control group to 58.4 in the nonsmoking asbestos workers, 122.6 for smokers in the control group, and 601.6 for smoking asbestos workers. The lung cancer relative risk with combined exposure (53.24) is far larger than the sum of the

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individual risks for cigarette smoking and asbestos exposure separately, and is quite close to the product of the separate mortality ratios (5.17 and 10.85) together.

Accurate data on the intensity of asbestos exposure for individual workers (dose) were not available for this group of insulation workers, and so an asbestos dose–response relationship was not examined. Dosage data were available for cigarette smokers in this population, however, and the ratio of observed to expected lung cancer deaths (with the expected deaths calculated from the rates in nonsmoking non-asbestos-exposed controls) increased from 5.33 in asbestos workers who never smoked regularly to 7.02 in pipe and cigar smokers, 36.56 in ex-smokers, 50.82 in smokers of fewer than 20 cigarettes per day, and 87.36 in asbestos workers who smoked one pack or more per day.

Interaction between smoking and asbestos exposure in the development of lung cancer has also been explored in other populations. In some studies the numbers have been too small to clearly differentiate between an additive and a multiplicative effect with combined exposure; however, the data have been consistent with an effect that is at least more than additive. This interaction of cigarette smoking and asbestos exposure has been demonstrated in asbestos factory workers (Berry et al. 1972, 1985), Quebec miners and millers (McDonald et al. 1980; Liddell et al. 1984), amosite asbestos factory workers (Selikoff, Seidman, and Hammond 1980) and Finnish anthophyllite miners and millers (Meurman et al. 1979).

A dose–response relationship between cigarette smoking and lung cancer in the general population has been readily demonstrated in a number of prospective mortality studies (US DHHS 1982); however, dose–response relationships for asbestos exposure and lung cancer have been more difficult to establish. The carcinogenicity of asbestos may vary with the type of asbestos, and possibly with the length or diameter of the fiber. There are also potential differences in the carcinogenic risk associated with the different stages and processes of converting asbestos from the raw mineral in the mine into a finished manufactured product. As a result, it is difficult to classify the asbestos exposure of different study populations with a single measurement that quantifies the carcinogenic dose. Even if such a scale were agreed upon, actual measurements of asbestos dust levels in the work environment are often not available. Measures of dust exposures for individual workers are even less frequently available. The quantification of asbestos dust exposure has frequently used estimates of likely exposures based on work conditions and job classification, rather than actual measurements of asbestos dust in the air, because of the absence of these measurements for most workers. This lack of information has been particularly problematic for workers employed more than 20 years ago, a group now at high

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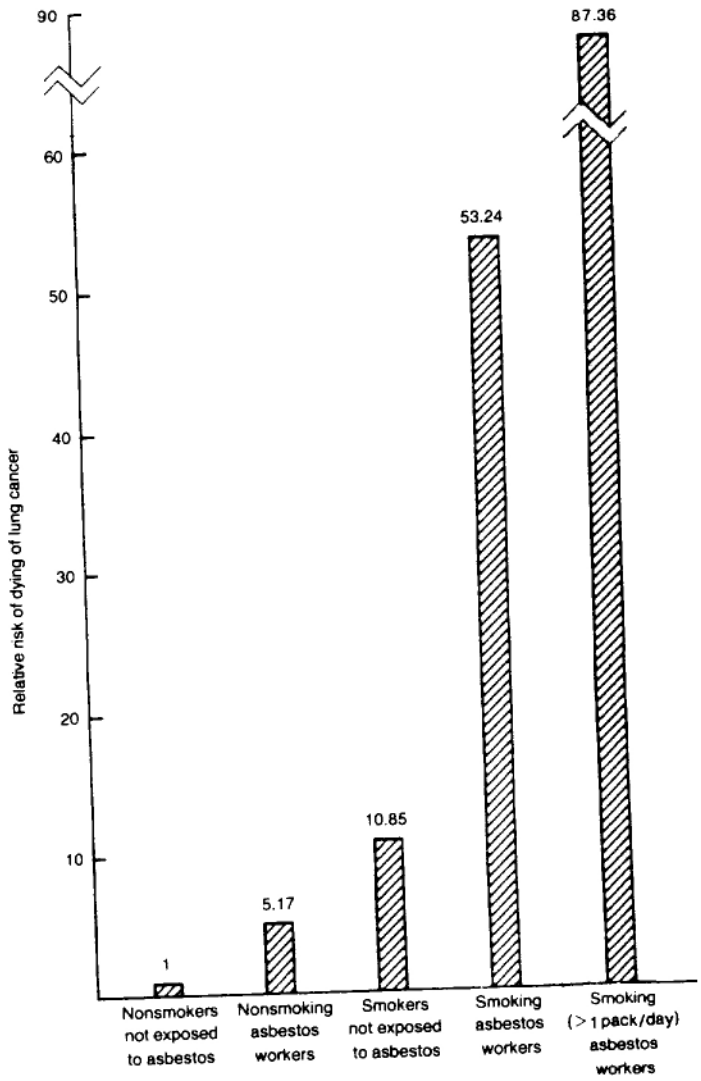


FIGURE 2.—Relative risk of dying of lung cancer for smoking and nonsmoking asbestos workers and smoking and nonsmoking control group members

SOURCE: Hammond et al. (1979).

risk of developing lung cancer. Finally, cumulative asbestos exposure, age, and cumulative cigarette smoking exposure are generally

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correlated. Older employees worked under conditions of much higher asbestos exposure than their younger counterparts, and these same older cohorts probably also had higher prevalences of cigarette smoking, as described in the chapter on smoking patterns by occupation. Confounding between cumulative asbestos exposure and cumulative cigarette smoke exposure may result when dose–response relationships between cumulative asbestos exposure and lung cancer are examined without a control for differences in smoking habits among the different asbestos exposure groups.

Berry and colleagues (1972) examined dose–response relationships in a population of 1,300 male and 480 female asbestos factory workers in Great Britain. Workers were categorized as having low to moderate asbestos exposure or severe asbestos exposure, and the expected number of lung cancer deaths was calculated from standardized mortality rates for lung cancer for the greater London area. An adjustment for cigarette smoking status, derived from the mortality study of British physicians by Doll and Hill (1964), was used to estimate rates for smokers and nonsmokers. The results are presented in Table 3. The small number of lung cancer deaths makes interpretation somewhat difficult, but it appears that the increased lung cancer death rate is limited to smokers with severe asbestos exposure.

McDonald and colleagues (1980) examined Quebec miners and presented evidence for a dose–response relationship between cumulative asbestos exposure and lung cancer risk in the smoking miners. They compared the lung cancer mortality rates in the Quebec miners with the mortality rates for the Province of Quebec. Table 5 shows the SMRs for lung cancer in miners by level of cumulative asbestos exposure and smoking habits. Heavy smokers consistently had higher SMRs than moderate smokers at the same level of cumulative asbestos exposure, and the SMRs increased with increasing cumulative exposure to asbestos in each of the smoking categories. Using the same population of miners, these authors conducted a case–control study of 245 lung cancer victims and a similar number of control miners matched for smoking habits and year of birth. The distribution of cumulative asbestos dust exposure was examined, and the results in cigarette smoking miners showed an increase in relative risk with increasing cumulative exposure. The relative risk of cigarette smokers in the lowest exposure category (<30 mppcf•y) was set at 1.0, and the relative risk increased to 1.12 at 30 to 300 mppcf•y of exposure, 1.58 at 300 to 1,000 mppcf•y, and 1.99 at $\geq 1{,}000$ mppcf•y of exposure.

A more quantitative description of the smoking habits of the same Quebec miners was provided by Liddell and colleagues (1984). Their data are presented in Table 6. The dust exposure measurements were made as particles per cubic foot with midget impingers, and

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TABLE 5.—Deaths from lung cancer in relation to dust exposure and smoking habit

Smoking habit	Dust exposure (mppcf•y) accumulated to age 45							
	<30		30–299		≥300		All	
	0	SMR	0	SMR	0	SMR	0	SMR
Nonsmokers	5	0.18	6	0.36	8	1.24	19	0.38
Moderate smokers	73	1.14	64	1.35	52	2.31	189	1.41
Heavy smokers	13	2.12	11	2.39	10	4.50	34	2.63
All smoking habits	91	0.93	81	1.18	70	2.25	242	1.23

SOURCE: Liddell et al. (1984).

individual exposures were calculated on the basis of the work histories and the measurements of impinger dust counts in the work environment between 1949 and 1966. These counts were then converted to fibers per mL. Two hundred and twenty-three cases of lung cancer were identified and matched to 715 controls born in the same year, and a case–control analysis was conducted. As is shown in Table 6, the relative risk of developing lung cancer increases with increasing asbestos exposure category for each of the cumulative pack-year categories. The analysis also suggests that the interaction between cigarette smoking and asbestos exposure is greater than additive.

Thus the studies that have examined the question of a dose–response relationship for asbestos exposure and lung cancer in the face of an adequate control for cigarette smoking have shown an increasing risk of lung cancer as asbestos exposure increases. This suggests that a dose–response relationship for asbestos exposure and lung cancer does exist, and that it is not explained by differences in smoking habits.

Threshold

The question whether a level of asbestos exposure exists below which an exposure does not result in an increased risk of lung cancer is one that is both technically extremely difficult to answer and extremely important to those required to make policy with regard to asbestos exposure. Current understanding of carcinogenesis and host defenses against cancer are not advanced sufficiently to allow either the acceptance or the rejection of a threshold. It is common practice to assume a linear relationship between the dose of a carcinogen and the development of carcinoma, and to assume that the dose–response relationship does not have a threshold. The linear nonthreshold model allows the extrapolation of data obtained for higher exposures

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TABLE 6.—Risks of lung cancer, by cigarette smoking and asbestos exposure, relative to all 223 cases and 715 referents for whom smoking histories were reliable; unmatched analysis

Pack-years[1]		Exposure accumulated up to 9 years before death of case (f mLy)			
		Low (< 100)	Medium (< 1,000)	High and very high (≥ 1,000)	All
0	Number of cases	6	7	10	23
	Number of referents	103	61	37	201
	Relative risk	0.19	0.37	0.87	0.37
1. < 40	Number of cases	29	27	34	90
	Number of referents	123	93	63	279
	Relative risk	0.76	0.93	1.73	1.03
≥ 40	Number of cases	40	35	35	110
	Number of referents	117	79	39	235
	Relative risk	1.10	1.42	2.88	1.50
All	Number of cases	75	69	79	223
	Number of referents	343	233	139	715
	Relative risk	0.70	0.95	1.82	1.00

[1] Number of cigarettes a day/20 x duration in years.
SOURCE: Liddell et al. (1984).

to the very low exposures. This extrapolation is substituted for the examination of the very large populations that would have to be examined in order to demonstrate the small expected excess risk with low dose exposure. Such models are particularly attractive for exposures for which human epidemiologic data are limited or absent. As discussed earlier, however, minimal exposure to cigarette smoke and asbestos is probably a nearly universal experience in urbanized society. Because of the large population exposed, more careful examination of the available evidence on the risks of these exposures is necessary.

The number of cigarettes smoked per day by an individual is a readily available measure of the dose of smoke exposure in the active cigarette smoker; therefore, it has been possible to examine relatively completely the dose–response relationship for cigarette smoking and lung cancer. There is a consistent increased risk for lung cancer among smokers in the lowest category of number of cigarettes smoked per day in the major prospective mortality studies on smoking (US DHHS 1982). In the study of U.S. veterans (Kahn 1966), a relative risk for lung cancer of 3.77 was demonstrated in those who smoked only occasionally compared with those who had never smoked regularly (the relative risk for those who smoked 1 to 9 cigarettes per day was 4.07 compared with those who never smoked

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regularly). It seems clear that for the active cigarette smoker there is no safe cigarette and no safe level of cigarette smoking (US DHHS 1982). Furthermore, recent data (IARC, in press) suggest that repetitive exposure to environmental tobacco smoke may be accompanied by an increased risk of lung cancer, thereby suggesting that the dose–response relationship may extend even to those individuals who do not actively smoke cigarettes.

The quantification of asbestos exposure is far more difficult. One method is to quantitatively estimate the number of asbestos fibers in digested lung tissue. Asbestos fibers are demonstrable in the lungs of the majority of urban dwellers (Churg and Warnock 1977); however, the number of fibers per gram of lung tissue in urban dwellers without known asbestos exposure is usually several orders of magnitude below that found in occupationally exposed workers, and the type of asbestos varies as well. Churg and Warnock (1979) assessed this urban asbestos exposure as a risk factor for lung cancer by comparing the number of asbestos bodies in 103 patients with lung cancer compared with the number in control patients matched for age, sex, smoking habits, and in some cases, occupation. No differences in the number of asbestos bodies per gram of lung tissue were found between the lung cancer patients and the control population, suggesting that, at this level of exposure, asbestos did not increase the risk of lung cancer in these patients. However, the small number of patients in this study limits the power of the study to find a small effect of asbestos lung burden on lung cancer risk.

Confounding by cigarette smoking is another potential source of bias in evaluating the effects of low levels of asbestos exposure. Several of the studies presented in Table 1 do not show excess lung cancer risks at low levels of asbestos exposure, a pattern consistent with the existence of a threshold. However, lung cancer rates in the general population are determined largely by smoking habits, and if the asbestos-exposed populations have even modestly lower lifetime smoking rates, the effect of asbestos exposure may be masked. This bias is of particular importance at the relatively low levels of asbestos exposure at which the effect of cigarette smoking would be expected to predominate. Thus, in interpreting standardized mortality ratios at or below 1, careful consideration must be given to confounding by the smoking habits of the workforce before concluding that the levels of asbestos exposure experienced by these populations do not result in an increased lung cancer risk. In addition, modest differences in the number of cigarettes smoked per day or the age of initiation of regular smoking between the exposed population and the population from which the SMR is derived could counterbalance a modest risk due to asbestos exposure even in populations with similar smoking prevalences.

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For lung cancer, the measurement of a threshold in epidemiologic studies is further constrained by the certainty with which the absence of an effect can be established. The precision and the accuracy of an estimation of the expected number of deaths in a workforce is heavily influenced by the detail with which the smoking behaviors are determined and the accuracy with which the lung cancer risk of a given smoking history can be estimated.

In the U.S. population during 1977, 10 percent of the men who died between the ages of 50 and 70 died of lung cancer (McKay et al. 1982). Therefore, a workforce with smoking patterns similar to the U.S. population would be expected to have a similar mortality experience, in the absence of any asbestos exposure. A 10 percent increase in the risk of lung cancer in a workforce (SMR 110, RR 1.1) due to asbestos exposure would mean that 1 percent of the deaths among workers aged 50 to 70 would be excess lung cancers due to asbestos, a level of risk unacceptable as the basis for an industrial hygiene standard. However, even with carefully determined smoking histories for a worksite, no data are currently available that would allow the calculation of expected death rates in smokers and nonsmokers with precision sufficient to establish that an increase of 10 percent was not simply an error in the estimates. In addition, estimates of the smoking habits of the U.S. population are not known with enough precision to adjust national or regional death rates for the smoking patterns of a given workforce so that a 10 percent difference could be considered significant. The result is a dilemma for those who would try to measure a threshold level, or an "acceptable" exposure level, for occupational exposure to asbestos: an effect too small to measure in statistical terms is still too large to be acceptable in human terms.

A final caution in the determination of a threshold for lung cancer risk secondary to asbestos exposure, and in the use of such a threshold to establish environmental dust standards, is the potential differences between a threshold for lung cancer and one for mesothelioma or other asbestos-related disease. Mesothelioma, which is not associated with cigarette smoking, may occur following exposure to low levels of asbestos, and a level of dust exposure defined as a "safe" level for lung cancer risk may possibly continue to produce an increased risk of mesothelioma.

A pragmatic approach to the problems of defining a threshold or establishing safe levels has been to define asbestos exposure standards on the basis of the lowest level of asbestos dust exposure that can be produced with existing technology. This approach reduces the risk, but does not answer the question whether the exposure of a worker is "safe."

An alternate approach has been to use the existing exposure–response data. In the face of uncertainty about the shape of the

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exposure–response curve for asbestos exposure and lung cancer and whether a threshold exists, an assumption that asbestos has a linear exposure–response relationship with lung cancer and no threshold for effect has been suggested as both reasonable and a way to set standards (Peto 1979; NRC 1984). By definition, in this approach there can be no "safe" level of exposure (i.e., no threshold), only an "acceptable" degree of risk. However, using this method, once an "acceptable" level of lung cancer in a working population has been defined, the level of asbestos exposure that would result in that level of risk can be estimated. A corollary of this approach is that asbestos is assumed to contribute to the lung cancer that develops in populations of workers who have been exposed to asbestos regardless of their level of exposure; by extension, the asbestos found in the lungs of urban dwellers with no known occupational asbestos exposure is assumed to make a small (but finite and definable) contribution to all lung cancers. The evidence that does exist (Churg and Warnock 1977) suggests that asbestos exposure makes no "measurable" contribution to lung cancer in individuals without a definable exposure, but it is impossible to establish the absence of "any" effect.

If the issues of liability can be separated from the issue of threshold, then the problem of reducing and eliminating asbestos-related disease and disability could be approached with a broader focus. The focus could be expanded beyond improving technology for reducing exposure to asbestos to include other methods of reducing the cancer risk associated with asbestos exposure. If the goal is to reduce the lung cancer deaths associated with asbestos rather than simply reducing the levels of asbestos dust in the worksite, then the deaths due to the interaction between smoking and asbestos must be dealt with, and the elimination of smoking will be a potent adjunct to environmental asbestos dust control in this task, particularly for those workers who have already received substantial asbestos exposure. A public health "feasibility" threshold could then be defined, not in terms of what dust levels were achievable, but rather in terms of what lung cancer death rates were achievable. This threshold would be the lowest cancer risk achievable, given our current technology, and would include minimizing asbestos exposure, maximizing smoking cessation, and applying techniques for early diagnosis and treatment.

In summary, although the level of asbestos exposure that occurs in the general population does not appear to be accompanied by an increased risk of lung cancer, the demonstration of a clear threshold below which there is no effect in occupationally exposed populations is not possible.

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TABLE 7.—Lung cancer mortality ratios with cessation of cigarette smoking in male smokers who smoked more than 20 cigarettes per day compared with those who never smoked regularly

Years since cessation	Not exposed to asbestos[1]	Asbestos insulation workers[2]
Current smokers	11.69	10.4
Under 1 year	17.7	
1–4 years	10.1	11.5
5–9 years	6.5	4.2
≥10 years	1.8	3.4
Never smoked regularly	1	1

[1] Data from Hammond (1972).
[2] Data from Hammond (1979).

Cessation of Exposure

A decline in the relative risk of developing lung cancer following cessation of cigarette smoking was demonstrated in cigarette-smoking asbestos workers by Hammond and colleagues (1979). Table 7 shows the lung cancer mortality ratios in asbestos workers who are current smokers and who have quit for varying periods of time, compared with those workers who have never smoked regularly. A companion set of numbers is provided of the relative risks for lung cancer in men not exposed to asbestos, but who are current smokers or have quit for varying periods of time, derived from the American Cancer Society study of 1 million men and women (Hammond 1972).

Several authors have attempted to approach the question of the risk of lung cancer following cessation of asbestos exposure by examining the relative risks of asbestos exposure in workers following retirement (Walker 1984; Selikoff, Hammond et al. 1980). The data in Figure 3 and Table 8 reveal that the relative risk for lung cancer in asbestos workers increases and then declines with the increasing number of years from initial exposure. The workers with the longest interval from onset of exposure are also of the greatest age within the populations examined. Because of this link with age, the interpretation of this decline in relative risk as indicating that cessation of asbestos exposure results in a decline in lung cancer risk must be made with great caution. Examination of national age-specific mortality rates for lung cancer (Figure 4) also shows a decline in male lung cancer death rates with increasing age. This decline with age is an artifact of the cross-sectional nature of data

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presented in Figure 4. When cancer death rates are examined by birth cohort (Figure 5), no decline with age can be demonstrated. The explanation for this seeming discordance in the data is the differences in pattern of cigarette smoking in different birth cohorts in the U.S. population (Figure 6) (US DHHS 1982). Those birth cohorts that currently represent the oldest age groups have lower smoking prevalences than the birth cohorts in the younger ages (those born between 1910 and 1930), and this decreased smoking prevalence resulted in a decreased lung cancer mortality. The risk ratios presented in Figure 3 are comparisons with the risk in the general population, and therefore represent the combined effect of the increased smoking prevalence among asbestos workers and the increased risk due to the asbestos exposure. To the extent that the age-related changes in smoking prevalence among older asbestos workers presented in Table 9 represent a return toward or below the smoking prevalence in the general population, a decline in the risk ratio among older asbestos workers would be expected. Regardless of the reason for the change in risk ratio among older workers (i.e., either differences in smoking behavior or decline in risk following cessation of asbestos exposure), the magnitude of the decline is modest, particularly when the rapidly increasing baseline risk of lung cancer in the general population with increasing age used to calculate these risk ratios is considered.

A somewhat different approach to this question was taken by Seidman and colleagues (1979), who examined the mortality experience of a group of workers exposed to asbestos over a very limited period of time during World War II and followed them for 35 years after the onset of this exposure. These workers had an extremely intense exposure to asbestos, but only very brief exposures with no subsequent asbestos work-exposure history. If the risk of lung cancer declines significantly following the cessation of exposure to asbestos, then these workers would be expected to have a declining risk of developing lung cancer with increasing duration from the onset of asbestos exposure. Figure 7 shows the ratio of observed to expected lung cancer deaths for the 10-year periods beginning 5, 15, and 25 years after the onset of exposure in workers who had worked less than 9 months and those who had worked more than 9 months in this plant. In both cases the risk is greater in workers for the 10-year period beginning 25 years after onset of exposure than for the period beginning 15 years after exposure. The small number of deaths recorded in the study limits its interpretation; however, the data are consistent with the conclusion that cessation of asbestos exposure may not be associated with a decline in the relative risk of developing lung cancer with increasing duration of time since last exposure.

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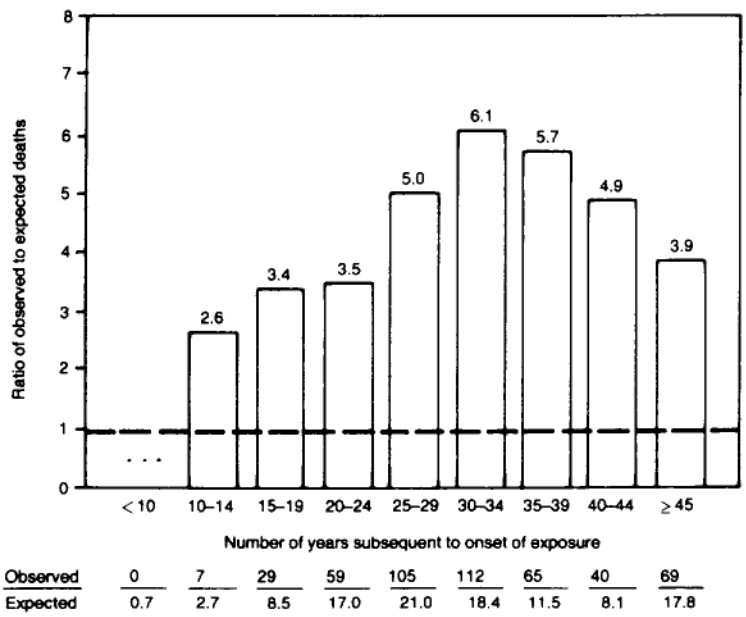


FIGURE 3.—Ratios of observed to expected deaths from lung cancer among 17,800 asbestos insulation workers observed prospectively, 1967 and 1976, in 5-year periods subsequent to beginning employment in this trade

NOTE: The decline in ratios after the 30- to 35-year period may be the result of a "survivor effect," because deaths associated with cigarette smoking (e.g., myocardial infarction, lung cancer) tend to selectively change the composition of the surviving cohort in relation to smoking status with time.

SOURCE: Selikoff, Hammond et al. (1980).

A similar result was reported by Blot and colleagues (1980) in a case–control study of male lung cancer patients. They found a small excess risk of developing lung cancer in workers who had been employed in shipyards for only a few years during World War II, and the relative risk in these workers was similar to that for workers who had worked regularly in the shipyards.

In summary, the data suggest that elimination of further asbestos exposure may prevent the further increase in relative risk that would accompany an increase in cumulative exposure. However, the relative risk of developing lung cancer persists even after prolonged avoidance of additional asbestos exposure. In contrast, the cessation of cigarette smoking appears to reduce the risk of developing lung cancer in asbestos insulation workers compared with those workers who continue to smoke, and the time course of this reduction in risk

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TABLE 8.—Changes in the ratio of observed to expected deaths with time since first employment, four cohort studies

Years since initial exposure	North American insulators[1]		Quebec miners and millers[2]		Factory workers[3]		New York–New Jersey insulators[4]		Asbestos cement workers[5]	
≤ 10	2.55	(7)					0.00	(0)	0.77	(1)
11–15	3.40	(29)							1.25	(3)
16–20	3.48	(59)	0.00	(0)	2.38	(4)	8.67	(26)	1.54	(6)
21–25	5.00	(105)							2.33	(7)
26–30	6.08	(112)	1.94	(7)	3.73	(23)			3.33	(5)
31–35	5.68	(65)					6.63	(67)	3.08	(4)
36–40	4.93	(40)	4.19	(16)	1.37	(6)				
41–45	3.89	(69)								
46–≥ 50			1.67	(5)						
Total number of deaths		(486)		(28)		(33)		(93)		(26)

[1] Data from Selikoff, Hammond et al. (1980).
[2] Data from Nicholson et al. (1979).
[3] Data from Nicholson et al. (1979).
[4] Data from Selikoff et al. (1979).
[5] Data from Weill et al. (1979).
NOTE: Number of deaths given in parentheses.
SOURCE: Walker (1984).

is similar to that found among smokers in the general population who stop smoking.

Mechanisms of Carcinogenesis in Cigarette-Smoking Asbestos Workers

An increased risk of developing lung cancer has been observed with all commercially used types of asbestos. Most studies indicate that crocidolite exposure may produce a higher human lung cancer risk than chrysotile (Weill et al. 1979; Enterline and Henderson 1973), but some studies have shown the opposite (McDonald et al. 1983a, b; Dement et al. 1982). All of the four major histologic types of bronchogenic carcinoma develop in asbestos workers who smoke (Churg 1985; Auerbach et al. 1984; Whitwell et al. 1974). Although an increased risk of lung cancer with exposure to asbestos in nonsmokers has been demonstrated in a number of epidemiologic studies (Hammond et al. 1979; McDonald et al. 1980), it remains unclear whether the asbestos fiber by itself acts as a complete carcinogen for lung cancer in the respiratory tract of man. This is in contrast to the role of asbestos as a carcinogen in mesothelioma,

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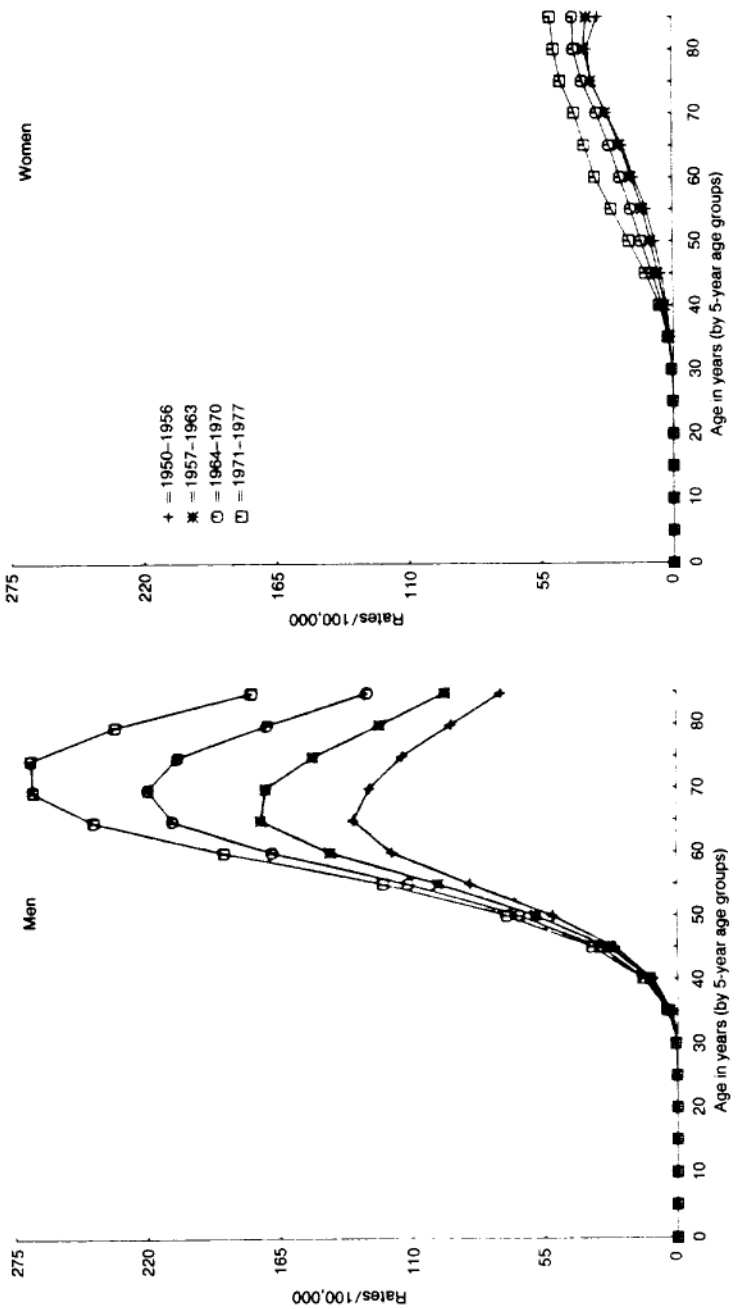


FIGURE 4.—Age-specific mortality rates for cancer of the bronchus, trachea, and lung, white men and women, United States

SOURCE: McKay et al. (1982).

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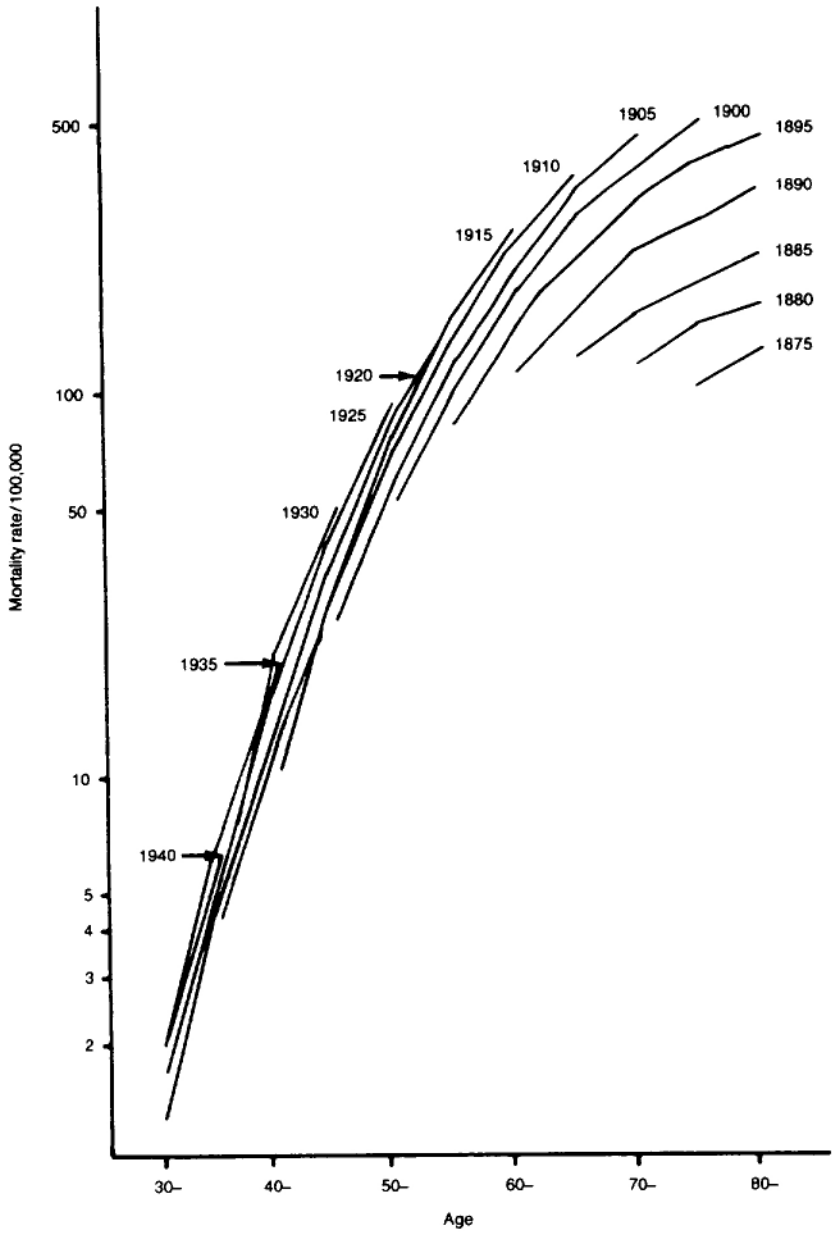


FIGURE 5.—Age-specific mortality rates for cancer of the bronchus and lung, by birth cohort and age at death, men, United States, 1950–1975

SOURCE. Data derived from McKay et al. (1982).

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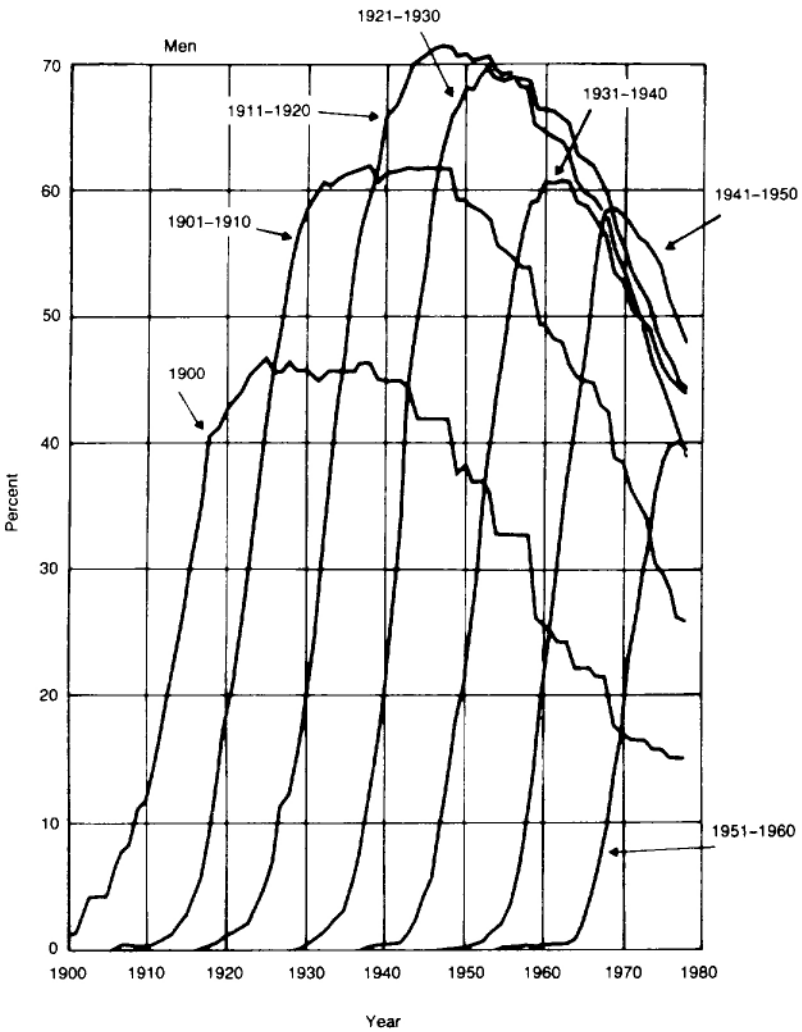


FIGURE 6.—Changes in the prevalence of cigarette smoking among successive birth cohorts of men, 1900–1978

NOTE: Calculated from the results of more than 13,000 interviews conducted during the last two quarters of 1978, provided by the National Center for Health Statistics, Division of Health Interview Statistics.
SOURCE: US DHHS (1982).

where asbestos exposure alone is clearly able to produce the tumor and where cigarette smoking does not alter the mesothelioma risk.

Laboratory investigations have been undertaken to evaluate the mechanisms through which asbestos interacts with the combustion products of cigarettes to induce neoplasms. In this regard, the carcinogenic properties of polycyclic aromatic hydrocarbons (PAH), documented chemical carcinogens in cigarette smoke, have been

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TABLE 9.—Prevalence of smoking among asbestos insulation workers whose smoking history was known

Age	Current smokers	Former smokers	Never smoked regularly	Pipe and cigar
25–29	64.8	19.3	13.0	2.9
30–34	61.0	19.3	13.5	6.[illegible]
35–39	60.9	22.2	11.6	4.9
40–44	61.3	25.0	9.2	4.5
45–49	55.8	28.8	9.8	5.6
50–54	53.7	32.2	9.1	5.0
55–59	50.1	34.1	9.8	6.0
60–64	45.4	35.1	10.4	9.1
65–69	42.3	33.7	12.4	11.6
70–74	30.7	34.3	17.5	17.5
75–79	51.5	34.3	7.1	7.1
80–84	37.1	33.3	11.1	18.5
≥85	30.0	35.0	25	10.0

Source: Hammond et al. (1979).

evaluated in combination with asbestos both in tissue cultures and in grafts of respiratory tract epithelium (reviewed in Craighead and Mossman 1982; Mossman, Light et al. 1983). This section summarizes the results of these experimental studies.

Animal Studies of the Carcinogenic Interactions Between Cigarette Smoke and Asbestos

When animals are administered asbestos in inhalation chambers or by intratracheal instillation, differences among species and strains appear to influence the occurrence of lesions. For example, only benign lesions (papillomas and adenomas) are found in hamsters, guinea pigs, and rabbits after prolonged inhalation of asbestos (Botham and Holt 1972a, b; Gardner 1942; Reeves et al. 1974), whereas cats (Vorwald et al. 1951) and nonhuman primates (Wagner 1963; Webster 1970) develop fibrosis of the lung but not tumors. Small numbers of neoplasms (squamous cell carcinoma, adenocarcinoma, small and large cell carcinoma) have been reported in rats (Davis et al. 1978; Reeves 1976; Reeves et al. 1974; Wagner et al. 1974), but benign neoplasms and fibrosarcomas (tumors rare in the human lung) predominate. Mice also appear to develop both benign and malignant tumors after inhalation of asbestos (Bozelka et al. 1983; Gardner 1942). Bozelka and colleagues (1983) found a large

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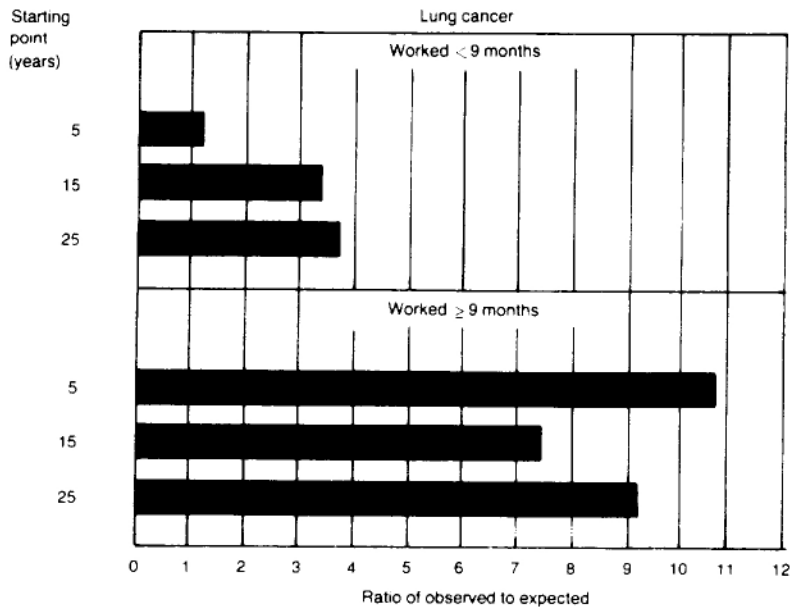


FIGURE 7.—Observed compared with expected weighted average probabilities of lung cancer death in 10-year periods, starting at 5-, 15-, and 25-year points after beginning of work in an amosite asbestos factory, 1941–1945, for men who worked less than or more than 9 months

NOTE: Computed by assigning weights of 55 and 45 percent to the probabilities given in Seidman and colleagues (1979) for men aged 40 to 49 and 50 to 59, respectively, at the start of the 10-year periods.
SOURCE: Seidman et al. (1979).

number of lesions of questionable malignancy in the lungs of Balb/c mice 12 to 18 months after a 75-day exposure to chrysotile asbestos.

Unfortunately, it is difficult to evaluate many of these animal studies critically because satisfactory controls were not employed and data on exposure regimens and concentrations of asbestos are often not available. In addition, adequate pathologic documentation of the lesions is often lacking. Benign adenomas could occur spontaneously in many lesser species (Mitruka et al. 1976), and luxuriant squamous metaplasia and bronchiolization of the respiratory mucosa may be misinterpreted as malignant lesions. These last epithelial changes may occur as a response to injury induced by asbestos (Davis et al. 1978; Mossman et al. 1980; Reeves et al. 1974; Wagner 1963; Woodworth et al. 1983a, b).

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Several investigators have administered chrysotile to rats and hamsters in combination with either cigarette smoke or benzo[a]pyrene (BaP), a major polycyclic aromatic hydrocarbon (PAH) in cigarette smoke (Table 10) (Miller et al. 1965; Pylev and Shabad 1973; Shabad et al. 1974; Smith et al. 1968; Wehner et al. 1975). A striking increase in neoplasms (both benign and malignant) of the respiratory tract was observed. In contrast, a synergistic effect on tumor development was not apparent in rats exposed to asbestos and cigarette smoke by inhalation (Shabad et al. 1974; Wehner et al. 1975); however, the majority of the animals in these studies died prematurely of pulmonary fibrosis.

The effects of asbestos on the carcinogenicity of PAH in the respiratory tract have been evaluated using grafts of tracheal tissue implanted into syngeneic animals. Two model systems have been developed. In the first, the tracheas of rats are excised and formed into tubular sacs by ligatures at the ends and then transplanted subcutaneously (Topping and Nettesheim 1980; Topping et al. 1980). When relatively large amounts of chrysotile are introduced into the lumina of these grafts, inflammatory changes appear and fibrosarcomas develop in a substantial proportion of animals (Topping et al. 1980). On the other hand, epithelial tumors (carcinomas) appear when low concentrations of the PAH dimethylbenz[a]anthracene are introduced into the tracheal grafts before chrysotile (Topping and Nettesheim 1980). The amounts of PAH used in these experiments were insufficient to cause tumors; therefore, the asbestos acted as a promoting agent.

In the second model system, organ cultures of hamster trachea are exposed to crocidolite asbestos and implanted into syngeneic recipients after various periods of incubation in vitro (Craighead and Mossman 1979; Mossman and Craighead 1979, 1981, 1982). Neoplasms failed to develop in these experiments. However, tumors, the majority of which were carcinomas, were found when the PAH 3-methylcholanthrene (3MC) was coated on the surface of the crocidolite fibers and precipitated onto the epithelial surfaces of the tracheal organ cultures prior to transplantation. This tissue served as the nidus for the development of squamous cell carcinomas in the hamsters implanted with the cultures. In these experiments, asbestos appeared to be a carrier of PAH, because 3MC also produced tumors when absorbed to nonfibrous particulates such as kaolin, hematite, and carbon (Mossman and Craighead 1979, 1982).

Concepts of Carcinogenesis

The concepts of initiation and promotion were developed to explain the complex, multistep process of chemical carcinogenesis. "Initiation" is defined as the irreversible DNA damage of a cell induced by a carcinogenic agent. In contrast, tumor "promotion" is a

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TABLE 10.—Tumors occurring in rodents after exposure to asbestos in combination with components of cigarette smoke

Number of tumors/Number of animals					
Chrysotile	Agent alone	Combination	Tumor types	Animal	Reference
Inhalation					
5/51	12/51 (smoke)	9/51 (+smoke)	Adenoma, papilloma, carcinoma	Rat	Wehner et al. (1975)
0/46	ND[1]	0/16 (+smoke) 0/21 (+BaP[2])	ND	Rat	Shabad et al. (1974)
Intratracheal instillation					
ND	8/37 (BaP)	18/35 (+BaP)	Adenoma, papilloma, carcinoma	Hamster	Smith et al. (1968)
0/17	10/34 (BaP)	24/31 (+BaP)	Adenoma, papilloma, carcinoma	Hamster	Smith et al. (1968)
0/49	0/19 (BaP)	6/11 (+BaP mixed) 6/21 (+BaP adsorbed)	Adenoma, carcinoma, reticulosarcoma, mesothelioma	Rat	Pylev and Shabad (1973)
0/10	4/10 (BaP)	15/10[3] (+BaP)	Papilloma, carcinoma	Hamster	Miller et al. (1965)

[1] ND = no details provided.
[2] BaP = benzo[a]pyrene.
[3] Animals developed multiple tumors.

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sequential process whereby a second, but unrelated, generally noncarcinogenic substance acts to enhance the effect of an initiator. Initiated cells undergo proliferative changes and differentiation that ultimately result in transformation to a malignant lesion. Much of the information that has accumulated on classical tumor promoters and their mechanisms of action was derived from studies with mice in which the animal's skin was painted with PAH, followed by repeated applications of phorbol esters (or related compounds) (reviewed in Slaga et al. 1982). Nonetheless, the concepts of initiation and promotion appear broadly relevant to carcinogenesis in the mammary gland, liver, colon, urinary bladder, brain, and lung (Marx 1978). In this regard, a wide variety of chemical, physical, and infectious agents interact with tissues to induce a constellation of inflammatory and proliferative changes ultimately resulting in malignancy.

It is doubtful that the action of asbestos in increasing lung cancer risk is as a tumor initiator (reviewed in Craighead and Mossman 1982; Mossman and Craighead 1981). Few epithelial tumors develop in experimental animals when PAH are not used in conjunction with asbestos. Moreover, chrysotile and crocidolite do not seem to damage the DNA of hamster or human tracheobronchial epithelial cells (Fornace 1982; Mossman, Eastman et al. 1983). In most (but not all) studies using cell culture systems, asbestos is neither mutagenic nor carcinogenic (Chamberlain and Tarmy 1977; Daniel 1983; Kaplan et al. 1980; Reiss et al. 1982), but the malignant transformation of hamster embryo fibroblastic cells by asbestos, glass fibers, and silica particles has been reported recently (Hesterberg and Barrett 1984; Oshimura et al. 1984). Under these circumstances, asbestos may not act like a classical mutagen, but appears to cause alterations in chromosomal structure (Barrett et al. 1983), perhaps consequent to its cytotoxic effects.

In contrast, asbestos exhibits many of the properties of classical tumor promoters when introduced into grafts of tracheal tissue (Topping and Nettesheim 1980) and monolayer cultures of hamster and human tracheobronchial tissues (reviewed in Craighead and Mossman 1982; Mossman and Craighead 1981; Mossman, Light et al. 1983). Like the phorbol esters, asbestos appears to induce perturbations of the plasma membranes of cells, such as the stimulation of membrane-associated enzymes (Mossman et al. 1979) and the generation of oxygen free radicals (Mossman and Landesman 1983). In addition, both asbestos and fibrous glass induce the biosynthesis of polyamines, important biochemical markers of cell division and proliferative changes in the tracheobronchial mucociliary epithelium (Landesman and Mossman 1982; Marsh and Mossman 1984). This is accompanied by the development of squamous metaplasia, a putative premalignant change. These alterations in cell function and

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structure are not observed in tissues exposed to nonfibrous mineral analogs of asbestos and glass, an observation indicating that the fibrous geometry of the material is important (Woodworth et al. 1983b).

Cigarette smoke contains ciliostatic and toxic chemicals that impair mucociliary transport and the function of phagocytic cells (Warr and Martin 1978). Thus, intrapulmonary deposition and clearance of asbestos might be affected, resulting in increased retention of asbestos in the lungs. In addition, the development of squamous metaplasia consequent to exposure to both PAH and asbestos (Mossman et al. 1984) might contribute to the retention in the respiratory tract of asbestos and the constituents of cigarette smoke.

Studies using artificial membranes and cells in culture suggest other possible mechanisms of synergism between PAH and asbestos. PAH are not carcinogenic in their natural state and must be metabolized by a mixed-function, microsomal enzyme system (aryl hydrocarbon hydroxylase, AHH) to degradative products and electrophilic forms interacting with DNA (Freudenthal and Jones 1976). In this regard, the association (adduct formation) of modified metabolites of PAH with the DNA of "target" cells is thought to be a critical event in initiation of those cells. A number of studies suggest that the addition of asbestos and PAH to tracheobronchial epithelial cells (Mossman and Craighead 1982), microsomal preparations from lungs (Kandaswami and O'Brien 1981), and phagocytes (McLemore et al. 1979) affects the normal metabolism of PAH as measured by an increase (or decrease) in activity of AHH enzymes. Unfortunately, these results are inconsistent, possibly a reflection of the different experimental systems evaluated. Accordingly, this important area of carcinogenesis needs further exploration.

PAH are ubiquitous in the environment and are associated with airborne particulates (Natusch et al. 1974). Thus, the ability of asbestos and other particles to act as "condensation nuclei" for chemical carcinogens has been explored using tracheobronchial epithelial cells (Mossman, Eastman et al. 1983; Eastman et al. 1983) and artificial or isolated cell membranes (Lakowicz and Bevan 1979; Lakowicz et al. 1978). Transfer of PAH to cell membranes by asbestos appears to occur more rapidly than with use of nonfibrous particulates (Lakowicz and Bevan 1979; Lakowicz et al. 1978). Moreover, the normal uptake of BaP and the formation of BaP-DNA adducts by tracheal epithelial cells are increased when BaP is adsorbed to chrysotile and crocidolite asbestos (Mossman, Eastman et al. 1983; Eastman et al. 1983).

The pulmonary alveolar macrophage (PAM) is a key cell in the response of the host to asbestos. PAMs accumulate at sites of deposition of asbestos in the tracheobronchial tree (Brody et al.

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1981), a process associated with activation and release of lysosomal enzymes (Davies et al. 1974) and the generation of oxygen free radicals (McCord and Wong 1979). In addition, these cells possess the enzymatic capability to convert PAH to active metabolites (Autrup et al. 1978) and may facilitate the transfer of hydrocarbons to tracheobronchial epithelial cells and other cell types (Shatos and Mossman 1983). Thus, either damage to or activation of macrophages by asbestos and the components of cigarette smoke could influence the process of carcinogenesis.

Conclusions

Several mechanisms by which cigarette smoke and asbestos may interact to increase carcinogenic risk are possible, but they remain unproved in man. First, asbestos fibers could serve as carriers of the carcinogens of cigarette smoke into the cell. Physical transport of this type has been demonstrated experimentally, and there is evidence to suggest that asbestos transfers PAH to cell membranes with unusual efficiency in comparison with other particulates. While this mechanism is an intriguing possibility, it presupposes the interaction of smoke constituents with aerosols of asbestos fibers in the atmosphere. Events of this nature remain hypothetical and unproved. A second mechanism is based on experimental evidence accumulated in both animals and cell culture systems. In this schema, asbestos serves as a promoter in the respiratory epithelium to alter the properties of the epithelial cells and to enhance neoplastic transformation in cells initiated by the combustion products of cigarettes. Biological evidence supporting this mechanism of carcinogenesis is compelling in experimental models of carcinogenesis, but not easily tested in man.

The possible role of macrophages in the metabolism of PAH adsorbed to asbestos is an intriguing consideration. These cells are biologically activated in the smoker and in the lungs of those exposed to asbestos. They frequently accumulate in large numbers in the airspaces of individuals exposed to these and other pollutants. One can only speculate on whether or not the alveolar macrophage contributes to the metabolism of chemical carcinogens under these circumstances.

Although obvious information gaps exist, consideration of the experimental results described here and the contemporary concepts of neoplastic transformation suggest several mechanisms of interaction between components of cigarette smoke and asbestos. On the one hand, asbestos appears to resemble a classical tumor promoter after initiation of tracheobronchial epithelial cells by the carcinogenic chemicals found in cigarette smoke. Alternatively, asbestos appears to act as a vehicle for the transfer of PAH across cell membranes and affects the metabolism of these carcinogens, factors

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favoring the process of initiation. Finally, asbestos and the toxic constituents of cigarette smoke injure cells, a situation potentially encouraging the retention of these inhalants in the respiratory tract.

Chronic Lung Disease

Cigarette smoke (US DHHS 1984) and asbestos exposure (Selikoff and Lee 1978) are well-established causes of chronic lung injury. As in the preceding discussion of lung cancer, the enormous body of literature that established the pathogenicity of each of these agents is not presented; rather, this section focuses on the effects of combined exposure. In contrast to their effect on the risk of developing lung cancer, asbestos and cigarette smoke produce different patterns of injury in the lung. The pattern of lung injury associated with cigarette smoking is characterized by inflammation, excess mucus production, narrowing of the airway lumen, and emphysema (US DHHS 1984). The result is a reduction in maximal expiratory flow rates and increased static lung volumes. The pattern of lung injury associated with asbestos is fibrosis of the small airways extending into the alveolar structures with obliteration of alveoli, leading to a reticular nodular pattern of interstitial fibrosis on chest roentgenogram and decreased lung volumes, with relative preservation of the forced expiratory volume in 1 second (FEV_1) as a percent of the forced vital capacity (FVC) (Selikoff and Lee 1978).

In spite of these relatively distinct patterns of lung injury, interpretation of the pattern of injury in combined exposure is difficult. Both agents may act separately, but simultaneously, to injure the lung. The injury in an individual worker is the combination of the injuries due to cigarette smoke, asbestos and other environmental agents, and all other injurious processes that have occurred during that individual's lifetime. The presence of a lung injury secondary to one agent or process does not prevent the lung from being injured by a second agent. In evaluating impairment in an asbestos-exposed smoker, it may be difficult to apportion the impairment between the two agents because both cigarette smoking and asbestos exposure may alter a given lung function test in the same direction (e.g., both of them reduce the diffusing capacity (DLCO)), or they may change a test in opposite directions (e.g., an increase in total lung capacity (TLC) due to smoking may mask a decline in TLC due to asbestos). When a given physiologic test is influenced in opposite directions by cigarette smoking and asbestos, the degree of injury to the lung may be underestimated by the change in that test. For example, the relative preservation of TLC in cigarette-smoking asbestos workers does not represent a relative protection of the lung in combined exposure, but rather reflects the emphysematous destruction of alveolar walls secondary to cigarette

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smoking (which increases TLC) being combined with the asbestos-related fibrosis and obliteration of other alveolar units (which reduces TLC).

Interstitial fibrosis of the lung is a well-described and well-established sequel of heavy asbestos exposure. In an individual, the fibrosis is attributed to asbestos when a pattern of lung injury on chest roentgenograph or lung biopsy consistent with that found in asbestos-exposed populations is found in conjunction with a history of significant asbestos exposure or with levels of asbestos in lung tissue consistent with significant asbestos exposure. Fibrosis due to other causes such as exposure to coal dust, silica, or infection needs to be considered in evaluating individual patients, and both diagnosis and attribution to a specific etiologic agent may be difficult in the very early stages of the fibrotic process. However, by the time the process has progressed to the degree that it causes significant disability or death, the diagnosis is usually readily evident and the substantial asbestos exposure generally necessary to cause this degree of fibrosis is also easily identifiable.

Chronic Lung Disease Death Rates

Cigarette-induced chronic lung injury does not produce the extensive fibrosis commonly found in individuals dying of asbestos-induced interstitial fibrosis, and therefore does not interfere in the diagnosis, or attribution to asbestos, of the severe fibrotic lung disease in these individuals. However, cigarette smoking can cause significant lung destruction and disability, and therefore it may contribute to the mortality and degree of disability in individuals with asbestos-induced interstitial fibrosis, independent of any effect of cigarette smoking on the degree or extent of fibrosis. In addition, because death and disability occur only after extensive lung injury, the independent (i.e., additive) lung injuries due to smoking and asbestos might sum to produce a level of disability that could exert a synergistic effect on death rates.

Frank (1979) presented data on the death rates in smoking and nonsmoking asbestos insulation workers (Table 11). The population was drawn from the 17,800 asbestos insulation workers studied by Hammond and colleagues (1979) and included those workers with more than 20 years of exposure whose smoking habits were known. The age-standardized death rates from chronic lung disease (including asbestosis) were increased by either cigarette smoking or asbestos exposure, and the rate in cigarette-smoking asbestos workers was well above the sum of the rates for non-asbestos-exposed smokers and nonsmoking asbestos workers. This "synergism" was also present when only asbestosis deaths were considered, with the death rate almost three times higher in cigarette-smoking asbestos workers than in nonsmoking asbestos workers. This study revealed a

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greater than additive effect for cigarette smoking and asbestos exposure on death rates from chronic lung disease and asbestosis. This may reflect a "synergistic" effect on death rates of the "addition" of the two separate injuries, rather than an effect of cigarette smoking on the degree of fibrosis produced by a given dose of asbestos. In addition, these data reflect the fact that a death certification of asbestosis does not rule out the possibility of a second disease process existing in the lungs of that individual.

Pulmonary Function Testing

The most frequently used measures of lung function are lung volumes and measures of maximal expiratory airflow, either as the volume expired during a given time (e.g., forced expiratory volume in 1 second, FEV_1) or as the rate of expiratory airflow at a given lung volume or between two lung volumes (e.g., forced expiratory flow from 25 to 75 percent of the forced vital capacity, $FEF_{25-75\%}$). Classically, diseases are divided by their pattern of abnormality on lung function testing into obstructive (processes that predominately limit expiratory airflow) and restrictive (processes that predominately decrease lung volumes and specifically decrease the total lung capacity). Both of these processes may occur in a single individual, resulting in a mixed pattern (both reduced lung volumes and reduction in volume-adjusted expiratory flow rates).

Obstructive lung disease is marked by reductions in the rate of expiratory airflow; normal or, more typically, increased TLC; and substantial increases in residual volume (RV) and functional residual capacity (FRC) (Figure 8). Restrictive diseases are marked by a reduction in TLC. The flow rates in restrictive disease are usually normal or even increased once an adjustment for the decreased lung volume has been made. FEV_1 is obviously limited by the total volume that can be expired, as well as by the amount of obstruction to expiratory airflow. For this reason, FEV_1 is commonly divided by the forced vital capacity (FVC), and expressed as the percentage of the FVC that can be expired in 1 second ($FEV_1/FVC\%$). This adjustment of FEV_1 for reductions in FVC aids in separating the decline in FEV_1 that is due to a restrictive process (i.e., reduced TLC) from that which represents increased resistance to, and decreased driving pressure for, expiratory airflow.

The pattern of lung function change in cigarette smokers has been well described (US DHHS 1984), and consists of a reduced FEV_1 and $FEV_1/FVC\%$, an increased RV and FRC, and an increased TLC (particularly in those individuals with emphysema). In addition, $FEF_{25-75\%}$, DLCO, and flows at specific lung volumes are also usually reduced.

The pattern of change with the development of interstitial fibrosis due to asbestos is also clear. Figure 9 shows the changes in lung

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TABLE 11.—Age-standardized death rates for combinations of cigarette smoking, no smoking, asbestos exposure, and no asbestos exposure; selected causes of death

Group	All causes	All cancer	Noninfectious pulmonary diseases (total includes asbestosis)	Asbestosis	All other causes
Death rates per 100,000 man-years					
I. No asbestos work and no smoking	980.9	208.2	28.8	—[1]	743.9
II. No asbestos work, but smoking	1580.7	353.1	103.8	—[1]	1123.8
III. Asbestos work and no smoking	1430.9	563.9	77.1	77.1	789.9
IV. Asbestos work and smoking	2659.0	1317.0	286.5	225.5	1005.5
Mortality ratios					
No asbestos work and no smoking (I ÷ I)	1.00	1.00	1.00		1.00
No asbestos work, but smoking (II ÷ I)	1.61	1.70	3.60		1.51
Asbestos work and no smoking (III ÷ I)	1.46	2.71	2.68		1.06
Asbestos work and smoking (IV ÷ I)	2.71	6.33	9.95		1.42
Excess in death rates					
V. Smoking only (II–I)	599.8	144.9	75.0	—[1]	379.9
VI. Asbestos work only (III–I)	450.0	355.7	48.3	77.1	46.0
VII. Synergism (IV–I–V–VI)	628.3	608.2	134.4	148.4	-114.3
Percent excess in death rates					
Smoking only (100V ÷ I)	61	70	260		51
Asbestos work only (100VI ÷ I)	46	171	168		6
Synergism (100VII ÷ I)	64	292	467		-15

NOTE: Rate per 100,000 man-years standardized for age on the distribution of the man-years of all the asbestos insulation workers ≥ 20 years after onset of asbestos work. Rates for the asbestos work-exposure groups are based on cause of death coded according to the best available evidence.

[1] Death rates not available for the no asbestos work-exposure groups.

SOURCE: Frank (1979).

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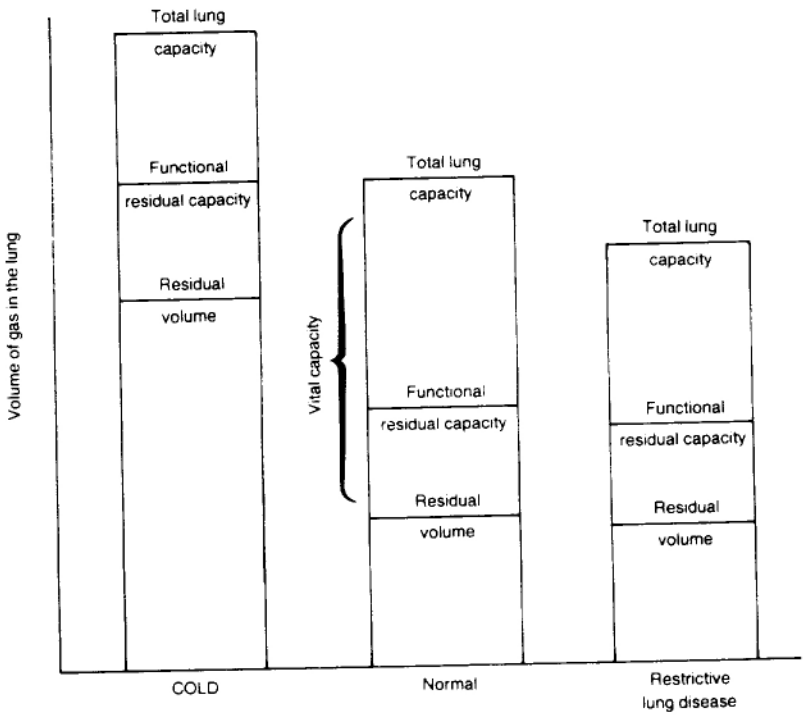


FIGURE 8.—Lung volumes in normal individuals and in patients with chronic obstructive lung disease and restrictive lung disease

volumes and Figure 10 shows the changes in the forced expiratory flow rates for the Quebec asbestos workers at several levels of increasing cumulative exposure to asbestos dust (Becklake et al. 1972). The lung function tests were performed on 1,027 men aged 21 to 65 who represented an age-stratified random sample of the 6,180 men employed in the Quebec asbestos mines and mills on October 31, 1966. An additional 184 men between the ages of 61 and 65 were also studied to increase the number of workers in the highest exposure categories. The data in the figures represent the averages of the test values for smokers and nonsmokers after they had been standardized for age, height, and weight. Smokers were defined as those who had ever smoked at least one cigarette per day for 1 year; therefore, this category includes former smokers.

The pattern in nonsmoking asbestos workers is that of restriction; there is a steadily declining TLC with increasing dust exposure.

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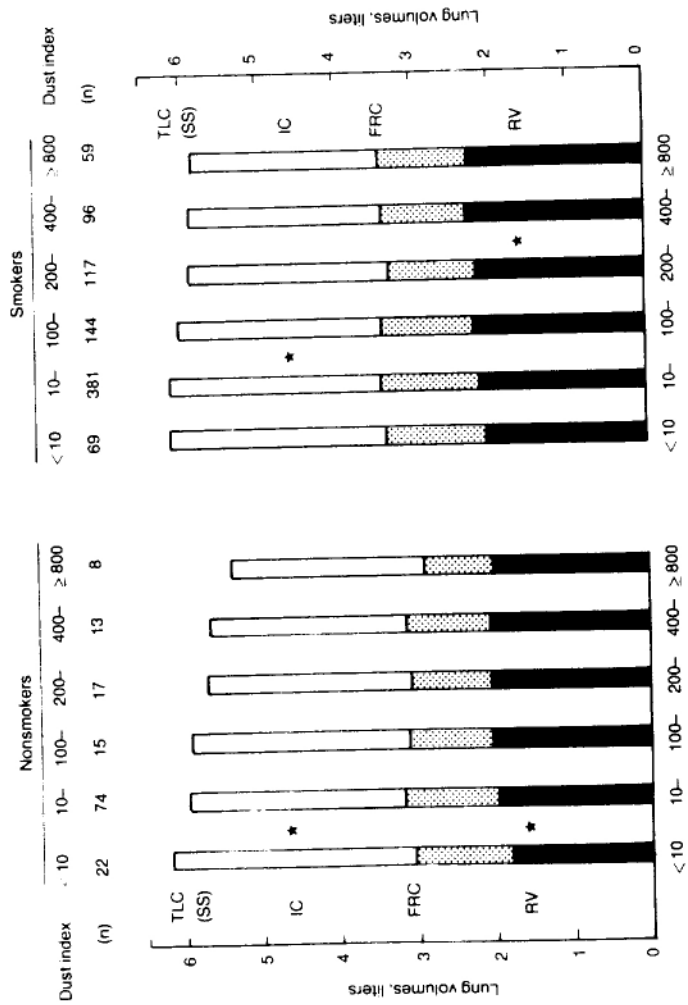


FIGURE 9.—Standardized mean values for subdivisions of lung volume (TLC[SS], IC, FRC, and RV) in nonsmokers and smokers, divided by dust index

NOTE: (n) = number of individuals in each subgroup.
SOURCE: Becklake et al. (1972).

FEV_1 also declines with increasing exposure, but this decline can be accounted for by the decline in FVC, as $FEV_1/FVC\%$ does not decline with increasing exposure in nonsmokers and is above 80 percent in all but the lowest exposure category. $FEF_{25-75\%}$ is also preserved in all but the two highest exposure categories. The FEF_{25-}

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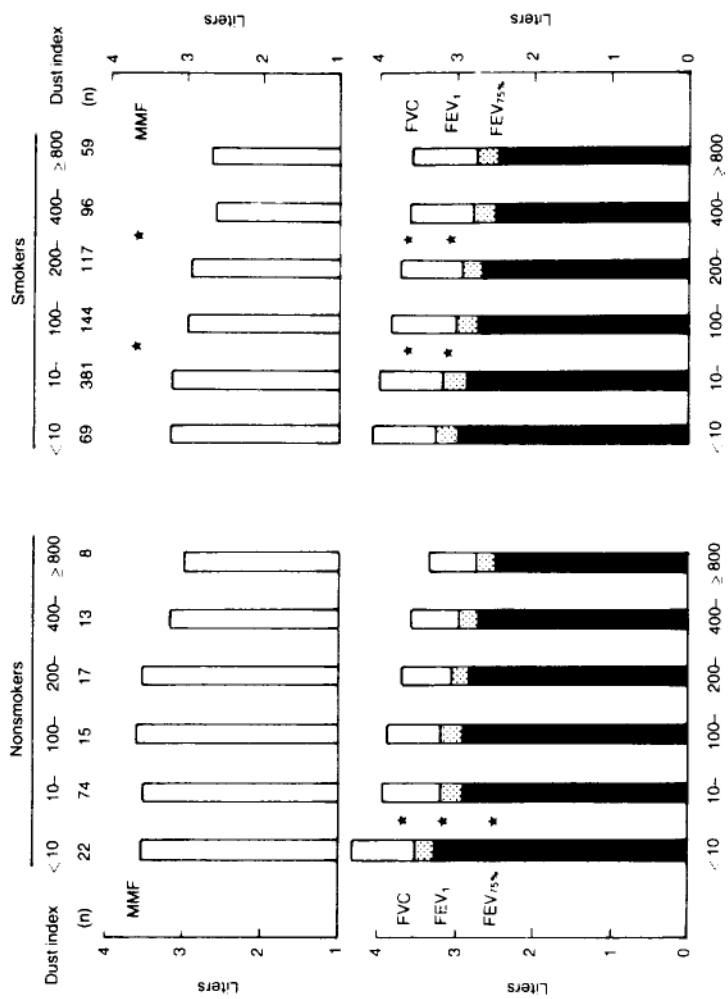


FIGURE 10.—Standardized mean values for flow rates (MMF, $FEV_{75\%}$, FEV_1, and FVC) in nonsmokers and smokers, divided by dust index

NOTE: (n) = number of individuals in each subgroup.
SOURCE: Becklake et al. (1972).

$_{75\%}$ measurement would also be expected to decline with a fall in FVC, independent of any change in the degree of obstruction to airflow. Thus, in this group of nonsmoking asbestos workers, the pattern of asbestos-induced lung disease is a reduction in lung volumes with preservation of $FEV_1/FVC\%$.

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The changes in lung function in the smoking asbestos workers in this study can be contrasted with those of nonsmoking asbestos workers with comparable cumulative exposure histories (Figures 9 and 10). The static lung volumes (Figure 9) are larger for smokers than nonsmokers at each level of cumulative asbestos exposure. $FEF_{25-75\%}$ and FEV_1 are lower, as is $FEV_1/FEV\%$. There is a progressive decline in $FEV_1/FVC\%$ with increasing cumulative asbestos exposure in the smokers but not in the nonsmokers. This decline is probably attributable to the increase in cumulative cigarette smoking exposure (and related injury) that occurs with increasing cumulative asbestos exposure (Rossiter and Weill 1974), because of the correlation between these cumulative measures. The picture that evolves from this study of the effect of combined cigarette smoke and asbestos exposure is one of an obstructive process superimposed upon a restrictive process. In addition, in the population of workers with relatively heavy asbestos exposure, TLC is reduced in both smokers and nonsmokers, suggesting that the restrictive pulmonary process exerts a greater effect than those changes that tend to increase TLC (e.g., emphysema). The relative preservation of TLC that occurs in cigarette-smoking asbestos workers in comparison with nonsmoking workers should not be interpreted as a protective effect of smoking, because it almost certainly represents more extensive lung damage (i.e., the combination of emphysematous and fibrotic processes) in the lungs of the cigarette smokers. It is also important to note that the data from this study show a relatively clear dose–response relationship between cumulative asbestos exposure and degree of restrictive impairment.

The pattern of lung function response in smoking and nonsmoking workers found in this study is consistent with the premise that asbestos exposure causes a relatively pure restrictive lung disease and cigarette smoking causes a relatively pure obstructive process. In combined exposure, the lung functional changes represent the combination of the effects of these two independent processes. A number of other studies have examined the lung function in smoking and nonsmoking asbestos workers, and the data from these studies can be used to explore this relationship further.

A general morbidity study was conducted of civilian naval dockyard workers in Great Britain, and lung function tests were performed on 612 male registered asbestos workers (Harries and Lumley 1977). The measurements were standardized to a height of 1.7 meters and to a constant age within each of five age ranges. Smoking habits were classified as smoker, nonsmoker, or ex-smoker. TLC showed no relationship to age, smoking status, or duration of asbestos exposure. There was a tendency for smokers to have a lower FEV_1 than nonsmokers, and the difference increased with age. FEV_1 and duration of asbestos exposure were related only for those aged

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50 to 59. The differences in FVC between smokers and nonsmokers were less than the differences in FEV_1, demonstrating a relative preservation of FEV_1/FVC in nonsmokers, and a relationship between duration of exposure and FVC was again present only in the 50- to 59-year-old age group. The absence of a relationship between TLC and duration of exposure may be due to the somewhat lower intensity of asbestos exposure in this population in comparison with the Quebec miners.

In a companion study of the same naval dockyards, Rossiter and Harries (1979) examined the lung function in 1,200 men aged 50 to 59. The sample included all men in the register of asbestos workers, 1 in 3 of those currently in occupations where intermittent exposure to asbestos might occur, and 1 in 30 of the remainder. Lung function measurements were standardized to age 55 and a height of 1.7 meters. Smoking was characterized as nonsmoker, ex-smoker, or current smoker, and lung function was analyzed by duration of exposure to asbestos. FEV_1 was lower in the smokers than in the nonsmokers, and the workers in the registered asbestos-exposure group had lower values than workers in other occupational groups. This was particularly true of the group of asbestos laggers who had been employed prior to 1957. The differences in FVC among the different smoking habits were less than the differences for FEV_1. The FEV_1/FVC ratio was markedly influenced by smoking. Even among those workers employed before 1957, the FEV_1/FVC ratio was preserved in nonsmokers but declined among cigarette smokers.

Weill and colleagues (1975) adopted a somewhat different approach by developing predictive equations specific for the smoking status of the worker, as well as age and height, for the individual function tests. $FEF_{25-75\%}$ was lower and declined more rapidly in smokers than in nonsmokers (Figure 11) in the population used to develop the predictive equations. The researchers applied these smoking-specific regression equations to 859 workers who were employed in two asbestos manufacturing plants in New Orleans on November 3, 1969. Dust exposure measurements were derived from midget impinger samples taken between 1952 and 1969 and from estimates of exposures derived from interviews with employees who had worked prior to this time period. Figures 12 and 13 reveal a decline in TLC with increasing cumulative asbestos exposure; as would be expected, this decline is accompanied by declines in the vital capacity, FEV_1, and $FEF_{25-75\%}$. However, there is no decline in FEV_1/FVC with increasing duration of exposure. The decline in TLC and vital capacity at the lower exposure levels occurred entirely in the group with x-ray changes, but for the two highest exposure categories, the decline in TLC and vital capacity occurred even in the group with no roentgenographic changes. Again, this study suggests that the effect of asbestos dust exposure in a manufacturing plant is

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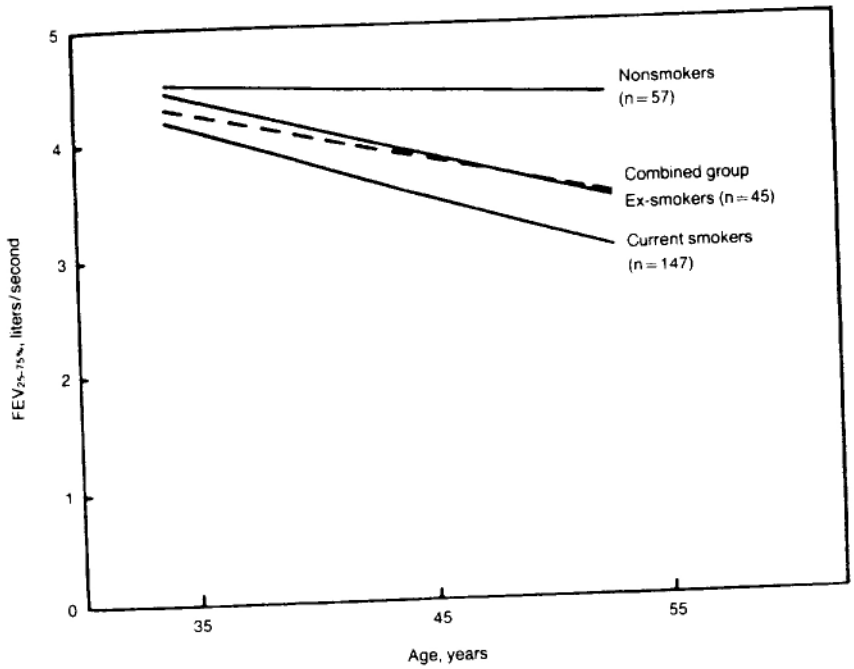


FIGURE 11.—Relationship between $FEV_{25-75\%}$ and age for the smokers, ex-smokers, and nonsmokers in the standard group (height taken as 175 cm [5 feet 9 inches])

SOURCE: Weill et al. (1975).

largely that of a restrictive process producing a decline in TLC, with the decline in FEV_1 and maximal midexpiratory flow between 25 and 75 percent of FVC ($MMF_{25-75\%}$) being a reflection of the decline in lung volumes rather than an indication of the presence of airflow obstruction.

Several analyses have focused on the pattern of pulmonary function response rather than on isolated test values (Fornier-Massey and Becklake 1975, Becklake et al. 1976; Muldoon and Turner-Warwick 1972; Murphy et al. 1972, 1978). These authors were attempting to determine whether asbestos exposure results in chronic obstructive lung disease, either in the absence of cigarette smoking or in excess of the level to be expected solely from smoking. The stratified sample of 1,027 Quebec asbestos miners and millers described earlier in this section was also analyzed by the pattern of pulmonary function response (Fornier-Massey and Becklake 1975;

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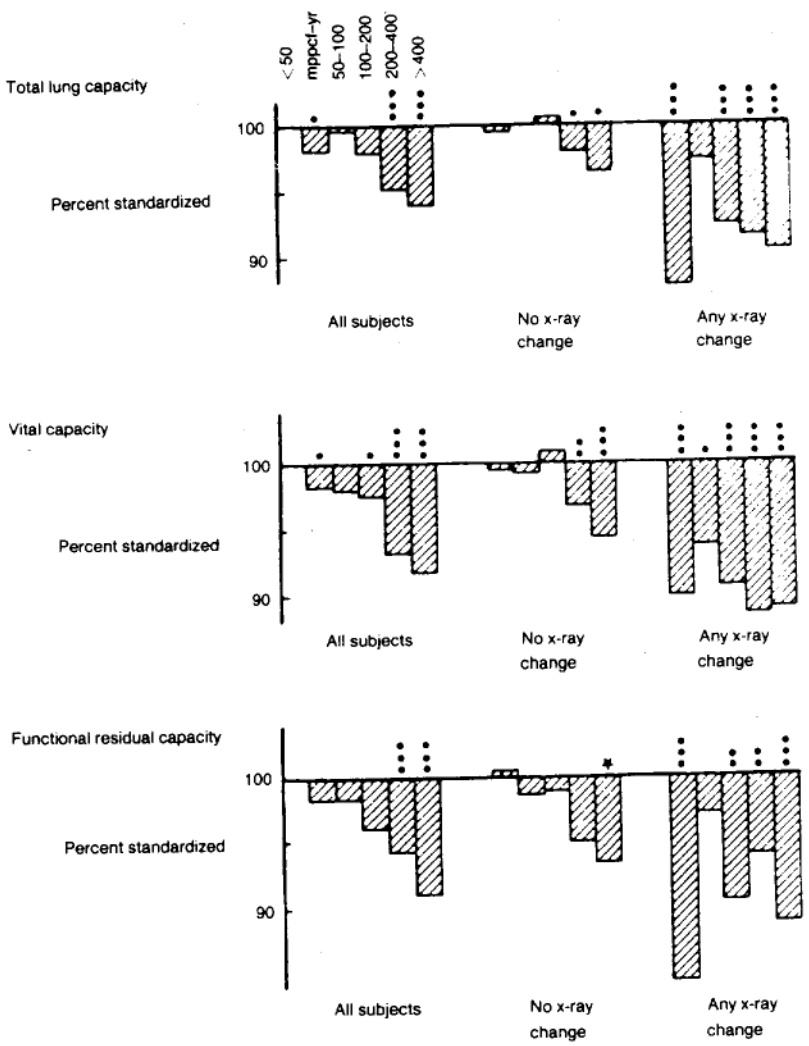


FIGURE 12.—Relationship between lung volumes and dust exposure

SOURCE: Weill et al. (1975).

Becklake et al. 1976). These workers were categorized as having a normal, undifferentiated, obstructive, or restrictive pulmonary function picture on the basis of a combined score of the percentage deviations from the predicted value of five pulmonary function tests

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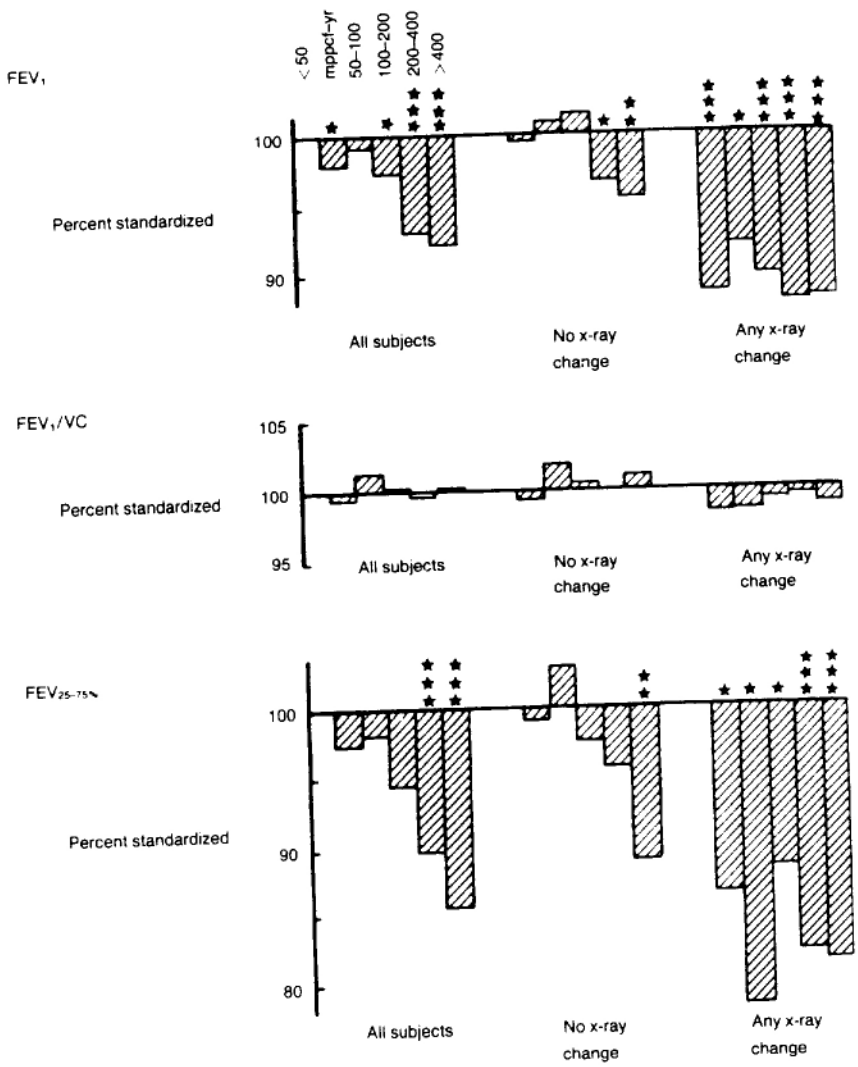


FIGURE 13.—Relationship between expiratory flow and dust exposure

SOURCE: Weill et al. (1975).

(Table 12). The deviation of the percentage predicted value was scored from 7 through 13 for each value, with lower numbers representing those measurements indicative of restrictive disease

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and higher codes representing those values indicative of obstructive disease. Scores of 45 to 55 were considered consistent with a normal profile when all five coded values were between 9 and 11, and consistent with an undifferentiated profile when a mathematical balance of codes under, equal to, and over 10 resulted in a score of 45 to 55. Scores under 45 were assumed to represent restrictive profiles and scores over 55 to represent obstructive profiles. Forty-three percent of the population had normal lung function profiles, and 26.5 percent had undifferentiated lung profiles. The remainder was divided relatively evenly between the restrictive and obstructive lung profiles, with 14.9 percent having a restrictive defect and 14.3 percent having an obstructive picture. In Table 13 are revealed the results in smokers and nonsmokers, stratified by increasing asbestos exposure category. The data seem to suggest that neither obstructive nor restrictive lung disease occurs in nonsmoking asbestos workers and that restrictive and obstructive lung disease occur with equal frequency in asbestos miners who smoke. In addition, it appears that there is, if anything, a negative dose–response relationship between restrictive lung disease and increasing cumulative asbestos exposure. These results are particularly remarkable in the face of data from the same group of workers presented earlier in this section, which show a relatively clear dose–response relationship between cumulative asbestos exposure and decline in TLC and FEV_1 in both smokers and nonsmokers. The authors have interpreted this data to suggest that an association between smoking habit and the development of asbestos-related fibrosis may exist and that asbestos workers who smoke may develop either obstructive or restrictive lung disease. The inconsistencies between the data on pattern pulmonary function tests and the measures of individual test responses described earlier may be explained by the effects of changes in lung volumes on some of the measurements used to code the lung function profile. $FEV_{75\%}$ and $MMEF_{25-75\%}$ are measurements that, when reduced, are used in this coding scheme to define an individual as being obstructed. Both of these are measurements of airflow obstruction in the presence of normal lung volumes, but may also be reduced in the presence of diminished lung volumes secondary to restrictive lung disease. Indeed, examination of the pattern of pulmonary function response in nonsmoking asbestos miners (Figure 10) reveals that with increasing cumulative asbestos exposure, the decline in TLC in these workers was accompanied by a decline in $FEV_{75\%}$ and $MMEF_{25-75\%}$. This pattern, consistent with progressive restrictive lung disease, would define the worker by the coding scheme as having obstruction, or would counterbalance those scores for a restrictive category, thereby placing the worker in the undifferentiated category. A similar effect would occur in asbestos miners who smoke. As can be seen in Figure 10, the decline in FEV_1,

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TABLE 12.—Coding of lung function profile

Code	Volumes (RV, TLC)	Flow rates ($FEV_{75\%}$ MMF)	(FEV_1/FVC)% percent predicted
7	<70	>130	>116
8	70–79	121–130	111–115
9	80–89	111–120	110–106
10	90–110	90–110	95–105
11	111–120	80–89	90–94
12	121–130	70–79	85–89
13	>130	<70	<84

SOURCE: Fornier-Massey and Becklake (1975).

$FEV_{75\%}$, and $MMEF_{25-75\%}$ is greater in smoking asbestos miners than in nonsmoking miners. This pattern, which is consistent with a combination of restriction and obstruction in these workers, would result in a progressive increase in the coding scheme obstructive score, and therefore may account for the absence of a dose–response relationship between asbestos exposure and restrictive lung disease in the asbestos workers who smoke. With increasing severity of restrictive lung disease, more and more workers would be categorized as having an obstructive or undifferentiated pattern and thus would drop out of the restrictive category.

A similar approach was taken by Muldoon and Turner-Warwick (1972), who categorized the lung function results in a consecutive series of 75 subjects with a history of exposure to asbestos who were referred to the Pneumoconiosis Medical Panel of London. The researchers categorized workers as having obstructive, restrictive, mixed, or normal lung function. They reported that the workers with obstruction did not have heavier smoking histories than the subjects with restrictive or normal lung function. However, examination of the data presented in their report reveals that, although the percentage of current smokers in the obstructive and restrictive groups was somewhat similar, there were marked differences in the frequency of former smokers. Indeed, all of the workers who had obstructive disease had a history of cigarette smoking. There were 13 workers in the group; 8 were current cigarette smokers and 5 were former cigarette smokers, of whom 3 had stopped smoking less than 1 year prior to the study. Of the entire group examined, there were only four workers who had never smoked cigarettes, and all of these workers fell into the restrictive category.

Murphy and colleagues (1972, 1978) also attempted to answer the question whether an increased prevalence of obstructive lung disease occurs in asbestos workers. They examined a group of 101 shipyard

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TABLE 13.–Effects of chrysotile exposure on the health of 1,015 current Quebec asbestos workers

Dust index[1]	<10	10–99	100–199	200–399	400–799	≥800
		Nonsmokers				
Prevalence percent[2]						
Chronic bronchitis	10	19	19	46	21	49
Dyspnea	0	19	24	31	13	44
Function profile–[3] prevalence percent						
Restrictive	3	3	3	1	1	1
Obstructive	0	1	0			
Percentage fall in function[2]						
VC	0	–10	–16	–18	–19	–23
FEV_1	0	–9	–9	–13	–15	–22
$DLCO_{ss}$, rest	0	–11	–15	–18	–12	–15
$DLCO_{ss}$, exercise	0	–8	–9	–18	–18	–20
		Smokers				
Prevalence percent[2]						
Chronic bronchitis	23	22	30	29	46	45
Dyspnea	4	15	18	21	30	32
Function profile–[3] prevalence percent						
Restrictive	8	14	16	10	4	13
Obstructive	12	12	13	12	23	12
Percentage fall in function[2]						
VC	0	–3	–7	–10	–13	–14
FEV_1	0	–3	–8	–10	–15	–15
$DLCO_{ss}$, rest	0	–4	–3	+5	–3	0
$DLCO_{ss}$, exercise	0	0	–2	0	–5	–7

NOTE: For all measurements, prevalence percent has been age-standardized to the total working population as of October 31, 1966. This was to allow for the smaller of number of men for whom function profiles were analyzed.

[1] Expressed in million particles per cubic foot years.[3]

[2] Based on a total sample of 1,015 men.[1]

[3] Based on 995 men.[2]

SOURCE: Becklake et al. (1976).

pipe coverers and compared them with 95 control subjects. The prevalence of smoking in these two populations was approximately the same. There were significant differences between the asbestos-exposed workers and the control population in vital capacity and FEV_1 in measurements taken both in 1966 and in 1972. However, there was no difference between the two groups in FEV_1 as a percent of FVC at either time point. In 1972, there was a significant difference between the two groups in the reported symptom of wheezing apart from colds. When this symptom was combined with the prevalence of an abnormal FEV_1/FVC%, using the criteria of Ferris and Anderson (1962) for obstructive lung disease, the asbestos workers had a significant higher prevalence of obstructive lung disease in comparison with the control population. However, this

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increased prevalence resulted from their reported symptoms and not from differences in measured pulmonary function.

In summary, lung function has been examined in several populations of smoking and nonsmoking asbestos workers. In populations of nonsmoking asbestos workers, a dose-related decline in TLC and a decline in FEV_1 and in $FEF_{25-75\%}$ consistent with the decline in TLC can be identified, a pattern consistent with a primarily restrictive lung function profile. In populations of cigarette-smoking asbestos workers, the decline in TLC is somewhat less than in nonsmoking asbestos workers and the decline in FEV_1 and $FEF_{25-75\%}$ is somewhat more. The percentage decline in FEV_1 compared with the percentage decline in FVC is greater in smoking asbestos workers, but not in nonsmoking asbestos workers. When smoking asbestos workers are compared with control populations with similar smoking habits, there is a significantly greater decline in FVC and TLC, but the ratio of FEV_1 to FVC is similar in the asbestos-exposed and the non-asbestos-exposed populations. The data are therefore consistent with independent effects of asbestos and cigarette smoking on lung function. This issue has been examined statistically by Samet and colleagues (1979) and by Rossiter and Weill (1974); an additive effect of smoking and asbestos exposure on the FVC was present, but there was no statistically demonstrable synergism.

Regan and colleagues (1971) evaluated the relative power of 16 clinical-radiological-pulmonary function variables in evaluating asbestosis and chronic airway disease. A decreased diffusing capacity for carbon monoxide (DLCO) and a decrease in the vital capacity had the greatest power to measure the severity of either obstructive or restrictive lung disease in workers with both smoking and asbestos exposure, but had little ability to distinguish between the two processes. The best indicator for distinguishing between restrictive lung disease and obstructive airway disease was FEV_1 as a percentage of the vital capacity. This variable had a better ability to distinguish between obstructive and restrictive disease than either the clinical or the chest roentgenogram findings or other tests of pulmonary function.

The absence of an effect of asbestos exposure on $FEV_1/FVC\%$ must be interpreted with caution. Although this test is the best measure of the presence of airflow obstruction in the presence of restrictive lung disease, it is not sensitive to changes in the small airways. Because both cigarette smoking and asbestos exposure have been shown to result in changes in the small airways of the lung, it is important to examine the effects of these two exposures on tests of small airway function.

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Small Airways Function

Airways in the lung with diameters of 2 mm or less are considered small airways and consist of bronchioles and respiratory bronchioles (airways with both nonrespiratory epithelium and alveoli in their walls). Considerable obstruction can be present in these airways without significantly altering the airway resistance or lung mechanics. In addition, abnormalities in the small airways are a prominent part of the abnormality present in chronic obstructive lung disease (COLD). The relationship of cigarette smoking to abnormalities in tests of small airways function, and of pathologic abnormalities of the small airways to functional changes, was reviewed in a previous Report of the Surgeon General (US DHHS 1984). Changes in the small airways of cigarette smokers may occur within the first few years of smoking, are more prevalent in heavy smokers, and increase in frequency with increasing duration of the smoking habit. Because the small airways are also involved in people who develop cigarette-induced COLD, tests of small airways function are usually abnormal in people with chronic airflow obstruction on conventional spirometry; however, it is not yet clear whether the early and reversible inflammatory changes in the small airways of smokers are the first stage in the pathophysiologic process of developing COLD or are merely a nonspecific irritant response to smoke that does not predispose to the development of COLD.

The response of the lung to asbestos also involves the small airways, and there has been considerable interest in functional changes of the small airways of asbestos workers. Relevant questions are these: Does asbestos cause changes in the small airways independent of smoking? Do the morphologic changes in the small airways caused by smoking differ from those caused by asbestos? Do the changes in the small airways of asbestos workers progress to airflow obstruction, as measured by standard spirometry, independent of cigarette smoking?

Woolcock and colleagues (1969) demonstrated that a group of bronchitic subjects with normal lung volumes and flow rates had abnormal tests of small airways function. Cosio and colleagues (1978) and Berend and colleagues (1979) were able to correlate abnormalities of tests of small airways function with morphologic changes in the small airways. The morphologic changes consisted of a respiratory bronchiolitis with goblet cell metaplasia, inflammation of the bronchiolar wall, smooth muscle hypertrophy, peribronchiolar fibrosis, and pigmentation of the bronchiole. Tests of small airways function (closing capacity and slope of the single breath nitrogen washout) were abnormal, with lower degrees of pathologic change; however, abnormalities on spirometric testing (FEV_1/FVC and $FEF_{25-75\%}$) were also correlated with more severe morphologic changes in the small airways.

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The changes in the small airways of asbestos workers have been examined (Wright and Churg 1984; Churg and Wright 1984), and differences in the pattern of injury from that produced by cigarette smoking alone were identified. The researchers examined lung sections from 15 patients who had been exposed to asbestos and had abnormalities of the respiratory bronchioles, and compared these individuals with 15 control subjects matched for age, sex, and smoking status. Almost all of the subjects smoked (13 of 15), so it was not possible to examine the differences between smoking and nonsmoking asbestos workers or to rule out an interaction between smoking and asbestos. However, two distinct patterns seem to emerge. Churg and Wright found changes in the membranous bronchioles of the cigarette-smoking controls similar to those found by others (Cosio et al. 1978; Berend et al. 1979), including inflammation, pigmentation, and periobronchiolar fibrosis. The changes in the membranous bronchioles of the asbestos workers (almost all of whom were smokers) were qualitatively identical to those in the non-asbestos-exposed smokers; but quantitatively, the degree of fibrosis, the amount of pigmentation, and the percentage of membranous bronchioles involved was greater in the asbestos-exposed individuals. In the asbestos-exposed group, 67 percent of the membranous bronchioles showed marked fibrosis in comparison with 19 percent in the control population of smokers. The clearest distinction and the most diagnostically useful lesions occurred in the respiratory bronchioles and alveolar ducts. Forty-eight percent of the respiratory bronchioles and 35 percent of the alveolar ducts showed marked fibrosis in the asbestos-exposed group in contrast to 4 percent of the respiratory bronchioles and 0 percent of the alveolar ducts in the control population. These data suggest that cigarette smoking produces an inflammatory response with only modest amounts of fibrosis in the membranous bronchioles, and that the addition of asbestos exposure results in a marked increase in the fibrosis around the membranous bronchioles and an extension of this fibrosis to the respiratory bronchioles and alveolar ducts. Because there were so few nonsmokers examined in this study, the questions whether asbestos exposure alone causes an inflammatory response and whether the fibrotic lesions characteristic of asbestos exposure are influenced by smoking could not be addressed.

Given this description of the pathologic response of the small airways to cigarette smoke and asbestos dust, examination of the physiologic testing of the small airways in asbestos workers should focus on several questions: Does asbestos exposure alter the function of the small airways in people who have never smoked? Does this alteration in small airways function result in reductions in the rate of expiratory airflow (as occurs in cigarette smokers) independent of the reductions in lung volume that occur secondary to asbestos

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exposure? (The increased resistance in the small airways may be compensated for by an increased elastic recoil of the lung available to drive expiratory airflow.) Does asbestos exposure increase the prevalence of abnormalities on tests of small airways function above that expected from smoking alone?

A number of researchers have examined small airways function in asbestos workers. Jodoin and colleagues (1971) examined 24 workers with normal chest roentgenograms whose asbestos exposure ranged from 6 months to 24 years. Two groups with comparable age and smoking prevalence, but with differing exposure to asbestos dust, were defined among those 24 workers. The more heavily exposed group had a 30 percent increase in lung static recoil pressure and had reduced rates of expiratory airflow for any given transpulmonary pressure, suggesting increased resistance in the small airways. This increased resistance did not result in obstruction on spirometric testing, as both $FEV_1/FVC\%$ and $FEF_{25-75\%}$ actually increased in the workers with heavier asbestos exposure. In five of the subjects with heavier exposure, but with a normal FEV_1 and $FEV_1/FVC\%$, the maximal expiratory flow was reduced throughout the entire range of lung volume despite an increased driving pressure, suggesting that the degree of small airway obstruction was greater than the degree of increase in driving pressure. However, all five of the subjects were cigarette smokers; therefore, the reduced airflow could not be identified as due to the asbestos. The authors provided no separate analysis of the data for the nonsmokers in the study.

Several other authors (Harless et al. 1978; Cohen et al. 1984; Rodriguez-Roisin et al. 1980; Siracusa et al. 1983) have also presented evidence suggesting that asbestos exposure results in small airway dysfunction; however, the data on nonsmokers were not presented in a manner to allow evaluation as a separate group, or included ex-smokers with never smokers, making interpretation difficult.

Begin and colleagues (1983) examined airways function in 17 lifetime nonsmoking asbestos workers with an average of 28 years of exposure in the asbestos mines and mills of Quebec. Seven workers met the diagnostic criteria for asbestosis and 10 did not; none of the workers met the diagnostic criteria for chronic bronchitis, emphysema, or asthma. The lifetime nonsmokers without asbestosis had relatively normal lung function, but there was a slightly lower maximal expiratory flow at 25 percent of the vital capacity and a significantly elevated isoflow volume, suggesting dysfunction in the small airways. The seven workers with asbestosis had clear evidence of small airway obstruction with a threefold or fourfold increase in upstream resistance at low lung volumes. These data were supported by histologic evidence of peripheral airway obstruction and narrowing on lung biopsies in three of these men. However, this obstruction

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in the small airways was not severe enough to significantly reduce the usual spirometric parameters of airflow obstruction, and none of these men had a significant reduction in $FEV_1/FVC\%$. The authors attributed this phenomenon to the higher pressures available to drive airflow in these workers with restrictive lung disease.

Cohen and colleagues (1984) attempted to examine the relationship of smoking and asbestos exposure in a cross-sectional study of a group of asbestos litigants. Unfortunately, ex-smokers were included with the group of nonsmokers. This results in an increasing prevalence of ex-smokers with increasing age, and ex-smokers have reduced lung function (US DHHS 1984); correspondingly, with increasing duration of asbestos exposure, there would also be an increasing prevalence of ex-smokers. This confounding of their exposure data makes meaningful interpretation impossible.

In summary, the evidence suggests that asbestos exposure can result in small airways dysfunction in nonsmoking workers, but this small airways dysfunction does not result in obstruction on standard spirometric testing. $FEV_1/FVC\%$ remains normal in these nonsmoking asbestos workers even in the presence of substantial increases in the airway resistance at low lung volumes and decreases in TLC. This picture differs from that in small airway dysfunction in cigarette smokers, where there is a decline in the $FEV_1/FVC\%$. This difference may be accounted for by the differences in elastic recoil pressure of the lung produced by these two injuries. Asbestos exposure results in increased elastic recoil of the lung, which provides an increased driving pressure that compensates for the increased resistance in the small airways. Thus, the rate of expiratory airflow is preserved. In contrast, the elastic recoil either remains normal or frequently decreases (in emphysema) with cigarette-induced lung injury, and therefore there is no compensatory increase in driving pressure to maintain the rate of expiratory airflow in the presence of an increased resistance in the small airways. In combined exposure to cigarette smoke and asbestos, the largely inflammatory response in the small airways due to smoking may occur conjointly with the largely fibrotic response in the same airways due to asbestos, and the resultant increase in the resistance in the small airways may be large enough to reduce expiratory airflow even in the presence of an increased elastic recoil.

In conclusion, asbestos exposure can result in reduced lung volumes in both smoking and nonsmoking workers, and may result in small airway dysfunction. However, the evidence does not suggest that airflow obstruction, as measured by a reduced FEV_1/FVC, is a result of asbestos exposure in nonsmoking asbestos workers or that it is worse than would be expected from the smoking habits of asbestos workers who smoke.

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Chest Roentgenographic Changes

One of the hallmarks of interstitial fibrosis due to asbestos is an abnormal chest roentgenogram, and despite the fact that biopsy-proven disease may be present with a normal roentgenogram (Epler et al. 1978), the x ray commonly reflects both the presence and the extent of fibrosis. Occasionally, particularly in early asbestos-induced lung disease, the chest roentgenogram may not be abnormal and the only abnormalities may be a reduced diffusing capacity or decreased lung volumes. The chest roentgenogram is less frequently abnormal in cigarette-induced chronic obstructive lung disease, but roentgenographic abnormalities can occur, particularly in advanced disease or when extensive emphysema is present. The abnormalities produced by these two processes are usually quite different on chest roentgenogram once the disease process is sufficiently advanced, and confusion about the roentgenographic diagnosis in severe disease is unusual.

The radiographic changes associated with asbestos include small irregular opacities, which commonly begin as a reticular pattern in the lower lung fields and may progress to diffuse interstitial densities throughout the entire lung with reduced lung volumes (Selikoff and Lee 1978; Fraser and Pare 1979). The abnormalities that have been reported with COLD include overinflation, prominence of lung markings ("dirty lungs"), tubular shadows, and in the presence of significant emphysema, oligemia, and bullae (Fraser and Pare 1979).

Roentgenographic Changes in Non-Asbestos-Exposed Populations

The literature establishing asbestos as a cause of interstitial fibrosis is extensive, and no significant scientific debate remains over the potential for occupational asbestos exposure to result in interstitial fibrosis; substantial numbers of asbestos workers have developed interstitial fibrosis as a direct consequence of their inhalation of asbestos dust. A review of this evidence is beyond the scope of this chapter and can be found elsewhere (Selikoff and Lee 1978). The questions raised by the combination of cigarette smoking and asbestos exposure do not include whether cigarette smoking is an independent competing cause of the extensive fibrotic process found in many workers following prolonged heavy exposure to asbestos. Cigarette smoking has not been shown to independently cause this kind of reaction in the lung. Therefore, this section focuses on three questions concerning the relationship of cigarette smoking to the roentgenographic changes caused by asbestos. In the absence of asbestos exposure, are the chest roentgenograms of cigarette smokers more likely to be interpreted as positive for interstitial fibrosis than those of nonsmokers? Do cigarette-smoking asbestos workers

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have a higher prevalence of chest roentgenograms interpreted as positive for interstitial fibrosis than nonsmoking asbestos workers? Do cigarette-smoking asbestos workers have more severe interstitial fibrosis on chest roentgenograms than nonsmoking asbestos workers for comparable asbestos exposures?

The determination of whether radiologic findings consistent with interstitial fibrosis are present is part of the standard clinical interpretation of the chest roentgenogram. However, the International Labour Office (ILO) (1980) developed a classification by which the roentogenographic changes of pneumonconiosis can be measured and reported in a standardized way. Small opacities are characterized as rounded or irregular, and the profusion of the opacities is also described and quantitated on a numerical scale (from 0/0 to 3/4). This classification was designed as a descriptive rather than a clinical tool; as such, it is structured to be sensitive to the earliest roentgenographic changes. This sensitivity allows the investigation of early or mild disease, but also may reduce specificity. Using this classification, other mild, but not pneumoconiotic, disease in the general population may be interpreted as positive. Indeed, given the variety of causes of interstitial fibrosis other than inhalation of inorganic dust, the absence of any false positives by this classification would be surprising, and therefore the questions are the magnitude of this false positive rate and whether cigarette smoking influences that rate.

The semiquantitative ILO classification system can have substantial variability of interpretation, particularly at the lower levels of abnormality (Werner 1980). Table 14 shows the differences between the highest and lowest categorizations of 32,695 chest roentgenograms interpreted according to the ILO classification by three different readers as part of a study of asbestos-related disease. In general, there was good agreement, but in a number of cases marked differences of interpretations occurred, including the same radiographs being interpreted by different readers as negative (0/0) and as substantially positive (2/2). Werner discussed some of the problems generated by these differences in interpretation and offered some potential remedies, but the data pointed out that a system designed to be sensitive to low levels of abnormality may be expected to have a some variability of classification, particularly around the threshold of abnormality.

Weiss (1967, 1969) published a pair of studies evaluating the prevalence of a roentgenographic interpretation of interstitial fibrosis in smokers and nonsmokers drawn from the general population. The first study involved the examination of 70 mm chest photofluorograms of 999 men and women who came consecutively to the central survey unit of the Philadelphia Tuberculosis and Health Association. The films were evaluated for increased bronchovascular

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TABLE 14.—Analysis of x rays of asbestos workers, lowest readings by highest readings (ILO U/C scale)

Lowest reading	Highest reading												
	0/-	0/0	0/1	1/0	1/1	1/2	2/1	2/2	2/3	3/2	3/3	3/4	Total
0/-	2	857	94	47	56	15	2	6	2		2		1083
0/0		20449	3406	2162	2699	693	153	283	47		18		29910
0/1			46	149	385	152	39	85	12	1	2		871
1/0				29	189	100	43	69	10	1	2		443
1/1					53	55	39	101	32	6	7	1	294
1/2						1	3	25	10		6	1	46
2/1								8	5		3		16
2/2								3	9	3	6	2	23
2/3									2		6		8
3/2													0
3/3											1		1
3/4													0
Total	2	21306	3546	2387	3382	1016	279	580	129	11	53	4	32695

SOURCE: Werner (1980)

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markings or diffuse pulmonary fibrosis; 3.1 percent of the subjects had abnormal films, with a prevalence of 1.5 percent in nonsmokers and 4.4 percent in cigarette smokers. Dose–response relationships were present for the number of cigarettes smoked per day and for the duration of smoking. A second study evaluated 2,825 adults, again using 70 mm photofluorograms; this time interpretation was by readers other than the author, and the purpose of the evaluation was to examine the population for COLD rather than for interstitial fibrosis. The prevalence of diffuse interstitial fibrosis was 0.6 percent in nonsmokers and 2.1 percent in smokers.

Kilburn (1981) criticized these studies on the basis of their use of 70 mm films and the failure to use the ILO criteria for grading the roentgenographs. Epstein and colleagues (1984) applied the ILO criteria to 200 admission chest roentgenograms at an urban university medical center. Small opacities with profusions of 1/0 or greater were found in 22 (11 percent) of the subjects, none of whom had a documentable dust exposure or any known medical disease that caused interstitial lung disease. Of the 22, 12 (55 percent) were current or former cigarette smokers. Murphy and colleagues (1978) also used the ILO criteria in examining 68 shipfitters and pipefitters without known exposure to asbestos who were selected to serve as a control group for a study of similar workers with known exposure to asbestos. Of the control workers, 60 had chest roentgenograms classified as 0/1 or less, 6 (8.8 percent) had readings of 1/0 to 1/2, and 1 had a reading higher than 1/2. A previous study of the same group of workers (Murphy et al. 1972) had classified 14 percent of the controls as having slight abnormalities (1/0 to 1/2) and 2 percent as has having moderately advanced abnormalities (2/1 to 2/3). None of the control group were classified has having more advanced disease, and the results were not presented by smoking status.

In summary, the data suggest that a small percentage of chest roentgenograms of the general population may have changes that can be interpreted as interstitial fibrosis, and that slightly larger percentages of hospitalized patients and shipyard workers with no known asbestos exposure may have chest roentgenograms read as positive for interstitial fibrosis by the ILO criteria. Both the prevalence in these populations and the severity of the changes are far lower than those found in populations with significant asbestos exposures (Murphy et al. 1978), and they may reflect the sensitivity of the chest roentgenogram and the ILO classification to other causes of lung injury. The "dirty lung" described in smokers (Fraser and Pare 1979) may contribute to the smoking-related prevalence of "diffuse interstitial fibrosis" described by Weiss (1969) in the general population, but it is unlikely to be confused with the more advanced forms of fibrosis found in severe asbestos-related lung injury. However, the prevalence of changes in the general population,

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particularly in the population of shipyard workers with no known asbestos exposure, suggests that classifying a mildly positive chest roentgenogram as asbestosis in the absence of a clear exposure history should require other confirming evidence of asbestos-induced lung injury. This caution may be particularly true for cigarette smokers.

Interstitial Fibrosis in Asbestos-Exposed Populations

As was mentioned earlier, cigarette smoking is not a competing cause of the diffuse severe interstitial fibrosis that occurs in some workers secondary to their inhalation of asbestos dust. However, modest peribronchiolar fibrosis (Cosio et al. 1978; Berend et al. 1979) and occasional fibrosis of respiratory bronchioles (Wright and Churg 1984) do occur as a response of the small airways to cigarette smoking, in addition to the periobronchiolar inflammation that is the predominant early response to cigarette smoking. These bronchioles are also the site of the early response to asbestos dust (Craighead et al. 1982), and therefore the threshold for radiologic perception of an abnormality may be crossed more frequently, or earlier, or at a lower dose of asbestos exposure in cigarette-smoking asbestos workers than in nonsmoking workers. In addition, the inflammatory response to cigarette smoke may enable or facilitate the fibrotic response to asbestos dust. Therefore, the question of a different exposure–response relationship between asbestos exposure and roentgenographic changes for smoking and nonsmoking asbestos workers should be considered.

Weiss (1984) recently reviewed the evidence relating cigarette smoking and roentgenographic fibrosis in asbestos-exposed populations. In Table 15, drawn from this review, is shown the prevalence of radiologic "asbestosis" in studies of asbestos-exposed populations. In general, the prevalence was higher in smokers than in nonsmokers; in several studies the difference was statistically significant. The highest prevalence ratios for smokers compared with nonsmokers are recorded in the populations with the lowest overall prevalence of roentgenographic fibrosis, and it is the studies where a high prevalence of disease is present that show similar rates of roentgenographic fibrosis among smokers and nonsmokers (if studies of populations of less than 100 are ignored). This observation is in part an obligatory result of the mathematics involved (a given difference in prevalence between smokers and nonsmokers produces a smaller prevalence ratio when there is a high prevalence than when there is a low prevalence), but it is also the effect that would be expected if the effect of smoking were a small independent risk of radiologic fibrosis or if the effect was to increase the frequency with which

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smoking asbestos workers cross the threshold for perception of roentgenologic abnormality.

The demonstration of an increased prevalence of roentgenographic changes interpreted as fibrosis in cigarette smokers does not establish that the changes are produced by smoking. As has been discussed earlier, cigarette smokers may have had a different cumulative asbestos exposure than nonsmokers in some of the populations studied. Liddell and colleagues (1982) examined the prevalence of roentgenographic fibrosis in a group of 515 asbestos miners born between 1891 and 1920 and found an increased prevalence of roentgenographic fibrosis with increasing age and cumulative asbestos exposure. Smokers and nonsmokers had similar prevalences of changes, but the smokers had marginally lower cumulative asbestos exposure. Harries and colleagues (1976) examined a younger population of shipyard workers with a lower prevalence of roentgenographic fibrosis (Table 16). The prevalence of changes was slightly higher in smokers than in nonsmokers, and seemed to increase in smokers after 10 to 14 years of asbestos exposure in comparison with after 20 to 24 years of asbestos exposure for nonsmokers. Dosage measures were not available for this study. Samet and colleagues (1979) examined a population of 383 asbestos workers with a prevalence of roentgenographic fibrosis (1/0 or greater) of 33.7 percent. They tested for interaction between smoking and asbestos exposure and found a small additive effect for roentgenographic changes, but no synergism between cigarette smoking and asbestos exposure. Rossiter and Berry (1978) examined the interaction of smoking and duration of asbestos exposure in a population with a lower prevalence of roentgenographic fibrosis and found a duration–response relationship for asbestos exposure only among cigarette smokers. The number of workers at risk in the nonsmoking category was small, however, making it difficult to determine whether the absence of a dose–response relationship in nonsmokers resulted from differences between smokers and nonsmokers or was simply a reflection of the low rate of disease in the population.

In summary, cigarette smokers appear to have a higher prevalence of radiologic abnormality compatible with interstitial fibrosis than nonsmokers among populations of asbestos-exposed individuals with low prevalence of roentgenographic fibrosis (and presumably low levels of asbestos exposure). This difference is not apparent in populations with higher prevalences of roentgenographic fibrosis (and presumably higher asbestos exposures). One study (Harries et al. 1976) suggested that cigarette smokers develop an abnormal chest roentgenogram after a shorter duration of asbestos exposure than nonsmokers. There is little evidence to suggest that smokers develop more severe fibrosis (in contrast with a higher prevalence of fibrosis)

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TABLE 15.—Results of prevalence studies of the cigarette factor in asbestosis

Study	Smokers			Nonsmokers			Prevalence ratio[1]	95% confidence limits	
		Asbestosis			Asbestosis				
	Number	Number	Percent	Number	Number	Percent		Lower	Upper
Weiss (1971)	73	29	39.73	25	6	24.00	1.66	0.81	3.76
Langlands et al. (1971)	91	35	38.46	33	9	27.27	1.41	0.56	2.53
Harries et al. (1972)	1,635	49	3.00	808	20	2.48	1.21	0.72	2.03
Harries et al. (1976)	17,788	181	1.02	5,552	11	0.20	5.10	2.98	8.85
Weiss and Theodos (1978)									
Chrysotile	31	8	25.81	9	2	22.22	1.16	0.29	4.57
Chrysotile + amosite	38	26	42.11	10	0	0.00	∞	1.26[2]	56.31[2]
Hedenberg et al. (1978)	103	7	6.80	94	1	1.06	6.42	1.07	38.34
Rossiter and Harries (1979)	944	39	4.13	142	3	2.11	1.96	0.65	6.30
McMillan et al. (1980)	1,346	18	1.34	385	0	0.00	∞	1.09[2]	102.23[2]
Selikoff et al. (1980)	228	180	78.95	56	44	78.57	1.00	—	—
Pearle (1982)	99	9	9.09	32	1	3.13	2.90	0.43	20.06
Liddell (1982)	341	89	26.10	174	46	26.44	0.99	0.61	1.59

[1] Smokers to nonsmokers.

[2] Calculated by substituting 0.5 for 0 cases of pulmonary fibrosis in the nonsmoker group.

SOURCE: Weiss (1984).

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TABLE 16.—Prevalence (percentage) of suspected or definite pulmonary fibrosis among 23,340 male in-yard British dockyard workers during 1972 and 1973, by smoking habit and duration of asbestos exposure

Asbestos exposure (year)	Smoking habit					
	Nonsmokers		Ex-smokers		Smokers	
	Number	With fibrosis (percent)	Number	With fibrosis (percent)	Number	With fibrosis (percent)
<5	3,516	0.1	2,746	0.4	7,300	0.6
5–9	784	0.2	581	0.3	1,686	0.5
10–14	392	0.0	442	1.1	979	1.5
15–19	293	0.3	320	1.6	869	2.5
20–24	208	1.0	330	1.7	667	3.1
25–29	140	1.1	214	2.6	486	2.8
≥30	219	0.9	357	2.2	811	3.1
Total	5,552	0.2	4,990	0.8	12,798	1.1

SOURCE: Weiss (1984) (data derived from Harries et al (1976))

than nonsmokers. These data are consistent either with a small independent risk of interstitial fibrosis on chest roentgenogram produced by smoking (as suggested by the studies in non-asbestos-exposed populations) being added to the risk of fibrosis due to asbestos exposure or with the combination of asbestos-induced and smoking-induced changes in the small airways resulting in asbestos workers who smoke crossing the threshold for perceptible abnormality earlier than nonsmokers. However, it is clear that if cigarette smoking contributes to the development of interstitial fibrosis in asbestos-exposed workers, the contribution is a minor one in comparison with the effect of asbestos dust exposure.

Immunologic Response to Cigarette Smoke and Asbestos Dust

There is an extensive literature on both animal models and humans regarding alterations in the immune system following exposure to either asbestos or cigarette smoke; however, clinical and laboratory studies of combined exposure to asbestos and cigarette smoke are more limited.

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Humoral Immunity

Two independent studies (Kagan et al. 1977; Huuskonen et al. 1978) reported elevated polyclonal immunoglobulin (Ig) levels in populations of workers with asbestosis. Lange (1980) also correlated serum Ig levels with asbestosis. This study differentiated groups by sex and age, characteristics that can also affect the immune system. Cigarette smoking did not significantly correlate with serum Ig levels, whereas individuals with roentgenographically demonstrated asbestosis had increased levels of IgA and IgG. Asbestos workers, including those with interstitial fibrosis, were also evaluated for symptoms of chronic bronchitis. Male workers exhibiting symptoms for longer than 5 years had lower IgG and IgA values than asbestos workers without chronic bronchitis or with symptoms of bronchitis present for less than 5 years. Elevated IgA or IgM levels were found in a subgroup of male asbestos workers who were heavy smokers, as assessed by the duration of smoking multiplied by the average number of cigarettes smoked per day. The authors concluded that the asbestotic process and not the presence of chronic bronchitis was responsible for the high serum IgA and IgG levels (variable results have been reported regarding the level of serum IgA with chronic bronchitis) (Falk et al. 1970; Medici and Buergi 1971; Varpela et al. 1977). The immunoglobulin level alterations were found in workers with demonstrable lung disease. Therefore, it is unclear whether this alteration is involved in the pathogenesis of the disease or is an epiphenomenon, because the measurements were made when disease was already present.

Cellular Immunity

Wagner and colleagues (1979) evaluated factors affecting the peripheral blood leukocytes and T lymphocytes in 138 asbestos-exposed men. T lymphocyte subsets were identified by the ability of lymphocytes to rosette with erythrocytes, after incubation either for 1 1/2 hours (T helper cells) or overnight (T suppressor cells). Age, length of asbestos exposure, smoking history, evidence of roentgenographic fibrosis or pleural changes, and spirometric abnormalities were assessed. The smoking history in these asbestos-exposed workers was the factor that correlated best with lymphocyte changes. The group with roentgenographic changes of asbestosis and a history of smoking had an increased percentage in E-rosettes after 1 1/2 hours. This suggests an increase in the number of the T helper cells. Among workers with parenchymal chest roentgenographic changes, those who smoked had an increased number of the T helper cells compared with those who did not smoke. The number of T suppressor cells was not affected by the smoking history or by roentgenographic change.

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Age and smoking as individual factors affecting lymphocyte percentage or number have also been assessed. There is some controversy about the effects on T lymphocytes. Silverman and colleagues (1975) showed no correlation between percentage of T lymphocytes and smoking or aging. Friedman and colleagues (1973) and Alexopoulos and Babitis (1976) did not demonstrate the effect of age on the percentage of T lymphocytes, but the absolute number of lymphocytes declined with age. Teasdale and colleagues (1976) and Smith and colleagues (1974) demonstrated a decline in the percentage and total number of T lymphocytes with age. Friedman and colleagues (1973) showed that the total number of leukocytes, including lymphocytes, increased in smokers until age 50, and then declined.

The effect of asbestos exposure on lymphocytes was studied by Kang and colleagues (1974) and by Kagan and colleagues (1977). The findings of both groups of investigators were similar. Kang and colleagues reported decreased erythrocyte-binding lymphocytes. Kagan and colleagues showed a decrease in percentage and in absolute number of T lymphocytes in a group of workers with asbestos exposure. Smoking as a contributing factor was not reported in these two studies.

More recently, these findings were substantiated by Miller and colleagues (1983) with the use of monoclonal antibody markers to differentiate T lymphocyte subsets. Smoking, length of asbestos exposure, and chest x-ray findings were evaluated. A decrease in percentage of T lymphocytes ($OK_{T(sub\ 3)^+}$) and in the suppressor subset of T lymphocytes ($OK_{T(sub\ 8)^+}$), with an increase in the ratio of helper T cells to suppressor cells ($OK_{T(sub\ 4)^-}/OK_{T(sub\ 8)^+}$), was found in the group of 40 asbestos-exposed individuals compared with nonexposed individuals. Those with short asbestos exposure (less than 5 years) were similar to controls, and those with more than 5 years of exposure had the abnormalities. When assessing radiographic changes, those without chest roentgenographic changes had lymphocyte parameters similar to nonexposed individuals, those with pleural plaques had increased circulating helper cells ($OK_{T(sub\ 4)^+}$), and those with interstitial changes had decreased percentages of T lymphocytes ($OK_{T(sub\ 3)^+}$) and suppressor cells ($OK_{T(sub\ 8)^+}$) and an increased ratio of helper to suppressor cells ($OK_{T(sub\ 4)^+}/OK_{T(sub\ 8)^+}$). Smoking habit did not influence these results. Miller and colleagues (1983) theorized several possibilities to explain the findings. The asbestos exposure may initially stimulate the immune system, accounting for the increase in the helper cells in subjects with pleural plaques. There may be an isolated toxic effect to suppressor cells affecting the percentage of this subset, and thus the total percentage of T lymphocytes. Lymphocytes may be distributed in organs (i.e., the lung) once fibers are inhaled, and thus the peripheral

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blood lymphocyte parameters are altered. Although the differences are most striking in subjects with roentgenographic changes, the lymphocyte alterations may not be related to the pathogenesis of these changes, but may be a secondary change due to chronic disease.

In other studies (Ginns et al. 1982; Miller et al. 1982), smoking was also found to cause T lymphocyte subset changes. These changes were found in heavy smokers (50 to 120 pack-years) and not in light to moderate smokers (10 to 49 pack-years). Heavy smokers had increased total T lymphocytes ($OK_{T\text{sub }3^{+}}$), a decreased percentage of T helper cells ($OK_{T\text{sub }4^{+}}$), an increased total number of T suppressor cells ($OK_{T\text{sub }8^{+}}$), and a decreased ratio of helper to suppressor cells.

De Shazo and colleagues (1983) also examined lymphocyte subsets in 31 current and former asbestos-cement workers compared with 52 healthy controls after adjustments had been made for possible confounding effects of age, race, and smoking. The asbestos workers had significantly decreased percentages and numbers of B and T lymphocytes in the peripheral blood. Analysis of T lymphocyte subpopulations revealed that total T cell numbers ($OK_{T\text{sub }3^{+}}$) and helper-inducer T cell numbers ($OK_{T\text{sub }8^{+}}$) were decreased by similar proportions. These decreases were negatively correlated with time since the end of exposure to asbestos. In both workers and controls, lymphocyte proliferative response to phytohemagglutinin was correlated positively with the number of ($OK_{T\text{sub }4^{+}}$) cells and negatively with age. No relationship was detected between any of the immunologic aberrations noted in the workers and the radiographic category of pneumoconiosis, estimates of cumulative asbestos exposure, or abnormalities of pulmonary function.

Lymphocyte function was assessed by Campbell and colleagues (1980) by the mitogen lymphocyte transformation response of peripheral blood lymphocytes. Allowing for the decline in response seen with increasing age, there was an increase in response to phytohemagglutinin (PHA) and pokeweed mitogen (PWM) in asbestos workers who smoked compared with ex-smokers and nonsmokers. These findings were in agreement with those reported by Haslam and colleagues (1978).

Sister Chromatid Exchange Frequency

An in vitro cytogenetic assay, sister chromatid exchange (SCE) frequency, has been utilized to demonstrate chromosomal breakage in different mammalian cell lines following exposure to asbestos. In a study reported by Rom and colleagues (1983), 25 asbestos insulators had a small increase in frequency of SCE in peripheral blood lymphocytes compared with controls. The SCE rate increased slightly with increasing years of exposure to asbestos, when age and smoking were controlled. Smokers had similar rates of occurrence of SCE among both controls and asbestos workers. In nonsmokers,

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those with asbestos exposure had a significantly increased SCE rate compared with controls. Butler (1980) and Crossen and Morgan (1980) did not detect a difference in SCE frequency.

Public Health Implications

The data are unequivocal that cigarette smoking and asbestos exposure have produced substantial death and disability. The residual public health questions generated by these data focus on how to reduce the future risk of illness and death. As asbestos exposures are reduced, clinically disabling interstitial fibrosis should become a rare phenomenon in workers currently beginning their work careers. As asbestos exposures are reduced, it will become increasingly difficult to identify an increase in lung cancer death rates among asbestos workers that is greater than those of the general population. While the risk of developing mesothelioma is not associated with smoking, the risk of developing mesothelioma should be reduced by the lower exposure levels that currently exist, but persists even at very low levels of exposure. A reduction in the current U.S. standard (2f/cc) is being considered; once adequate asbestos dust controls are applied and enforced, future gains in reducing asbestos exposure are likely to come from reducing the exposure of workers employed in jobs other than asbestos mining and manufacturing. These jobs include construction workers who may be exposed during the demolition or remodeling of existing structures constructed with asbestos materials, and maintenance workers who may be similarly exposed to existing asbestos-containing materials. Current concerns are the risk involved in removing asbestos from existing buildings in order to reduce environmental contamination and the need to educate the workers involved in these tasks to prevent their exposure as they remove these materials.

Unfortunately, little can be done to reduce the current asbestos burden in workers exposed prior to the introduction of environmental controls. For these workers, it is clear that the single most important intervention that would alter their future disease risk is the cessation of cigarette smoking. The elimination of cigarette smoking in this population would not only substantially reduce the number of future lung cancer deaths but also moderate the contribution of cigarette-induced COLD to the restrictive ventilatory limitation that may develop in these workers. The issues of liability and responsibility for the disease that is occurring in these workers will continue to be argued for an extended period of time, but these arguments should not confuse or impede the efforts to alter the future disease risk in these workers. The goal is not, and should not be, to eliminate only that disease burden attributable to future asbestos exposure, but rather to reduce as much as possible, by any

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means possible, the enormous risk of death and disability that currently exists for these workers. Smoking cessation is therefore an intrinsic and essential part of any effort to reduce asbestos-related disease and disability.

Summary and Conclusions

1. Asbestos exposure can increase the risk of developing lung cancer in both cigarette smokers and nonsmokers. The risk in cigarette-smoking asbestos workers is greater than the sum of the risks of the independent exposures, and is approximated by multiplying the risks of the separate exposures.
2. The risk of developing lung cancer in asbestos workers increases with increasing number of cigarettes smoked per day and increasing cumulative asbestos exposure.
3. The risk of developing lung cancer declines in asbestos workers who stop smoking when compared with asbestos workers who continue to smoke. Cessation of asbestos exposure may result in a lower risk of developing lung cancer than continued exposure, but the risk of developing lung cancer appears to remain significantly elevated even 25 years after cessation of exposure.
4. Cigarette smoking and asbestos exposure appear to have an independent and additive effect on lung function decline. Nonsmoking asbestos workers have decreased total lung capacities (restrictive disease). Cigarette-smoking asbestos workers develop both restrictive lung disease and chronic obstructive lung disease (as defined by an abnormal FEV_1/FVC), but the evidence does not suggest that cigarette-smoking asbestos workers have a lower FEV_1/FVC than would be expected from their smoking habits alone.
5. Both cigarette smoking and asbestos exposure result in an increased resistance to airflow in the small airways. In the absence of cigarette smoking, this increased resistance in the small airways does not appear to result in obstruction on standard spirometry as measured by FEV_1/FVC.
6. Asbestos exposure is the predominant cause of interstitial fibrosis in populations with substantial asbestos exposure. Cigarette smokers do have a slightly higher prevalence of chest radiographs interpreted as interstitial fibrosis than nonsmokers, but neither the frequency of these changes nor the severity of the changes approach levels found in populations with substantial asbestos exposure.
7. The promotion of smoking cessation should be an intrinsic part of efforts to control asbestos-related death and disability.

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CHAPTER 7

RESPIRATORY DISEASE IN COAL MINERS

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Introduction

An association between respiratory disease and coal mining has been recognized since the 16th century, when Agricola and Paracelsus wrote of the diseases of miners (Hunter 1978). The first description of coal workers' pneumoconiosis (CWP) was given in the early 1800s by Laennec (Meiklejohn 1951) when he described cystic and noncystic melanotic masses in the lung, and in addition, melanotic parenchymal infiltrates in the lung. The melanotic masses were almost certainly progressive massive fibrosis (PMF) and the black infiltrates, simple CWP. It is clear from Laennec's description that he recognized an association between coal mining and the deposition of "la matiere noire pulmonaire." An excellent history of coal miners' lung disease in Great Britain can be found in a series of articles by Meiklejohn (1951, 1952a, 1952b).

Over the years, a large number of names have been attached to the conditions that affect the lungs of coal miners. Many early physicians assumed that there was a single respiratory condition arising from coal dust exposure, which was variously referred to as spurious melanosis, miners' asthma, anthracosis, miners' phthisis, and silicosis. With the passage of time, it became evident that, aside from the lung diseases that commonly affect the general population, coal miners are prone to develop occupationally related lung diseases, namely coal workers' pneumoconiosis, silicosis, and chronic bronchitis (Morgan and Lapp 1976). Silicosis is covered elsewhere in this Report; therefore this chapter discusses coal workers' pneumoconiosis and chronic bronchitis.

The paramount importance of exposure to coal dust in the development of CWP is generally accepted, and complicated CWP is clearly associated with significant and often disabling chronic airflow limitation as well as with other respiratory impairments (Morgan and Seaton 1984; Morgan and Lapp 1976). Less certain is the magnitude of the role of coal mine dust as a cause or contributory factor in the development of bronchitis and emphysema. The effects of long-continued inhalation of coal and other dusts are currently of major interest to epidemiologists and to those practicing occupational medicine. Clearly the results of the studies designed to characterize the effects of coal dust on lung function are of vital importance to officials concerned with compensation for occupationally related pulmonary disability. In these studies it is important to evaluate as potentially independent effects the role of coal dust in producing radiologic CWP and the role of coal dust in producing physiologic airflow obstruction (Weeks and Wagner 1986). This separation of the radiologic and physiologic responses to coal dust is even more critical when considering the effects of combined exposure to coal dust and cigarette smoke.

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The respective contributions of cigarette smoking, dust exposure, and other environmental and occupational factors in the development of respiratory impairment in coal miners are examined in this chapter by reviewing the evidence currently available from mortality and morbidity studies of coal miners compared with appropriate reference populations and the evidence on the frequency and extent of pulmonary impairment in coal miners. The roles of dust, cigarette smoking, and various confounding factors are taken into account and apportioned where possible.

At the present time, there are approximately 150,000 underground coal miners in the United States. Ten years ago, the figure was about 170,000, but the closure of a number of mines in Appalachia has reduced the number of employed underground miners. In addition, 60,000 to 70,000 workers are employed in open cast or surface mines, but this number is constantly changing. Exposure to coal mine dust is greater in those employed underground; miners working at the face or in transportation are the most heavily exposed. Miners employed underground on maintenance and other activities are less exposed, and surface miners are the least exposed (Doyle 1970).

Prevalence of Smoking in Coal Miners

The prevalence of smoking for various populations of miners in different countries and during different time periods is presented in Table 1. In general, the prevalence of smoking among U.S. coal miners is currently similar to, or slightly higher than, the rates in the overall U.S. male population. However, coal mining as an occupation introduces a distortion in the pattern of smoking because of the prohibition against smoking while in the mine. As a result, the entire consumption of cigarettes by miners is limited to those periods when they are not underground; for a given number of cigarettes smoked per day, the pattern among miners would consist of periods of more intense smoking interspersed with long periods of not smoking (i.e., during working hours), in contrast to the more even consumption of cigarettes throughout the day that characterizes most cigarette smokers.

Coal Workers' Pneumoconiosis

Coal workers' pneumoconiosis (CWP) is defined as the deposition of coal mine dust in the lungs and the reaction of tissue to its presence (Morgan and Seaton 1984). However, the term is commonly applied only to the chest roentgenographic changes produced by coal dust, and the other tissue responses to coal dust are classified by their symptomatic, physiologic, or pathologic manifestations (e.g., chronic bronchitis, airflow obstruction, or emphysema). The radiologic

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TABLE 1.—Smoking characteristics of coal workers

Study	Number and type of population		Smoking characteristics (percent)			Comments
			SM	NS/EX		
Higgins et al. (1968)	755 mining town residents, Great Britain		75	25		
Tokuhata et al. (1970)	801 anthracite coal miners, Pennsylvania	Large colleries				
		Age <40	84.1	15.9		
		40–49	74.0	26.0		
		≥50	71.6	28.4		
		Independent				
		Age <40	76.4	23.6		
		40–49	80.5	19.5		
		≥50	77.3	22.7		
			SM	NS	EX	
Ashford et al. (1970)	30,000 underground and surface workers, Great Britain		78.7	15.3	6	
			SM	NS		
Rae et al. (1971)	3,379 workers, 20 colleries, Great Britain		79.2	20.8		Ex-smokers not differentiated from smokers
			SM	NS	EX	
Saric and Palaic (1971)	Lignite and brown coal miners, Yugoslavia		64.7	23.6	11.7	

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TABLE 1.—Continued

Study	Number and type of population	Smoking characteristics (percent)				Comments
Minette (1972)	204 coal miners, Belgium		SM 70.6	NS* 29.4		*Nonsmokers include smokers who did not inhale
Phelps (1972)	256 miners, U.S. Rocky Mountain region		SM 65.6	NS 34.3		
Skrabski-Kopp et al. (1972)	1,068 coal miners, Hungary		SM 75.6	NS/EX 24.4		
Lowe and Khosla (1972)	3,012 ex-coal miners, 9,361 controls, Great Britain	Ex-miners Controls	86.6 80.7			
Kibelstis et al. (1973)	Bituminous coal miners, United States		SM 50.8	NS 25.4	EX 23.8	20–39-year-old miners smoked at a rate above 65%
Ortmeyer et al. (1974)	Coal miners and ex-miners, Appalachia	Coal miners, Ex-miners	60.9 47.1	19.7 52.3	19.4	
Fairman et al. (1977)	987 surface coal miners, six U.S. States		70.7	29.3		

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TABLE 1.—Continued

Study	Number and type of population	Smoking characteristics (percent)				Comments
Armstrong et al. (1979)	Coal and gold miners, Australia		SM	NS/EX		
		Coal miners	58.7	41.3		
		Gold miners	66.3	33.7		
Szymczykiewicz (1979)	Miners, Poland		73.7			
Potkonjak (1979)	970 coal miners, 538 controls with no dust exposure	Miners	46	54		
		Controls	47.9	52.1		
Cochrane and Moore (1980)	Coal miners, Great Britain		SM	NS/EX	Pipe only	
		Age 25–34	71.3	24.3	3.8	
		SM/cigs				
		1–14	32			
		>14	39.3			
		Age 55–64	60	23.6	16	
		SM/cigs				
		1–14	32			
		>14	28			
Rom et al. (1981)	242 active and retired miners, Utah		SM	NS	EX	
			38	23.6	38.4	
Love and Miller (1982)	1,677 colliery workers, Great Britain		SM	NS	EX	16.5% were intermittent smokers
			66.1	12.8	4.5	

NOTE: SM = Smoker; EX = Ex-smoker; NS = Nonsmoker.

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manifestations of CWP are classified into two forms: simple, and complicated (often known as progressive massive fibrosis, PMF). Simple CWP is a reaction solely to the inhalation of coal dust. Although the efficiency and integrity of the lung defenses are important factors in the development of disease, cumulative dust exposure is of paramount importance. Characteristically, after a period of exposure, i.e., 10 to 15 years, small rounded opacities begin to appear in the upper lung fields of some miners. With continued exposure, they gradually spread to the middle and lower zones, and the increasing profusion of these opacities is used to categorize simple CWP on a 0 to 3 scale. The opacities are indistinguishable from those seen in silicosis. Simple CWP does not progress in the absence of further exposure. Moreover, increasing category of simple CWP is not associated with a decrement in ventilatory capacity (Cochrane et al. 1961; Gilson and Hugh-Jones 1955; Morgan et al. 1974).

Complicated CWP is defined as the presence of an opacity greater than 1 cm in diameter on the chest radiograph of a subject who already has simple CWP (ILO 1980), and the volume of lung occupied by the large opacities on the radiograph is used to categorize complicated CWP into category A, B, or C. For the most part, complicated CWP develops on a background of category 2 or category 3 simple CWP. Necessary for its development is the presence of a fairly high dust burden in the lungs, plus some other factor or factors as yet not fully recognized or understood.

Prevalence of Coal Workers' Pneumoconiosis

In 1969 the National Coal Study was commenced by the National Institute for Occupational Safety and Health (NIOSH) (Morgan et al. 1972). Selected for study were workers at 31 coal mines, of which 2 were anthracite and 29 were bituminous. In the initial survey, an overall CWP prevalence of nearly 30 percent was found; 2.5 percent had PMF. A decreasing prevalence was noted from east to west, and there was a clear-cut relationship between the years spent underground and radiographic category. The disease was much more common in workers at the face than in surface workers. The prevalence of CWP in this study was undoubtedly overestimated, however. Part of the reason was that the early films were interpreted according to the 1958 International Labour Office (ILO) classification. In addition, some of the readers were inexperienced and tended to overread. The second round of the National Coal Study revealed a prevalence of 8 percent; the findings at the third round were just under 5 percent, with 3.85 percent having category 1; 0.48 percent, category 2; 0.04 percent, category 3; and 0.17 percent, PMF.

The decline in the prevalence of pneumoconiosis noted between the first and third rounds of the National Coal Study is partly

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accounted for by the use of different readers, partly by more stringent reading criteria, partly from the use of the ILO standard films as yardsticks, and partly from improved coal dust control. An exodus of workers with higher categories of disease between the first and subsequent accumulations of subjects with radiographic evidence of pneumoconiosis also played a role, since those with CWP qualified for compensation.

Both simple CWP and PMF are related to cumulative lifetime exposure to coal dust. The reduction or elimination of category 2 and category 3 simple CWP through effective dust control not only is possible but is rapidly being achieved in the United States and Great Britain (Jacobsen 1980). Since complicated pneumoconiosis develops almost entirely in subjects who have the higher categories of simple CWP (i.e., those with a high dust burden), the effective prevention of category 2 and category 3 simple CWP should almost completely eliminate PMF as well. The removal from further coal dust exposure of miners with early categories of simple CWP should also aid in reducing the incidence of PMF.

Pulmonary Function Abnormalities in Simple and Complicated Coal Workers' Pneumoconiosis

The radiologic changes of simple CWP are associated with the development of certain relatively minor pulmonary impairments. These include an increased alveolar–arterial gradient for oxygen, abnormalities of the distribution of inspired gas, and a modest increase in lung volumes (Morgan and Lapp 1976). The increase in lung volumes is a consequence of the focal emphysema that is an integral part of the pathology found with simple CWP (Morgan and Seaton 1984).

Complicated pneumoconiosis is associated with a reduction in lung volume and diffusing capacity, ventilation perfusion mismatching, an obliteration and destruction of the pulmonary vascular bed that leads to nonhypoxic pulmonary hypertension and cor pulmonale, and with the presence of generalized airways obstruction (Gilson and Hugh-Jones and Seaton 1955; Lyons et al. and Seaton 1981; Morgan and Seaton 1984).

Relationship of Small Opacities to Emphysema and Airways Obstruction

The small opacities present in the lung in the various pneumoconioses can be classified as either rounded (regular) or irregular.

Small rounded opacities have a fairly rounded and regular margin. They are classified according to their size into p, q, and r types: p is up to 1.5 mm in diameter, q is between 1.5 and 3 mm, and r is between 3 and 10 mm. Usually only one type of opacity is present,

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but mixtures are occasionally found in the same lung. The reading of the film should be based on the predominant opacity noted.

Irregular opacities are also classified according to size: s opacities are up to 1.5 mm in width, t opacities are between 1.5 and 3 mm wide, and u opacities are between 3 and 10 mm. Irregular opacities are characteristically seen in asbestosis. In some smokers scanty irregular opacities may be observed.

Rounded and irregular opacities occasionally occur together, usually in a person who has experienced various exposures or in a person with either silicosis or coal workers' pneumoconiosis who also is a heavy smoker.

Lung Function in Subjects With Rounded or Regular Opacities

A number of investigations have shown that the p, or punctate, type of opacity seen in simple CWP is associated with a reduced diffusing capacity (Sartorelli et al. 1963; Lyons et al. 1967; Seaton et al. 1972; Musk et al. 1981). In addition, an increased parenchymal air space size has also been observed in subjects with a p type of opacity (Hankinson et al. 1979). No detectable difference in lung function between subjects with the p, q, or r type of opacity was observed in this study.

These physiological changes have also been demonstrated in nonsmoking miners with simple CWP (Hankinson et al. 1979; Seaton et al. 1972). The indices of lung function that were tested in the miners with the p and q opacities were similar (Hankinson et al. 1979) except for the diffusing capacity, which was significantly lower in those with the p type of lesion (Seaton et al. 1972). Static compliance was reduced marginally, but not significantly, with the q type of opacity. The type of opacity was not significantly related to differences in dynamic compliance at increased rates of breathing (Seaton et al. 1972).

Musk and colleagues (1981) examined the lung function in 125 coal miners identified in 1968 as having the simple pneumoconiosis of coal workers and reexamined 9 years later. Pulmonary function was related to both smoking history and coal dust exposure. Miners who smoked in 1978 had lower forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), and FEV_1/FVC ratio and a higher ratio of residual volume to total lung capacity (RV/TLC) compared with nonsmokers. Ex-smokers had a lower carbon monoxide diffusing capacity (DLCO) than nonsmokers. Total dust exposure was inversely related to FVC and lung elastic recoil at TLC. After correcting for the effects of age, height, and smoking category, miners whose radiographs showed predominantly p and r types of opacities had a reduced DLCO when compared with miners with the q type of opacity. In the researchers' experience, irregular opacities were also associated with a reduced DLCO, and were thought to

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reflect the presence of both emphysema and diffuse fibrosis. In addition, the r type of opacity, but not the p type, was associated with reduced maximal recoil at TLC, and reduced recoil at 50 percent of TLC and at 1 L below TLC, and with an increased RV and RV/TLC percent compared with miners with the q type of opacity. The decreased compliance in subjects with the r type of opacities noted by Musk and colleagues (1981) may be a consequence of the exposure of some of these subjects to silica. Irregular opacities were not associated with increased obstruction or with smoking; here the results of Musk and colleagues differ from almost all other studies.

Lung Function in Subjects With Irregular Opacities

The significance of irregular opacities in the lungs of coal miners has been the subject of a number of investigations. Lyons and colleagues (1974) pointed out that there was a positive association between the presence of irregular opacities and emphysema and impairment of FEV_1. Unfortunately, this was a post-mortem study in which no smoking histories were available. Subsequently, Amandus and colleagues (1976) investigated the significance of irregular opacities in the lungs of 6,166 working U.S. coal miners for whom complete smoking histories were available. Irregular opacities on the chest radiographs were shown to be associated with smoking, bronchitis, age, and years worked underground. Smoking was not associated with the presence of regular opacities. Although irregular opacities were observed in nonsmokers, they were 2.5 times more common in those who smoked. Among nonsmoking miners, there were no significant differences in the lung volumes or flow rates of the men with normal chest x rays, irregular opacities, rounded opacities, or mixed opacities. Smokers had similar FVCs in each of the radiologic categories when compared with nonsmokers, but FEV_1 and FEV_1/FVC were lower and RV and TLC were higher. In addition, smokers with irregular opacities had a lower FEV_1 and a higher RV and TLC than smokers with normal chest x rays or rounded opacities. A study by Cockroft, Berry, and colleagues (1982) of coal workers and ex-workers showed that irregular opacities were related to age, smoking, and underground exposure in those receiving disability benefits.

Cockcroft, Seal, and colleagues (1982) examined the relationships among lung function tests, irregular opacities on chest radiograph, and the pathologic changes of emphysema in 46 men who had been referred for lung function tests during life and who had died between 1970 and 1979. Irregular opacities on radiograph were associated with a reduced DLCO and reduced TLC, an increased pathologic score for emphysema, and to a lesser extent, an increased pathologic score for fibrosis. Smoking histories were obtained in all but five of these workers, and there was no association of smoking with any

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particular lung function or pathologic finding. However, almost all of the subjects in the study were current smokers (two were nonsmokers and two were former smokers), which limited the ability of the study to examine the effects of smoking.

The majority of the evidence indicates that simple CWP is associated with mild overdistension or hyperinflation of the lungs. There is some evidence, especially in miners with the p type of opacity, that there is also a reduction in DLCO. The decreased DLCO does not appear to be associated with increasing airways obstruction, but with focal dust emphysema. The available data indicate that cigarette smoking plays a much greater role in reducing DLCO than does the presence of simple CWP (Frans et al. 1975).

Irregular opacities occur occasionally in the lungs of coal miners and former miners. For the most part, they are associated with smoking, age, bronchitis, and years spent underground. Bronchitis may be the common denominator in the production of irregular opacities, and the increased prevalence of bronchitis in smoking coal miners may be the reason for the increased prevalence of irregular opacities found among smokers in some studies. Irregular opacities are seen in nonoccupationally exposed groups (Carilli et al. 1973), in subjects exposed to silica, in asbestos miners and millers (Morgan 1978), in workers who manufacture manmade fibers (Weill et al. 1983), and in workers with other conditions, suggesting that irregular opacities may be a nonspecific response associated with the presence of bronchitis, regardless of its etiology.

Respiratory Symptoms and Exposure to Coal Dust

The relationship between dust exposure and bronchitis was noted by Thackrah (1832) and Greenhow (1860) in the 19th century. Although these pioneer workers noted a higher prevalence of bronchitis and other respiratory ailments in the dusty trades as a whole, they particularly emphasized the importance of textile dust as a cause of bronchitis.

Until recently the use of the terms "chronic bronchitis" and "emphysema" implied that these two conditions were invariably associated and that both, for the most part, were related to cigarette smoking. In this context, "bronchitis" implied a condition characterized by cough and sputum, usually associated with a reduction in ventilatory capacity or frequently leading to one (Fletcher et al. 1959). Subjects with these symptoms who also had concomitant chronic airflow obstruction were usually diagnosed as having chronic bronchitis and emphysema, assuming from the association of the two diseases that they were part of the same process. At the time the committee appointed by the Medical Research Council (MRC) of Great Britain published its statement (*British Medical Journal*

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1966), it was known that not all subjects with chronic bronchitis showed an associated reduction of FEV_1, but the committee did not elaborate fully on the implications of the term "bronchitis." It was assumed, moreover, that there was a relationship between the symptoms of cough and sputum and a decreased ventilatory capacity, and that sooner or later most or all subjects with chronic bronchitis would develop some degree of irreversible airways obstruction. The MRC's (1965) division of bronchitis into obstructive bronchitis and simple bronchitis, a condition characterized by the presence of cough and sputum in the absence of airways obstruction, was the first step taken toward a better understanding of the implications of a diagnosis of bronchitis. Subsequently, the general use of the MRC questionnaire on chronic bronchitis for symptoms without reference to lung function led to an appreciation of the pathophysiology of this condition (MRC 1965), and the pathological features of bronchitis as described by Reid (1960) in her studies provided a means of quantitating the severity of the condition.

Bronchitis and Dust Exposure

Many of the studies showing an association between dust exposure and an increased prevalence of chronic bronchitis have been carried out with coal miners. Coal miners represent a clearly defined and relatively large group of subjects who seldom change their occupation, and thus present an ideal study population. Ashford and colleagues (1970) showed that the prevalence of cough and sputum increased with age and, it may be inferred, with cumulative dust exposure. Shortly thereafter, Rae and colleagues (1971) demonstrated a relationship to dust exposure. Kibelstis and colleagues (1973) showed, in a U.S. population of more than 9,000 working coal miners, that cough and sputum were related to dust exposure and also to cigarette smoking. When only nonsmokers were considered, there was a gradient in the prevalence of bronchitis from the least to the most dusty jobs. This occurred independent of age. In smokers, the effect of cigarette smoking almost completely overwhelmed the effects of dust and age, at least as far as symptoms were concerned. Similar findings have been reported in Belgian coal miners (Minette 1976; Vuylsteek and Depoorter 1978).

The effect of dust and cigarette smoke on bronchial gland dimensions in coal miners has recently been investigated (Douglas et al. 1982). These investigators demonstrated that both dust and cigarette smoking had an effect on the Reid index and that they led to mucous gland hypertrophy. There is thus a fairly widespread acceptance that the long-continued inhalation of coal dust and other dusts may lead to an increased prevalence of cough and sputum in the absence of cigarette smoking. Moreover, it has been demonstrated that the prevalence of dust-induced bronchitis is related to

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cumulative dust exposure (Rogan et al. 1973; Kibelstis et al. 1973). The topic of industrial bronchitis is more fully discussed in another chapter of this Report, but the data suggest that there is an independent and additive effect of coal dust exposure and cigarette smoking on the prevalence of chronic bronchitis.

Respiratory Mortality in Coal Miners

Early mortality data of coal miners showed a high death rate from respiratory disease. This was true for both Great Britain (Registrar General 1958) and the United States (Enterline 1964; Guralnick 1963). Although there may be some doubt as to the precise accuracy of such data, it is probably true that there was an increased standardized mortality ratio (SMR) for respiratory disease among coal miners. There was, however, little convincing evidence to establish that coal dust was a major causative factor in this increase. Tuberculosis, emphysema, and bronchiectasis were more common in coal miners, and most of the increased mortality could be explained by an increased prevalence of these diseases. In addition, Enterline (1964, 1972) had shown in a series of retrospective analyses that the SMR for coal miners as a group was elevated, but a substantial portion of the excess was a consequence of trauma and accidents. When deaths due to these excesses were excluded, excess mortality still persisted. Much of the excess was due to respiratory disease, and although the death rate for chronic bronchitis and emphysema was reported to be increased, so also were the death rates for tuberculosis and lung cancer. While it is easy to postulate a relationship between occupation and bronchitis, it is also clear that bronchitis and lung cancer have a common causative agent, namely cigarette smoke. In addition, coal miners, particularly in the United States, constituted a distinctly underprivileged group during the early part of this century, and as such suffered from overcrowding and poor medical care, both of which contributed significantly to a higher death rate from bronchiectasis and tuberculosis and other infectious diseases.

Over the past two decades, a number of well-controlled epidemiological studies of morbidity and mortality of coal miners have been carried out in both Great Britain and the United States. Liddell (1973a) looked at the frequency of time off from work because of illness in a cohort of 29,084 men. He showed that miners spent more time off work than nonminers. The highest rate of incapacity was present in the lowest paid workers; this applied as much to coal face miners as to surface workers. Pneumoconiosis was associated with greater time off work. An additional investigation of the mortality of 5,362 British miners who died in 1961 showed that they had higher death rates for accidents and pneumoconiosis than the general population, but lower death rates for cancer in general and for lung

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cancer in particular (Liddell 1973b). There was a wide disparity between the SMR of miners employed at the face (49) and the SMR of those working on the surface (82). This disparity can be explained in that surface miners may smoke while at work, but underground miners cannot, and that the less healthy miners tend to move away from coal face work and to be employed in easier jobs on the surface.

Ortmeyer and colleagues (1973; Lainhart et al. 1969) studied the death rate of Pennsylvania coal miners who had been awarded compensation for occupationally related respiratory disability. The overall SMR was the same as that of white men in Pennsylvania. Excess death rates were found in subjects with a reduced ventilatory capacity, in particular when the FEV_1/FVC was below 50 percent, and in ex-miners with stage B and C complicated CWP. "Disabled" miners with simple CWP had a normal SMR. Later, Ortmeyer and colleagues (1974) studied a group of randomly selected Appalachian miners and ex-miners. They showed that the overall life expectancy for miners and ex-miners combined was the same as that for the general U.S. population and for the States from which the cohort originated. The effects on mortality of the years worked underground, cigarette smoking, and airways obstruction were investigated. Ex-miners had a slightly but significantly increased death rate. Simple CWP had no effect on life expectancy; however, complicated CWP was associated with decreased longevity. Although both cigarette smoking and airways obstruction were associated with an increased SMR, the number of years of work underground had no discernible effect.

About the same time these reports were published, Cochrane (1973) described his findings from a 20-year followup of the male population of the Rhondda Fach in Wales. Survival rates for miners and ex-miners were independent of the radiographic presence of simple CWP or category A complicated pneumoconiosis. Further studies of the same cohort from the Rhondda Fach showed a normal life expectancy in those with simple CWP and category A complicated CWP (Cochrane et al. 1979). The death rate for bronchitis and other respiratory diseases was elevated. The smoking habits of this population were not examined.

A 20-year followup of a population sample from Derbyshire (Cochrane and Moore 1980), aged 25 to 34, included four groups of workers whose work was categorized as nondusty, pure coal mining, pure foundry, or other and mixed. There were no significant differences in the SMRs of the dust-exposed group of miners, compared with the non-dust-exposed group of miners; however, only 20 deaths were recorded in the study.

Rockette (1977), in a NIOSH-supported study, investigated the mortality rates among coal miners covered by the United Mine Workers of America (UMW) Health and Retirement Fund. Unfortu-

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nately, unlike the studies of Ortmeyer and colleagues (1973, 1974), in this investigation the population was not randomly chosen and smoking histories were not available. A 10 percent sample of miners eligible for benefits in January 1959 was randomly selected from the original 550,000. Doubt exists whether miners covered by the UMW Health and Retirement Fund are necessarily representative of U.S. coal miners as a whole. The SMR for all causes was 101.6 and for all cancer, 97.7. The SMRs for asthma, emphysema, and tuberculosis were significantly elevated at 174, 144, and 145, respectively. The SMR for lung cancer was minimally but significantly elevated at 112; however, a disproportionate number of miners from southwestern West Virginia were subsequently shown to have been included in the cohort. The death rate for lung cancer in this part of the United States is significantly higher than the rate for the United States as a whole and for other parts of West Virginia. In the absence of smoking histories, little can be made of such a small increment in mortality. Deaths due to accidents were high (SMR 144). The SMR for bronchitis was 89.7, but, as previously mentioned, the SMR for emphysema was elevated. There was a significantly increased death rate for stomach cancer, but the SMR for pneumoconiosis could not be determined because of difficulties with death certification and classification.

A lengthy report of coal miners' morbidity in relation to x-ray category, lung function, and exposure to airborne dust (Miller et al. 1981) described the findings for 31,611 British miners who were surveyed at 24 pits from 1953 to 1958. Again, the coal miners had a lower mortality than British men in general. Although this was attributed to the healthy worker effect, no supporting evidence for this conclusion was given. Miners with PMF had an increased death rate. Mortality from bronchitis was associated with increased dust exposure, but it is apparent that with increased dust exposure, there would also be an increased cumulative exposure to cigarette smoke. Appropriate data whereby the two effects could be separated were not available, since cumulative cigarette smoking history or, indeed, a smoking history of any kind was not available. Deaths from lung cancer were not increased.

Higgins and colleagues (1981), in a followup study of a group of miners from Richwood and Mullens, West Virginia, were unable to show any significant difference in the mortality of miners and ex-miners as compared with nonminers. The death rates from respiratory diseases were appreciably higher in coal miners; however, there are doubts as to the accuracy of the cause of death on the death certificates because compensation was often awarded to ex-miners' families solely on the basis of a death certificate that mentioned respiratory disease (Comptroller General 1980, 1982). Another problem encountered was that some miners had moved away from

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the district and could not be traced. In many instances, their status proved impossible to determine. A clear-cut effect of smoking on mortality was evident in nonminers, but was less evident in miners and ex-miners. Here again the advent of black lung compensation may have been an incentive for disability applicants to underestimate their smoking habits.

The publication of the Registrar General's Decennial Supplement (1970–1972) on occupational mortality (1978) indicated that mortality rates for coal miners were somewhat increased for both underground and surface workers. The SMR for most respiratory diseases other than lung cancer showed a mild to moderate increase.

Jacobsen (1976, 1977) concluded that coal miners as a group have a normal SMR. He also indicated that there was no excess death rate from bronchitis and emphysema among coal miners, nor was there an increase in mortality from these conditions with increasing time worked in dusty occupations. Among men with no pneumoconiosis, there was a clear and significant mortality gradient with increases in estimates of cumulative exposures to airborne dust. However, the decision to study the SMR of selected subgroups of miners whose cigarette smoking habits were unknown, and in whom other possible confounding factors may have been present, detracts from his conclusions. The demonstration that the presence of bronchitis in coal miners is associated with increased mortality and morbidity is of little special significance for coal miners because the same situation applies to the general population. The increased mortality and morbidity are for the most part attributable to cigarette smoking in the general population, and only if it were possible to show an increased death rate in nonsmoking bronchitic coal miners would this observation be convincing evidence that the presence of bronchitis of itself portends premature disability and death.

In conclusion, the majority of recent mortality studies have shown that coal miners have a normal life expectancy. Although there is an increased SMR in miners with PMF, the overall prevalence of PMF in working miners is so low that any effect it has on the SMR is more than counterbalanced by decreased death rates from lung cancer and heart disease. Although in certain studies, death rates from bronchitis and emphysema have been found to be elevated, this has not been a consistent finding; in other studies, especially those in which it has been possible to quantitate the effects of cigarette smoking, no increased death rates have been demonstrable. There is little or no evidence that the inhalation of coal mine dust contributes to excess morbidity or mortality in regard to lung conditions other than PMF, such as emphysema, asthma, tuberculosis, or pneumonia. By way of contrast, cigarette smoking has repeatedly been shown to have a clear and easily demonstrable effect on the death rate of both miners and nonminers. There is some recent suggestion that cigarette

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smoking prevalence increased in British coal miners between 1965 and 1975, possibly related to their increased standard of living, but it is too early for any discernible changes in cigarette consumption to be reflected in mortality and morbidity statistics.

Lung Function in Coal Miners

Although there is no substantial clinical effect of an increasing category of simple CWP on the ventilatory capacity of coal miners, most studies in which coal miners have been compared with a suitable reference population of nonminers have demonstrated a significant decrement in the ventilatory capacity of the miners (Higgins 1972). Regardless of radiographic evidence of simple CWP, FEV_1 of coal miners—or any other suitable index of ventilatory capacity—is generally reduced in comparison with FEV_1 of nonminers. This suggests that decrements in FEV_1 and simple CWP are both related to dust exposure, but the two measures represent separate biologic responses in the lung to the inhalation of coal dust.

Higgins studied three populations in the United Kingdom, all of which contained a significant proportion of miners and ex-miners, along with a comparable reference population. The areas chosen were Leigh, the Rhondda Fach, and Stavely (Higgins 1960; Cochrane et al. 1961). The reduction in the ventilatory capacity of miners that was observed could not be explained on the basis of cigarette smoking; indeed, coal miners at that time generally smoked less than nonminers. Since then, several other studies have found similar results and the data have been reviewed by Higgins (1972). Possible explanations for the observation that coal miners have a lower ventilatory capacity and that this finding is unrelated to radiographic findings are that (1) coal dust can produce or exacerbate emphysema or airway narrowing and that these changes occur independent of the changes that result in an abnormal radiograph, or (2) the lower ventilatory capacity in miners results from either industrial selection or differential migration. Thus, were the more healthy miners to leave their employment and move to other parts of the country to seek new jobs, those who remain would be less healthy and almost certainly have lower lung function. Although the second hypothesis is a consideration, especially during hard times when unemployment in the coal mines is high, recent studies have shown that it is the weaker and the less muscular man who is more likely to leave the coal mine within the first few months of his employment (McLintock 1971). Thus, the first hypothesis seems much more probable and requires further consideration.

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Emphysema, Exposure to Coal Dust, and Cigarette Smoking

The pathology associated with CWP, both simple and complicated, has been well described, and it is generally accepted that simple CWP has a relatively specific set of histological findings (College of American Pathologists 1979). Initially, dust starts to accumulate around the second division of respiratory bronchioles. As this occurs, there may be a little reticulin or, exceptionally, some collagenous fibrosis. Subsequently, the respiratory bronchiole dilates to form a condition known as focal emphysema. Gough (1947) and Heppleston (1947, 1954) suggested that this condition develops as a result of weakening and atrophy of the smooth muscle in the bronchiolar wall. The site at which focal emphysema develops is identical to that of the centrilobular emphysema found in cigarette smokers. Some researchers, however, believe that the focal emphysema of coal workers seldom extends to involve the gas-exchanging regions of the lung, namely, the respiratory bronchioles and alveoli (Heppleston 1972). Heppleston (1972) and Gough (1968), moreover, claimed to be able to distinguish focal emphysema from centrilobular emphysema, and suggested that the former is characterized by an absence of bronchiolitis in the smaller airways. Not all researchers accept these opinions (Cockcroft, Seal et al. 1982).

Dust exposure has long been associated with increasing severity of focal emphysema. Gough (1968) wrote that in a young coal miner with short exposure to dust, dying of accident or of nonpulmonary disease, there is an accumulation of coal dust specifically related to the terminal and respiratory bronchioles. The lungs can evidently withstand this deposition without harm for some years. Emphysema then develops, and in miners who have been exposed for 20 years, some degree of dilatation of the proximal order of the respiratory bronchiole is usual and may be marked. After 40 years of dust exposure, the majority of miners will show focal dust emphysema (FDE), although there is a surprising range in the quantity of dust deposited, and in the degree of emphysema, in miners working under similar conditions. FDE refers to dilatation of the respiratory bronchioles and there can be no doubt, because of the time sequence, that the dust deposition precedes the emphysema. Although Gough's remarks imply that there is a direct relationship between dust exposure and the development of focal emphysema, until recently his views were not entirely accepted. In a similar context, there is a clear-cut relationship between coal dust exposure and the development and progression of simple CWP (Jacobsen 1980).

Ryder and colleagues (1970) reported the results of a survey in which they correlated pathological, physiological, and radiological findings from the lungs of 247 deceased South Wales miners and ex-miners, most of whom had been diagnosed as suffering from coal workers' pneumoconiosis during life. The researchers were particu-

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larly concerned with the relationship of emphysema to dust exposure and to the radiological findings present antemortem in these subjects. A control series of autopsies was drawn from nonmining men autopsied at the same hospital and matched for age by decade. Whole lung sections were made and emphysema was quantified with standard techniques. Virtually all of the mining population had been examined by the Pneumoconiosis Panel during life, and most were receiving benefits. Post-mortem findings of emphysema were then related to clinical findings, ventilatory capacity measurements, and radiological findings. Emphysema was much more common among the disabled coal miners than among the control population of nonminers, but it is difficult to interpret this observation, as the miners were largely selected from among those who had respiratory disability and the control population was not selected in any similar way. They also found that miners with the punctate type of opacity were more likely to have emphysema than those with nodular or micronodular lesions. Lung function showed no correlation to progressive x-ray changes for simple pneumoconiosis, but declined with increasing severity of progressive massive fibrosis. The mean emphysema score increased with increasing age in the control population, but not in the miners. The absence of a relationship between emphysema score and age in the miners may be secondary to their having been selected (even at the younger ages) because they presented with respiratory disability. The mean emphysema score correlated well with antemortem measurements of FEV_1, but was not greater in those miners with categories B and C of progressive massive fibrosis than in miners with lesser degrees of radiologic change. The absence of smoking data in this population of disabled miners and the poor correlation of emphysema score with radiologic change makes it difficult to ascertain the relative contributions that cigarette smoking and coal dust exposure may have made to the emphysema found in this population.

A later publication on the same population of disabled miners (Lyons et al. 1972) included some smoking data. Lung function declined with increasing severity of radiologic progressive massive fibrosis, but actually improved with increasing severity of radiologic simple pneumoconiosis. This dichotomy of lung function and radiograph may be due to the selection of the autopsy population largely from those who had been disabled from pneumoconiosis in life, as the certification of disability may require more severe functional abnormalities in the absence of radiographic abnormalities than it would in the presence of advanced simple pneumoconiosis on the radiograph. They again showed a correlation of lower FEV_1 with increasing emphysema score, but not with the Reid index of bronchitis. Smokers had lower mean FEV_1 values than nonsmokers and ex-smokers among miners with simple pneumoconiosis and

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grade A PMF, but there was no difference in mean FEV_1 for smokers and nonsmokers among workers with more advanced PMF. The authors suggested that the emphysema is a more important determinant of ventilatory impairment than the radiograph and that the emphysema is due to coal dust in both simple pneumoconiosis and progressive massive fibrosis. However, they presented no data to evaluate the possibility that emphysematous change due to cigarette smoking may have been responsible for the link between emphysema score and lung function and for the absence of a correlation with the radiologic changes of pneumoconiosis.

Leigh and colleagues (1983) described the results of 886 post-mortem examinations of Australian miners, relating years spent underground at the coal face to bronchial gland wall ratio, the presence and extent of emphysema in the lungs, radiographic findings, and cigarette smoking history. Emphysema was related to years spent underground at the coal face and to radiological evidence of CWP. Radiological evidence of pneumoconiosis was negatively associated with smoking. Even more surprisingly, smoking was not correlated with gland wall ratio or emphysema. This absence of any relationship between cigarette smoking and emphysema is unique in the published literature and suggests a bias in the selection of subjects who underwent post-mortem examination or in the manner in which smoking habits were analyzed.

A relatively recent post-mortem study of coal miners and nonminers from South Wales compared the prevalence and extent of emphysema in subjects who had died of ischemic heart disease (Cockcroft, Berry et al. 1982). A greater percentage of smokers and ex-smokers had emphysema (17/34) than never smokers (1/5) among the coal miners, but there were too few cases of emphysema among the nonminers to compare smokers and nonsmokers. Coal miners were noted to have more emphysema than nonminers, but the frequency of emphysema in the control population was very low. While the degree of emphysema in these subjects was quantitated in the absence of knowledge of the deceased subject's occupation, the characteristic features of coal miners' lungs (i.e., the formation of macules and the presence of pigment and the accompanying focal emphysema) would invariably indicate the deceased subject's occupation during life. There was a legal requirement for a post-mortem examination for coal miners. Whether the pigment present also highlighted and accentuated the emphysema is unknown.

Ruckley and colleagues (1984) examined the lungs of 460 British coal miners at post-mortem examination for signs of dust-related fibrosis and emphysema. Smoking habits had been determined previously by questionnaire. The prevalence of emphysema was 9 percent in the nonsmoking miners whose lungs showed only circumscribed dust accumulations of which any solid center was less

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than 1 mm in size, 33 percent in nonsmoking miners with lungs showing one or more palpable lesions between 1 and 10 mm in size, and 75 percent in nonsmokers with PMF. The corresponding prevalences of emphysema among smokers with similar pathologic findings were 52.7 percent, 70.3 percent, and 85.3 percent, respectively. Ex-smokers generally had intermediate percentages. The percentage of the population with any emphysema increased with the increasing content of dust in the lung, but the percentage of the population with more than one-third of the lung affected showed no increase with increasing concentration of dust in the lung. These data suggest that both smoking and coal dust contribute to emphysema, but that extensive emphysematous change is more closely related to extent of cigarette smoking.

Morgan and colleagues (1971) examined lung volumes in coal miners and showed that both cigarette smoking and increasing simple CWP grade increased the TLC and RV, and the effects appeared to be additive. This suggests that simple coal workers' pneumoconiosis is associated with a slight loss of the elastic recoil. Such an observation is best explained by the presence of so-called focal dust emphysema (FDE).

In summary, there is little doubt that simple CWP and dust exposure may lead to the development of focal dust emphysema. The type of emphysema seen in coal miners is probably still best referred to as focal dust emphysema, since there is some evidence that it does not progress to severe centrilobular emphysema (Ruckley et al. 1984) in the absence of cigarette smoking. Whether a morbid anatomical distinction between the two conditions is possible is not certain.

Studies of right ventricular function in coal miners and ex-miners both during life and at post-mortem examination (Morgan and Seaton 1984) have shown that cor pulmonale or right ventricular hypertrophy do not occur except in cigarette smokers or in miners who have PMF (Fernie et al. 1983).

Dust Exposure, Cigarette Smoking, and Ventilatory Function

In a long-term prospective study of 3,581 miners who worked at the coal face, Rogan and colleagues (1973) showed that dust exposure was inversely related to ventilatory capacity. Lifetime cumulative exposures to coal dust were available. The researchers were able to demonstrate a progressive reduction in ventilatory capacity with increasing exposure to dust. The presence of pneumoconiosis was not associated with an additional decrement of ventilatory capacity beyond that due to cumulative dust exposure, smoking habits, and stature. Smokers showed a more rapid decline in FEV_1 than nonsmokers, but an effect of cumulative dust exposure was apparent in both smoking and nonsmoking miners. Among the nonsmokers,

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FEV_1 was generally lower in the most dust-exposed group than in the low exposure group, but the rate of decline per year remained the same from age 30 to age 60 in both exposure groups. The age-related regression coefficients were the same in the heavily and lightly dust-exposed nonsmokers. Subjects with PMF were excluded from the analysis. Among smokers, the rate of decline in FEV_1 with age was greater than for the nonsmokers in each exposure category, but the absolute FEV_1 in smokers at a given age was uniformly lower for the group with high dust exposure than the group with low dust exposure.

Kibelstis and colleagues (1973) were also able to demonstrate a slight effect of dust exposure on the ventilatory capacity of their nonsmoking miners. These investigators divided their population according to whether the men had worked at the face, in transportation, in miscellaneous other jobs, or on the surface. Dust measurements performed for these various jobs and work places had shown a gradient, with the greatest exposure at the coal face and least on the surface (Doyle 1970). Nevertheless, individual cumulative dust exposure measurements were not available for the subjects. When the nonsmoking coal face workers were compared with the nonsmoking surface workers, there was a slight but significant difference in FEV_1. Thus, the coal face workers had an FEV_1 of 98 percent of the predicted value; that of the surface workers was 102.4 percent. The difference in FEV_1 for the smoking and the nonsmoking coal face workers was 6 percent; the difference between the smoking surface workers and the nonsmoking surface workers was 10.5 percent. The effects of cigarette smoking were therefore substantially larger than those of dust exposure. Among the ex-smokers and nonsmokers, there was a significant difference in function between coal face workers and transportation workers and their counterparts who worked on the surface. Among the smokers, no such difference was present, with smoking apparently overwhelming the effects of dust. Airways obstruction was three times more common in the smokers than in the nonsmokers.

An extensive West German study of 6,700 workers employed in coal mines, steel works, cement works, asbestos factories, and other heavy industry related dust exposure to smoking habits and other factors (Deutsche Forschungsgemeinschaft 1978). Each subject underwent a clinical examination, chest radiograph, and spirometry along with measurements of airways resistance and arterial blood gas analyses. The study showed that the most important factors related to the prevalence of bronchitis and airways obstruction were age and smoking habits. Among younger workers, there seemed to be an additive effect of smoking, age, and dust, with the combined effect of all three equaling the sum of their separate effects. Among older

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workers, smoking appeared to play a relatively greater role in the production of airways obstruction.

Hankinson and colleagues (1977) characterized the physiological impairments that are associated with the inhalation of coal dust and cigarette smoke. This study relied on flow volume curves as a method of assessing ventilatory capacity, but in addition to the standard spirometric measurements, lung volumes were calculated by a radiological method using posteroanterior and lateral chest films. Since TLC could be calculated, it was possible to express the flow rates, not only as a percentage of vital capacity (VC) but also at absolute lung volumes. Four age- and height-matched groups were selected on the basis of their smoking history and on the presence of bronchitis, that is, cough and sputum. Thus the four groups consisted of smokers with bronchitis, smokers without bronchitis, nonsmokers with bronchitis, and nonsmokers without bronchitis. Flow-volume curves of the four groups are shown in Figures 1 and 2. The differences between the four groups reveal that cigarette smoking effects the flows at all lung volumes. In contrast, nonsmoking bronchitics for the most part showed decreased flows at high lung volumes, although there was some mean reduction in flows at lower lung volumes, indicating that the small airways were not entirely spared. When the flows were expressed at absolute lung volumes, it became evident that smokers had an increased RV and an increased TLC. In contrast, the nonsmoking subjects with and without bronchitis had a normal TLC and RV. The increased TLC suggests a loss of retractive forces in the lung and the presence of subclinical emphysema. Bronchitis in nonsmoking subjects was not associated with an increase in TLC.

A number of longitudinal studies have been carried out with groups of coal miners. Love and Miller (1982) followed 1,677 men from five British collieries for 11 years. Loss of FEV_1 was found to increase with cumulative dust exposure, after allowing for age, smoking, and colliery effect. The investigators classified smoking according to the smoking status that was recorded in all three surveys, that is, as nonsmokers, ex-smokers, or current smokers. Miners who were recorded as smokers at the first survey and as ex-smokers at the second and third surveys were designated as intermittent smokers. According to Love and Miller (1982), the average decrement in FEV_1 from the effects of dust was about one-third of that due to smoking. They further stated that if men left the industry because of ill health and respiratory impairment, the average loss of FEV_1 would have been underestimated. This could apply to men who retired from the workforce because of the effects of dust, cigarette smoking, or both in combination.

There are several problems with this study. First, only 1,677 subjects were studied, 29 percent of the population of 6,191 in the

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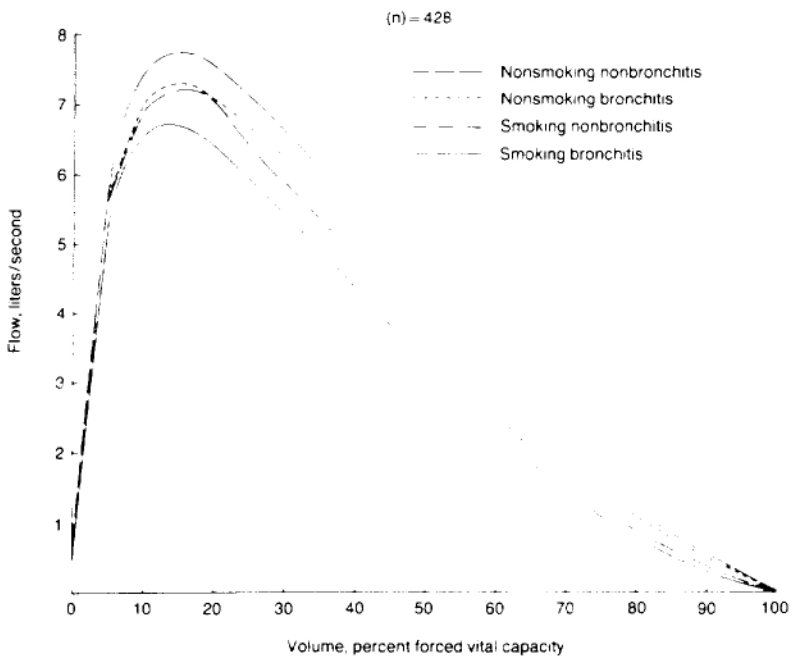


FIGURE 1.—Mean flow volume curves expressed as percentage of forced vital capacity

SOURCE: Hankinson et al. (1977)

first survey. No data were provided to establish that the 1,677 survivors had similar characteristics to the original 6,191 subjects. It is essential to know that the ventilatory capacities, age, height, and smoking habits of the survivors did not differ from those of the original cohort. Second, no quantification of smoking was available. FEV_1 was regressed against age, regular smoking habit, and dust. Unfortunately, smoking was treated as an unchanging variable such as height, although Fletcher and colleagues (1976) had shown that the effects of cigarette smoking increase with pack-years. Similarly, Kibelstis and colleagues (1973) showed that while cough and sputum relate well to current smoking habits, pack-years are a better predictor of the prevalence of airways obstruction.

Attfield (1985) examined changes in ventilatory function among smoking and nonsmoking miners in the United States. They recorded the decline in FEV_1 over an 11-year period in a group of 1,072 U.S. miners. Over that time the loss in FEV_1 was 0.1 L more in

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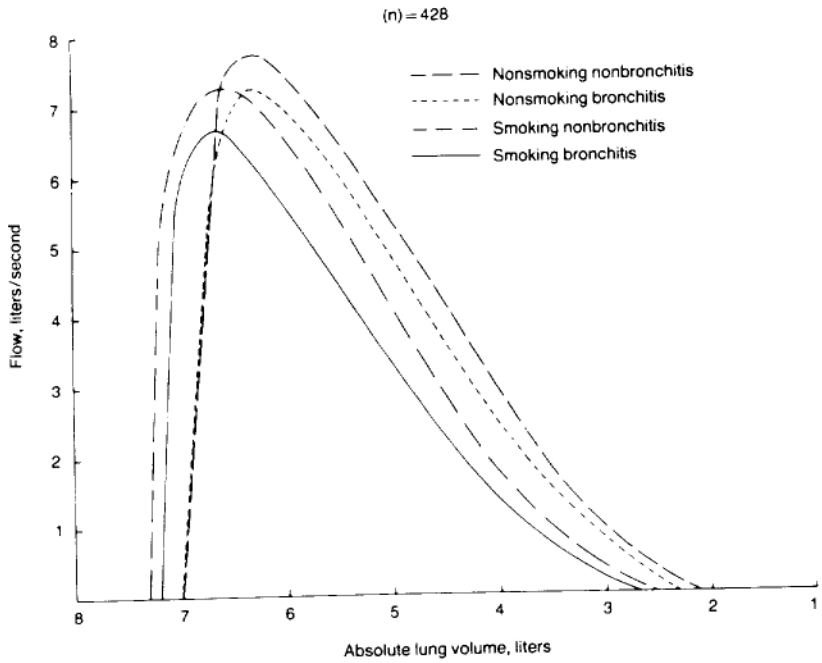


FIGURE 2.—Mean flow volume curves expressed as absolute lung volumes

SOURCE: Hankinson et al. (1977).

the smoking miners than in the nonsmoking miners, in a multiple regression model. The effect of coal dust exposure over the 11-year period ranged from 0.036 to 0.084 L, depending on the regression model used for the coal dust exposure.

The relative importance of cigarette smoking versus dust and other factors in occupational lung disease has been reviewed by Elmes (1981). He concluded that while control of occupational exposure to coal dust remains critical, substantial future improvement in respiratory health can be achieved by reducing the prevalence of smoking among miners.

Summary and Conclusions

1. Coal dust exposure is clearly the major etiologic factor in the production of the radiologic changes of coal workers' pneumoconiosis (CWP). Cigarette smoking probably increases the prevalence of irregular opacities on the chest roentgenograms

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of smoking coal miners, but appears to have little effect on the prevalence of small rounded opacities or complicated CWP.

2. Increasing category of simple radiologic CWP is not associated with increasing airflow obstruction, but increasing coal dust exposure is associated with increasing airflow obstruction in both smokers and nonsmokers.
3. Since the introduction of more effective controls to reduce the levels of coal dust exposure at the worksite, cigarette smoking has become the more significant contributor to reported cases of disabling airflow obstruction among coal miners.
4. Cigarette smoking and coal dust exposure appear to have an independent and additive effect on the prevalence of chronic cough and phlegm.
5. Increasing coal dust exposure is associated with a form of emphysema known as focal dust emphysema, but there is no definite evidence that extensive centrilobular emphysema occurs in the absence of cigarette smoking.
6. The majority of studies have shown that coal dust exposure is not associated with an increased risk for lung cancer.
7. Reduction in the levels of coal dust exposure is the only method available to reduce the prevalence of simple or complicated CWP. However, the prevalence of ventilatory disabilities in coal miners could be substantially reduced by reducing the prevalence of cigarette smoking, and efforts aimed at reducing ventilatory disability should include efforts to enhance successful smoking cessation.

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CHAPTER 8

SILICA-EXPOSED WORKERS

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Silica Exposure

The oxides of silicon (SiO_2) are found in a number of polymorphic structures consisting of three-dimensional networks of silica tetrahedra (Zoltai and Stout 1984). When SiO_2 is bound with cations, it is considered to be "combined" silica. When not combined, it exists in its "free" forms—polymorphic crystalline, cryptocrystalline (minute crystals), and amorphous (noncrystalline) (Parkes 1982). Whether SiO_2 is in a free form is important from the standpoint of occupational toxicity. The crystalline phases of SiO_2, including quartz, tridymite, and cristobalite, are recognized as causative agents in silicosis. Diatomite tends to form amorphous silica, and crystalline lenses are found in diatomaceous earth deposits. Diatomite is converted to the biologically active cristobalite with calcining at temperatures from 1000° C to 1723° C (Parkes 1982).

Occupational exposures to free silica are diverse. Major industries with recognized significant silica exposures include metal mining, coal mining, and nonmetallic mineral extraction, stone, clay, and glass processing, iron and steel foundries, and nonferrous foundries. A more complete listing of occupations with potential exposure to silica is found in Table 1. Some of these exposures, including silica flour production and use, sandblasting and certain mining, quarrying and tunneling operations, result in exposure predominantly to silica. However, many silica exposures, including most mining operations and foundry exposures, are mixed-dust exposures, which has implications for the type and extent of biological response seen among exposed workers.

A general pattern of noncompliance with the current permissible exposure limit (PEL) for free silica has been documented in recent papers appearing in the American medical literature. These reports have included the Occupational Safety and Health Administration (OSHA) compliance data for 205 foundries in which 40.6 percent of samples exceeded the PEL (Oudiz et al. 1983); OSHA data showing a 53 percent rate of noncompliance with the silica PEL in 27 silica flour mills (Banks, Morring, Boehlecke 1981; Banks, Morring, Boehlecke et al. 1981); and gross excesses (greater than hundredfold) of the silica standard in sandblasting operations, which remain a poorly regulated industrial process in the United States but are banned in several other developed countries (Samimi et al. 1974).

Population at Risk

Estimates of the population at risk for potential silica exposure are available from the National Institute for Occupational Safety and Health (NIOSH) National Occupational Hazard Survey, which was based on a probability sample of 5,000 industries between 1972 and 1974 (NIOSH 1978). From these survey results, NIOSH estimated

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TABLE 1.—Occupations with potential exposure to silica

Abrasive blasters	Oil purifiers
Abrasive makers	Oilstone workers
Auto garage workers	Optical equipment makers
Bisque-kiln workers	Paint mixers
Brick layers	Polishing soap makers
Buffers	Porcelain workers
Burhstone workers	Pottery workers
Carborundum makers	Pouncers (felt hat)
Casting cleaners (foundry)	Pulpstone workers
Cement makers	Quarry workers
Cement mixers	Quartz workers
Ceramic workers	Refractory makers
Chemical glass makers	Road constructors
Chippers	Rock crushers
Coal miners	Rock cutters
Construct workers	Rock drillers
Cosmetic makers	Rock grinders
Cutlery makers	Rock screeners
Diatomaceous earth calciners	Rubber compound mixers
Electronic equipment makers	Sand cutters
Enamellers	Sand pulverizers
Fertilizer makers	Sand blasters
Flint workers	Sandpaper makers
Foundry workers	Sandstone grinders
Furnace liners	Sawyers
Fused quartz workers	Scouring soap workers
Glass makers	Silica brick workers
Glaze mixers (pottery)	Silicon alloy makers
Granite cutters	Silver polishers
Granite workers	Slate workers
Grinding wheel makers	Smelters
Grindstone workers	Sodium silicate makers
Hard rock miners	Spacecraft workers
Insecticide makers	Stone bedrubbers
Insulators	Stone cutters
Jewelers	Stone planners
Jute workers	Street sweepers
Kiln liners	Subway construction workers
Masons	Tile makers
Metal buffers	Toothpaste makers
Metal burnishers	Tube mill liners
Metal polishers	Tumbline barrel workers
Miners	Tunnel construction workers
Mortar mixers	Whetstone workers
Mortarmen	Wood filler workers

SOURCE: Aspen Systems (1978).

that 3,200,000 active workers in 238,000 plants were potentially exposed to silica; however, this estimate was based on workers in an area where free silica is used, and the number of workers with clinically significant exposures would be appreciably lower. This estimate excluded former workers who were retired, working elsewhere, or disabled and the large industrial sector of agriculture where some silica dust exposure occurs (Popendorf et al. 1982).

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Significant physical factors for occupational respiratory disease risk include the percentage of free silica, the respirable fraction of the mineral dust (which may have a higher silica content (Ayer et al. 1973)), and the concentration of dust (total and respirable) in the worker's breathing zone. In addition, other workplace contaminants may combine with silica particles to alter the toxicity of the given mineral dust exposure. Individual factors such as pulmonary deposition and clearance, atopic status, genetic constitution, and immune response may also be important risk factors in silica-related disease; however, they are sometimes difficult to measure and have been less well studied. Hence, studies of workers exposed to silica must provide clear documentation of the exposures in the workplace as well as documentation of other personal and environmental factors that may influence biological response.

Smoking Behavior of Silica-Exposed Workers

The smoking behavior of workers in a variety of settings where silica exposure can occur is detailed in Table 2. These studies in the United States and abroad indicate that a very large proportion of people who are exposed to silica are also smokers.

Definitions of Health Effects

Several health effects are associated with occupational exposure to silica dust. The causal role silica plays in some disease responses, namely silicosis and silica-induced alveolar lipoproteinosis ("acute silicosis"), is quite clear and widely accepted. Silica is recognized as playing an important causal contributing role in a second group of pulmonary responses—silicotuberculosis, mixed-dust fibrosis (usually mixed with iron oxides), and the fibrosing alveolitis arising from exposure to calcined diatomaceous earth (diatomite pneumoconiosis) (Parkes 1982). Smoking appears to play no significant causal role in the etiology of the first two categories of silica-induced diseases. In a third group of health effects, silica dust appears to be a risk factor in simple chronic bronchitis as characterized by mucus hypersecretion and in chronic airways obstruction, which is often associated with a progressive decline in expiratory flow rates and is largely irreversible. This last group of pulmonary responses is nonspecific, recognized to be multifactorial and causally linked to cigarette smoking. A causal relationship between silica dust and chronic bronchitis or chronic airways obstruction is less clear. This issue is of considerable importance because of the prevalence of chronic bronchitis and chronic airways obstruction in modern society and the large size of the population at potential risk of silica exposure.

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TABLE 2.—Smoking characteristics of silica-exposed workers

Study	Number and type of population		Smoking characteristics (percent)			Comments
Prowse (1970)	240 gold miners, South Africa		SM 57	EX* 30	NS 12	* Not smoked in last 6 months
Brinkman et al. (1972)	301 automotive industry workers, aged 40–65		SM 65.8	NS/EX 34.2		
		Light (1–200)* Moderate (201–600) Heavy (≥600)	11 22.3 32.5			* Numerical rating of cigs/day × years smoked
Sluis-Cremer (1972)	Men exposed to dust, Carletonville, South Africa	Exposed workers Nonexposed workers	70 60.7	30 39.3		
Theriault et al. (3 papers) (1974)	792 granite workers, Vermont		SM 60.4	EX 25.6	NS 13.9	
Armstrong et al. (1979)	Coal and gold miners, Australia		SM	NS/EX		
		Gold miners	66.3	33.7		
Rom et al. (1983)	Trona miners, Wyoming		42.8	33.6	23.6	

NOTE: SM = Smoker; EX = Ex-smoker; NS = Nonsmoker.

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Epidemiological Findings

Early observers of occupational diseases, including Ramazzini in 1713 (1964), wrote about the respiratory problems of miners and stone cutters, and recognized silicosis among miners, stone cutters or hewers, and potters. Silicosis, and its previously described associated health effects, have been given a variety of names that reflect the several faces of silica exposure—dust consumption, ganister disease, grinders' asthma, grinders' consumption, grinders' rot, grit consumption, masons' disease, miners' asthma, miners' phthisis, potters' rot, rock tuberculosis, stonehewers' phthisis, and stonemasons' disease (Hunter 1955). Greenhow (1878), in his treatise on bronchitis, recognized that "irritants which act immediately upon the bronchial membrane may produce inflammation by means of either mechanical or chemical irritation. Fine coal and metal dust, stone and porcelain grit, and even the flue of cotton wool . . . inhaled into the lungs during various industrial processes are all of them mechanical irritants which become fruitful causes of bronchitis in certain classes of operatives" (p. 30).

Mortality studies of silica-exposed cohorts have consistently shown increased mortality rates for tuberculosis and nonmalignant respiratory disease, largely accounted for by silicosis (Guralnick 1962; Registrar General 1958, 1978; Davis et al. 1983; Armstrong et al. 1979; McDonald et al. 1978; Fox et al. 1981). Although none of these studies accounted for the effects of smoking, the consistency and magnitude of the increased rates suggest a causal relationship between silica exposure and these cause-specific mortality rates. Davis and colleagues (1983) demonstrated dose–response relationships between exposure category, tuberculosis, and silicosis, but found no excess mortality from bronchitis and pneumonia. Finkelstein and colleagues (1982) investigated mortality among 1,190 Ontario miners receiving compensation awards for silicosis and found nonmalignant respiratory disease (excluding tuberculosis) to be the most frequent cause of death (standard mortality rate, 765).

NIOSH recently assessed causes of disability among employees of the mining industry, based on the Social Security Disability Benefit Awards and Allowances to Workers for 1969–1973 and 1975–1976 (Osborne and Fischbach 1985). The observed proportional morbidity rate (PMR) for pneumoconiosis from silica and silicates (they were not distinguished) was found to be somewhat higher (4,894) than for other mining occupations. Workers employed in boring, drilling, and cutting jobs appeared to experience increased disability from respiratory diseases, specifically pneumoconiosis including silicosis. These findings, based on somewhat more recent exposures than the previously cited mortality studies, confirm the major mortality findings, but suffer from the same methodological problems. Again, smoking data were not available or analyzed, and it is recognized

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that those disabled in the mid-1970s very likely were exposed to silica three or four decades previously; therefore, their disabilities reflected previous dust exposures.

Early morbidity studies of workers exposed to silica dust focused on rates of sickness, respiratory symptoms, and physical findings, supplemented in the 1920s with chest radiography. The U.S. Public Health Service (US PHS) conducted the first major U.S. silicosis study of the hard-rock mining industry in 1913–1915 (Higgins et al. 1917; Lanza and Higgins 1915). Their studies reported that 60.4 percent of the 720 miners examined suffered from pulmonary diseases attributable to mine rock-dust exposure. Dust samples collected with a Draeger liter bag–granulated sugar filter apparatus were reported to average from 30 to 50 mg/m^3 (Higgins et al. 1917). Although these concentrations would appear to be quite high, they are difficult to interpret according to modern-day respirable dust sampling and analysis (x-ray diffraction for free silica content).

Subsequent US PHS silica studies included Harrington and Lanza's (1921) 1916–1919 study of copper miners in Butte, Montana, in which 42.4 percent were judged to have some dust-induced lung injury and 25.5 percent to have advanced disease. Dreessen and colleagues (1942) studied 727 metal miners in 1939, and Flinn and colleagues (1963) studied 67 underground mines employing 20,500 miners from 1958 to 1961, but found varying silicosis prevalence from mine to mine and widely divergent exposures to free silica. The silicosis prevalences of 9.1 percent and 3.4 percent, respectively, were found to be associated with longer duration of exposure and especially with face work exposures (Dreessen et al. 1942; Flinn et al. 1963). Earlier, Flinn and colleagues (1939) had reported an important study (1936–1937) of West Virginia potteries that included 2,516 workers with an overall silicosis prevalence of 7.8 percent. Free silica content ranged from 1 to 39 percent, dust concentrations varied from 3 to 440 million particles per cubic foot (mppcf), and mean particle diameters were judged to be 1.2 μm (but without data on the concentration of respirable dust). A strong dose–response relationship between dust concentration, duration of pottery exposure, and silicosis prevalence was documented. It was suggested that no new cases of silicosis would occur if dust concentrations in this industry were brought below 4 mppcf. Renes and colleagues (1950) studied 18 ferrous foundries in 1948–1949, and found 9.2 percent of 1,937 foundrymen to have pulmonary fibrosis. Free silica content averaged 30 percent, with a mean particle size of 3 μm, and 82 percent of the samples had levels below 6.9 mppcf. Mechanical shakeout operations were found to have the highest dust concentrations (10 to 75 mppcf), and silicosis was noted to be more prevalent among foundrymen with 20 or more years of exposure. It was suggested that conditions had improved in foundries and that most of the pulmonary fibrosis was

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due to previous exposures. Early studies of the refractory (silica) brick industry documented high percentages of free silica, often in the form of cristobalite and tridymite from burned bricks. Keatinge and Potter (1949) and Fulton and colleagues (1941) studied 1,035 exposed workers in this industry, finding 52 percent to have some stage of silicosis. A relationship with dust concentration and duration of exposure was again documented, as was an apparent increased risk among men exposed to burned brick dust (Keatinge and Potter 1949; Fulton et al. 1941).

Epidemiological studies of workers in the Vermont granite industry have provided an important and interesting chronology of data on the natural history of silica-associated respiratory diseases. Early US PHS studies of this industry (Russell et al. 1929) documented high dust concentrations (37 to 59 mppcf) and a very high prevalence of silicosis. On the basis of dust with a free silica content of 35 percent, a presumptive "safe limit" of dustiness was suggested to lie between 9 and 20 mppcf. A subsequent US PHS study (Russell 1941) essentially confirmed the findings of the original study, noted an increased progression of silicosis among the highly exposed cutters, and concluded that a limit below 10 mppcf for this industry would be desirable. Subsequent followup studies in 1955 by the US PHS and the Vermont State Board of Health (Hosey et al. 1957) found that the prevalence of silicosis had decreased from 45 percent in 1937–1938 to 15 percent in 1956, that the silica content of the dust averaged a somewhat lower 22 to 25 percent free silica, and that nearly all workers with silicosis had been exposed prior to implementation of dust controls in 1937. This report was consistent with an earlier report by Ashe (1955), and was subsequently supported by a further followup study by Ashe and Bergstrom (1965), which reported no cases of silicosis among 1,478 granite workers employed after 1937, and a study by Davis and colleagues (1983) that reported only one case in the same population.

All of these early studies of silica exposure concentrated on radiographic evidence of silicosis and tuberculosis and the association with silica content and concentration. These studies formed the basis for environmental control of silica exposures, demonstrated the effectiveness of dust control, and provided a widely held impression that silica exposures, and hence disease arising from silica exposures, were well controlled.

Beginning in the 1950s, British epidemiologists introduced standardized respiratory questionnaires, field spirometry, and sound epidemiological methodology to the study of bronchitis and chronic obstructive lung disease, and were the first to use these methods to assess respiratory effects among industrial workers. This allowed assessment of other risk factors, including cigarette smoking, and quantitation of major risk factors compared with appropriate

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reference populations. At the same time, on the basis of clinical case series, it was becoming clear that bronchitis and nonspecific airways obstruction were more common than pneumoconiosis among workers exposed to coal mine dust and silica dust. The significance of these health effects was not clear. Modern epidemiological studies began with the Higgins and colleagues (1959) investigation of Stavely, an English industrial town of 18,000 and home to a significant number of coal miners and foundry workers. This study and other cross-sectional studies of silica exposure that have assessed standardized respiratory symptoms, lung function, smoking, and occupation (only those with non-coal-mining silica exposures) are summarized in Table 3.

Review of these studies has found them to be heterogeneous in regard to workforce composition, free silica content and dust concentration (if reported), and other associated occupational exposures that may contribute to respiratory symptoms and declines in lung function. In some instances associated occupational exposures other than silica dust appear to be as important or more important than silica dust (Higgins et al. 1959; Gamble et al. 1979; Manfreda et al. 1982; Graham et al. 1984). Two of these studies found lung function to be somewhat better among exposed workers than among reference subjects (Clark et al. 1980; Graham et al. 1984). However, in both of these studies, one of potash miners and one of taconite miners, it is very likely that the free silica exposure, although not documented, was low. One study of fluorspar miners (Parsons et al. 1964) and one of copper miners (Federspiel et al. 1980) suggest a significant dust effect on bronchitis prevalence and a somewhat lower lung function among exposed miners. Specific environmental data on free silica content or dust concentration were not provided in either study, although most likely some of the dust exposure in these mines was silica.

Four of the studies reviewed in Table 3 have documented significant exposures to free silica with the relative absence of other exposures: the Welsh slate workers study (Glover et al. 1980), the Vermont granite workers study (Theriault, Burgess et al. 1974; Theriault, Peters, Fine 1974; Theriault, Peters, Johnson 1974) and two studies of South African gold miners (Sluis-Cremer et al. 1967; Wiles and Faure 1977). Silicosis was reported in all four study populations, ranging from 5 to 33 percent. Sluis-Cremer and colleagues (1967) surveyed the prevalence of chronic bronchitis in a mixed mining and nonmining population in Carletonville on the Witwatersrand, South Africa. Chronic bronchitis was more common among miners who smoked than among nonminers who smoked, but there were no significant differences in prevalence of bronchitis between miners and nonminers who did not smoke. The prevalence of bronchitis was substantially higher among smokers than among

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TABLE 3.—Major cross-sectional studies of workers occupationally exposed to silica

Study, country	Number and type of population	Age (mean or range)	Bronchitis (ratio)		Lung function						Pneumoconiosis (percent)	Comment
			S/NS	Exp/Not	S	NS	Δ	Exp	Not	Δ		
Higgins et al. (1959), United Kingdom	Current and ex-foundry workers; 105 exposed, 81 nondusty occupations	55 to 64	Not available for foundry workers alone	1.2	Not available for foundry workers alone			82.1 (Indirect MBC based on $FEV_{75\%}$)	90	-7.9	14.0	Foundry workers both "pure" with free silica exposure and "mixed" with chemical fumes (HCl, H_2SO_4, caustic soda, and benzol) and other dusts; increased respiratory symptoms and decreased lung function mainly in "mixed" foundry workers suggests other dusts and fumes likely more important than "pure" foundry work
Parsons et al. (1964), Canada	Fluorspar mining; 301 exposed, 56 controls	38.8 (20 to 70)	Not available	5.5	Generally higher for nonminers; decreased lung function in chronic bronchitic men appears more important than dust category (based on indirect MBC, MMF, PFR)						1.93	No specific SiO_2 exposures or dust measurements available; exposure determined from job category and tenure
Sluis-Cremer et al. (1967), South Africa	Gold mining; 562 exposed, 265 community controls	35 and older	1.8	1.22	Not studied						5	Free silica content range 50–70%, but generally low dust levels; smoking somewhat more common among miners; significant increase in chronic bronchitis prevalence among smoking and ex-smoking but not nonsmoking miners suggests possible interaction between smoking and "underground aerial pollution"

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TABLE 3.—Continued

Study, country	Number and type of population	Age (mean or range)	Bronchitis (ratio)		Lung function						Pneumoconiosis (percent)	Comment
			S/NS	Exp/Not	S	NS	Δ	Exp	Not	Δ		
Higgins et al. (1968), United Kingdom	80 foundry workers, 100 "nondusty" workers	25 to 34	Not reported	Not reported	Not reported separately for foundrymen			3.49	3.55	−.06	23.1	No environmental measurements, but typical SiO_2 foundry exposures; 9-year followup mortality higher among foundry workers than others, appreciably higher among foundry workers with silicosis
	43 foundry workers, 52 "nondusty" workers	55 to 64[1]						2.27 ($FEV_{75\%}$)	2.36	−.09		
Theriault et al. (3 papers) (1974), United States	792 granite workers	44	Not reported	Not reported	4.2 (FVC)	4.1	+.10	4.2	4.1	+.10	31	Single "A" radiograph reader; dose–response relationship between FVC and granite dust and quartz dust; 2 mL FVC/dust-year decline, 9 mL FVC/smoking-year decline
	189 marble workers	47										
Wiles and Faure (1977), South Africa	2,209 gold miners with ≥10 years' service	45 to 54	2.3	5.3 (low dust vs. high dust categories)	2.53	3.77 (MMEF)	−1.24	3.60	3.84 (low dust vs. high dust categories)	−.24	6.7	70–250 particles/cm^3 dust counts; 75% free SiO_2; significant dust exposure/chronic bronchitis dose–response relationship in all smoking categories; much stronger smoking effect on lung function, but no dose–response relationship

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TABLE 3.—Continued

Study, country	Number and type of population	Age (mean or range)	Bronchitis (ratio)		Lung function						Pneumoconiosis (percent)	Comment
			S/NS	Exp/Not	S	NS	Δ	Exp	Not	Δ		
Gamble et al. (1979), United States	121 talc miners	39.7	3.5	1.2	3.74	4.13	−.39	3.68	3.84	−.14	2.2 talc, .007 potash	20–40 μg/m³ free silica; 0.23–2.96 mg/m³ respirable dust; anthophyllite, tremolite, and crysotile asbestos fibers found; 17/24 jobs >2f/cc; decreased lung function and pleural thickening significantly associated
	1,077 potash miners (reference group)	39.2				(FEV_1)						
Clark et al. (1980), United States	240 iron ore miners, ≥20 years underground	49.3	None among nonsmoking miners reported	1.0	@78.5	81.4	−2.9	@81.4	80.0	+1.4	< 2	Taconite has iron, quartz, and numerous silicates, esp. grunerite-cummingtonite; 25–40% total dust quartz; significant smoking effect, no dust effect on lung function
	86 not exposed	50.1				(FEV_1/FVC)						
Federspiel et al. (1980), United States	133 surface workers	Not given	@8.4	None among nonsmoking nonminers	@85.5	92.5	−7.0	@92.5	98.0	−5.5	Not reported	No dust level or SiO_2% data; no SO_2 miner exposure, little or no surface worker SO_2 exposure; mining and smoking additive effect on bronchitis; significantly reduced nonsmoking miner FEV_1 and FVC and smoking miner FVC
	112 copper miners					(FEV_1)						

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TABLE 3.—Continued

Study, country	Number and type of population	Age (mean or range)	Bronchitis (ratio)		Lung function						Pneumoconiosis (percent)	Comment
			S/NS	Exp/Not	S	NS	Δ	Exp	Not	Δ		
Glover et al. (1980), United Kingdom	725 slate workers 530 nonexposed	≥18 ≥30	1.8	4.4	3.06 (FEV_1)	3.23	−.17	3.23	3.53	−.30	33	13–32% respirable quartz in respirable dust; no smoking category/radiographic opacity association; no dust concentrations available, but thought "high"; respiratory symptoms dependent on pneumonconiosis category per multiple regression, except nonsmokers with previous TB (in 40–50% of slate workers age >55)
Manfreda et al. (1982), Canada	241 hardrock miners 382 nonexposed men (community sample)	25 to 54	9.0	9.5	23	7	+16	0	7	−7	<1	Zinc, copper, nickel mining study; 6–9% silica in dust, 20–25% >TLV; some underground worker (95) NO_2 exposure, some smelter worker (107) SO_2 exposure (10% >TLV); low surface worker (39) dust exposure; nonsmoking miner bronchitis significantly increased; significantly reduced lung function in smelter workers, not miners; probable selection processes noted
					(Prevalence of FEV_1 abnormalities based on 95th percentile of nonsmoking general population)							

NOTE: Bronchitis ratios and lung function comparisons are of nonexposed smokers (S) and nonsmokers (NS) to assess smoking effect and of nonsmoking exposed workers (Exp) and nonexposed workers (Not) to assess exposure effect. Combined smoking and exposure effects are not shown, but are addressed under comment.

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nonsmokers in both the dust-exposed and the nonexposed populations. Evaluation of Vermont granite shed workers (Theriault, Burgess et al. 1974; Theriault, Peters, Fine 1974; Theriault, Peters, Johnson 1974) revealed that both smoking and cumulative dust exposure contributed to the differences in FVC and FEV_1 among these workers, but the effect of smoking was larger than the effect of dust exposure, using a multiple regression technique. A dose–response relationship between silica dust exposure and decreased lung function was demonstrated in both the Vermont granite shed workers and the South African gold miners (Wiles and Faure 1977). Glover and colleagues (1980) examined 725 workers and former workers from the slate mines and quarries of North Wales and 530 men from the same area who had never been exposed. The prevalence of chronic cough ranged from 5.2 percent in the nonsmokers not exposed to dust to 19.4 percent in the nonsmokers with dust exposure. Smokers with no exposure to dust had a prevalence of cough of 27.5 percent; the prevalence was 38.9 percent among the smokers with dust exposure. FEV_1 (standardized to a fixed height) was lower in the smokers than in the nonsmokers. The dust-exposed nonsmoking workers had a lower mean FEV_1, but the values for the dust-exposed and the nonexposed smokers were similar. The regression coefficients for FEV_1 with age were 20 mL per year in the nonexposed nonsmokers and 38 mL per year in the dust-exposed nonsmokers, but the coefficients for smokers were similar between the dust-exposed (40 mL/year) and nonexposed (46 mL/year) men. The absence of an effect of dust exposure among the smokers in some of these studies may be the result of the cessation of smoking by those workers with declining lung function, as suggested by the observation that the mean FEV_1 and regression coefficient for decline in FEV_1 with age among slate workers was worse in ex-smokers than in either current smokers or nonsmokers. In contrast, the values for ex-smokers in the general population were between those for smokers and those for nonsmokers.

Only a few prospective studies of silica-exposed workers have been reported in the literature. Four of these studies are summarized in Table 4 (Higgins et al. 1968; Pham et al. 1979; Kauffmann et al. 1982; Manfreda et al. 1984). Two other prospective studies of silica-exposed workers are not included in this table because of methodological questions. Brinkman and colleagues (1972) followed a group of foundry workers with silica exposure and with silicosis over an 11-year period. Only a third of the men known not to have died in that interval were restudied, however, raising questions about the validity of the finding of no apparent difference between the silica-exposed workers and the unexposed workers in decline in lung function over time. The original cross-sectional study found poorer lung function among silica-exposed workers and silicotics. Musk and

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colleagues (1977) conducted a 4-year followup study of Vermont granite workers and reported a substantially higher annual loss in lung function than predicted from previous cross-sectional studies of this population. However, reassessment of some of these data has raised questions about the adequacy of the pulmonary function testing (Graham et al. 1981). Reanalysis of the population revealed that Vermont granite workers had an annual decline in FEV_1 of 44 mL per year and those who had left the industry had a decline of 72 mL per year (Eisen et al. 1983). The smoking habits of those who continued working (20 pack-years) and those who had left the industry (27 pack-years) were similar. There was no statistically significant relationship between lifetime dust exposure and decline in FEV_1 for either the workers who were still working or those who had left the industry.

One of the four studies reviewed in Table 4 found no increased decline in lung function over time among silica-exposed workers (Higgins et al. 1968). On followup, however, the mortality rate among the foundrymen in the original study (Table 3) was appreciably higher, particularly among those with silicosis and among older workers. Smoking habits were recorded in this study, and the foundry workers who smoked had lower mean FEV_1 values than the nonsmoking foundry workers in both the 25 to 34 and the 55 to 64 age groups. Pham and colleagues (1979) found consistently increased declines with age in all measures of lung function studied (FEV_1, FVC/FEV_1, RV/TLC, and fractional uptake of CO) among silica-exposed steel workers compared with unexposed workers. Results for smoking and nonsmoking workers were not reported separately. Lung function of the exposed men in the original survey was somewhat higher than in the unexposed workers (although they had much more bronchitis), suggesting that selection processes (healthy worker effect) occurred in this study. Kauffmann and colleagues (1979, 1982) also found increased declines in smoking-adjusted lung function over time among workers exposed to mineral dust (especially silica), and argued that the mineral dust and silica exposures were most likely to be causal. Their findings are consistent with this conclusion, but exposures were assessed by type of job, and information on silica dose or interval progression over the 12 years of study is lacking. Manfreda and colleagues (1984), in a 5-year followup study of hard-rock miners and smelter workers, reported significant declines in FEV_1/FVC for both smoking and mining industry exposure. These effects were quantitatively similar, but may reflect more of a smelter effect than a mining (silica dust) effect, as that was the finding on their original cross-sectional study. The prospective study abstract does not address this question.

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TABLE 4.—Prospective studies of workers occupationally exposed to silica

Study, country	Number and type of population	Age (mean or range)	Annual decline in lung function						Comments
			S	NS	Δ	Exp	Not	Δ	
Higgins et al. (1968), United Kingdom	80 foundry workers, 100 "nondusty" workers	25–34	38*	21	−17	29	30	−1	Somewhat higher increased annual lung function decline in older men, not strongly associated with occupation, but strongly influenced by smoking
	43 foundry workers, 100 "nondusty" workers	55–74 (Ages in 1957)	32*	54 ($FEV_{.75}$)	−22	37	34	+3	*Heavy smokers only
Pham et al. (1979), France	196 steel (foundry and roll sheet) workers	49.5				7.4%	0.6%	−6.8%	At baseline, bronchitis prevalence significantly higher in steel vs. unexposed workers (37.8 vs. 17.5), lung function somewhat higher in steel workers; over 5-year followup, somewhat more increased steel worker bronchitis prevalence (45.3/21.9); more steelworker than unexposed worker all-parameter lung function consistent decline; no silica content or dust concentration environmental data
	186 unexposed workers	49.8 (Ages at first exam)				(%FEV predicted) Matched for age, height, smoking status			

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TABLE 4.—Continued

Study, country	Number and type of population	Age (mean or range)	Annual decline in lung function						Comments
			S	NS	Δ	Exp	Not	Δ	
Kauffmann et al. (1982), France	178 mineral dust exposed workers (55 exposed to silica)	41 (41)*	No smoking-specific lung function decline given			52 (57)	42 (42)	−10 (−15)	12-year followup study of 11 factories, including several mineral dust exposures, of which only silica is separable; no silica monitoring data; significant FEV_1 annual adjusted declines in mineral dust exposed workers (esp. silica exposed) interpreted as work related and consistent with silica-exposed worker original cross-sectional decreased lung function assessment
	177 unexposed workers	41				(FEV_1) Annual declines adjusted for smoking status and amount			* Numbers in parentheses, of 55 silica-exposed workers only
Manfreda et al. (1984), Canada	179 hard rock miners, 254 unexposed (community sample)	25–54	3.4% (Percentage decrease in FEV_1/FVC, over 5 years, adjusted for age and height)	2.0%	−1.4%	3.1% (Percentage decrease in FEV_1/FVC, over 5 years, adjusted for age, height, and smoking)	1.6%	−1.5%	(See Table 2 for cross-sectional results) Cough and phlegm prevalence greater among miners at baseline, no change over time; adjusted FEV_1 and FEV_1/FVC declines significant for smoking and FEV_1/FVC decline significant for mining exposure; data suggest FEV_1/FVC more sensitive indicator; data consistent with mining and smelter exposure and smoking additive effect

NOTE: S = Smoker; NS = Nonsmoker; Exp = Exposed; Not = Not exposed.

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Pathogenesis of Silica-Related Health Effects

The characteristic pathology of the various forms of silicosis are well described in recent texts dealing with occupational respiratory diseases (Parkes 1982; Kleinerman and Merchant 1983). The mature lesion of silicosis is the hyalinized nodule that is spherical and typically varies in size from 3 to 12 mm. The nodules are more commonly found in upper lobes, but are found throughout the lung and are frequently subpleural. Microscopically, the nodules have a whorled appearance composed of lamina of acellular hyalin. The borders of the lesions are typically serpiginous and are composed of pigment (especially if associated with a coal exposure), chronic inflammatory cells (mainly lymphocytes and plasmacytes), and connective tissue extending into the surrounding lung parenchyma. With phase microscopy, doubly refractile silica particles 1 to 5 μm in size may be observed within the lesions and within macrophages in the surrounding infiltrate.

Acute silicosis, or acute silicoproteinosis, differs from classical nodular silicosis in that the principal finding is alveolar proteinosis associated with a diffuse interstitial reaction. Scanning electron microscopy and x-ray microanalysis have demonstrated small birefringent silica and silicate particles (less than 1 μm in diameter) in these processes (Abraham 1978, 1984).

Progressive massive fibrosis may develop on a background of silicosis through the enlargement and sometimes the coalescence of the nodular lesions of silicosis into conglomerate silicosis. These lesions form most commonly in the apical or middle portion of the upper lobes and are frequently complicated by tuberculosis. Cavitation of these lesions may occur with or without tuberculous infection (Kleinerman and Merchant 1983).

The mechanisms that produce silicosis, and particularly conglomerate silicosis, are still not fully understood. The cellular events leading to lung injury appear to arise from the cytotoxicity of the respirable silica particle for a principal lung defender, the alveolar macrophage. Upon phagocytosis of the silica particle, cell death is caused by the release of proteolytic and hydrolytic enzymes into macrophage cytoplasm. The release of these cytoplasmic constituents, including the still biologically active silica particle and fibroblast stimulating factor, may then lead to fibrosis (Allison et al. 1966, 1977).

As has been noted with other types of pneumoconiosis, silicosis (and particularly conglomerate silicosis) is associated with a high prevalence of circulating autoantibodies (ANA and RF) (Jones et al. 1976; Turner-Warwick et al. 1977). Although silica exposure and particularly silicosis may be associated with rheumatoid arthritis and several other collagen-vascular diseases, the role of these antibodies in the etiology, onset, and progression of silicosis is not

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clear (Parkes 1982). Angiotensin$_1$-converting enzyme (ACE) elevation has also been reported among silicotics (Gronhagen-Riska 1979; Nordman et al. 1984). Nordman and colleagues (1984), in a case–reference study of the Finnish Occupational Diseases Register from 1965 to 1977, reported an association between ACE activity and progression of silicosis. Smoking, age, and bronchitis were not related to ACE activity, which was thought to reflect accumulation and increased degradation of macrophages. Histocompatibility antigens (HLA) have also been studied as possible genetic risk factors for silicosis, but with variable results. Koskinen and colleagues (1983) found that the prevalence of HLA-AW19 was higher in their Finnish silicosis patients than in the silica-exposed referent population and that the highest risk of developing advanced silicosis was associated with the phenotypic combination AW19 and B18. However, Sluis-Cremer and Maier (1984) reported only a decrease in HLA-B40 among 45 South African gold miners. These variable associations are statistically weak and may be related to the number of statistical tests performed on the multiple HLA antigens.

The pathogenesis of airways obstruction in silica-exposed workers is less well understood. Although increased rates of bronchitis and decreased lung function have been observed in epidemiological studies comparing silica-exposed and unexposed workers, it appears that these findings are largely separate from the clinical and epidemiological picture of silicosis. In the largest and best controlled study of a reasonably pure silica-exposed sample of 1,973 white gold miners (Irwig and Rocks 1978), chronic bronchitis was found to be equally common among those with radiographic evidence of silicosis and those without. The smoking habits of miners with radiographic silicosis and of those without silicosis were not significantly different statistically. Silicotics reported only more days away from work, a finding the authors suggested may have been as related to their compensation status as to their disease. Comparison of lung function between silicotics and their silica-exposed referants revealed equivalent FVC, FEV_1, and $FEF_{25-75\%}$ among silicotics.

Recent pathological evidence of a nonfibrous mineral dust small airway lesion has been provided by Churg and Wright (1983). This pathological process, which they labeled mineral dust airways disease (MDAD), is similar to that produced by tobacco smoke. This pathological process involves primarily respiratory bronchioles, with a lesser extension into alveolar ducts. This lesion generally involves more pigmentation and more thickening of the bronchiole walls than is typically found in cigarette smokers. In a recent study by Churg and colleagues (1985) of 13 cases of patients with MDAD, 7 had occupational histories consistent with a primary silica exposure. Only 1 of 121 cases without a clear history of dust exposure was found to have MDAD. Those with MDAD, matched for age and

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smoking habit with 13 cases without MDAD, were found to have significantly poorer lung function, including clinically relevant lower mean levels of FEV_1, $FEF_{25-75\%}$, and FVC and increased RV/TLC and ΔN_2 per liter as percentages of that predicted. It was also noted that significantly more membranous and respiratory bronchiole fibrosis occurred among subjects with MDAD. The similarity in location, morphology, and physiological impairment between the pathology induced by mineral dust and that observed with cigarette smoking suggests that the cellular events giving rise to them may be similar. Although a good deal is known about the pathogenesis of the process arising from cigarette smoke (US DHHS 1984), systematic experimental studies of mineral dust airways disease have not been reported.

Silica Exposure and Cancer

Initial concerns about the association between silica exposure and cancer arose during the 1930s among investigators in England, Canada, and South Africa. In the early research on this topic, the focus was on the proportion of lung cancers arising among autopsied cases of silicosis compared with that among nonsilicotics or members of the general public. All of the early research (Dible 1934: Anderson and Dible 1938; Kennaway and Kennaway 1947; Klotz 1939; Irvine 1939) was characterized by the lack of any data on smoking.

Early assessments of the association between silicosis and lung cancer were summarized by Hueper (1966). More recently, Heppleston (1985) summarized the autopsy findings from South Africa (Becker and Chatgidakis 1960; Chatgidakis 1963), from Switzerland (Ruttner and Heer 1969), and from Germany (Otto and Hinuber 1972), but again no smoking data were presented. The reports from South Africa and Switzerland showed no differences in the ratio of lung cancers between silicotics and controls. However, Otto and Hinuber (1972) showed that porcelain workers with silicosis had more than twice the proportion of lung cancers as the noncases. Early studies suggested that silicotics have an increased lung cancer risk (Dible 1934; Klotz 1939; Mittmann 1959) or that silicotics with respiratory cancer have greater concentrations of silica in lung tissue (Anderson and Dible 1938). However, data from Bridge (1938), Heppleston (1985), Hueper (1966), and Irvine (1939) suggested that lung cancer risk among silicotics is less than or equal to that of men without silicosis, regardless of their occupation. In reviewing the evidence, Hueper (1966) observed that the data support the idea that lung cancer is a coincidental finding among silicotics and that there is no etiological relationship.

None of these studies addressed the smoking status of the subjects, a crucial omission in any study of lung cancer. Furthermore, age was

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not adjusted, nor were there any quantitative estimates of the silica exposure or assessments of the severity of the silicotic lesions.

Epidemiologic Studies of Smoking, Silica Exposure, Silicosis, and Cancer

Silica-Exposed Cohort Studies

Occupational silica dust exposure is common in many industries; therefore this section is organized so that exposure studies in work settings that are similar can be examined together, i.e., metal ore mining, the steel industry, and workplaces where exposures are to silica only.

Metal Ore Mining

McDonald and colleagues (1978) conducted an enlarged followup study from 1937 to 1973 of the Homestake Veterans Association cohort that included 1,321 men with at least 21 years of employment at the mine. Standardized mortality ratios (SMRs) were calculated using South Dakota mortality rates as opposed to U.S. rates. The South Dakota lung cancer rates were lower than those for the United States as a whole. Using dust exposure data from company midget impinger samples, the authors examined the pneumoconiosis (mostly silicosis) and cancer risks in five categories of dustiness, collapsing them when indicated owing to small numbers. The data showed striking trends for pneumoconiosis and tuberculosis, but no gradients emerged for respiratory cancer.

Brown and colleagues (1985) also conducted an assessment of the Homestake gold miners. The cohort included 3,328 white male miners employed at least 1 year between 1940 and 1965 and followed until June 1, 1977. The authors calculated SMRs using person-years and contrasted mine mortality rates with rates for U.S. white men. An index of dust exposure by job location was assembled for the purpose of assessing dose–response gradients. The SMR for malignant neoplasms of the trachea, bronchus, and lung was 100, with no trends in latency or dust exposure by length of employment.

Katsnelson and Mokronosova (1979) examined the mortality at a U.S.S.R. gold mine and at several brick plants from 1948 to 1974. Dust concentrations were not specifically stated for workers in the gold mine, and an approximation of the SMR (which the authors termed "relative risk") was calculated to compare the cancer risk among gold miners with the cancer risk of residents of a nearby town (excluding those who worked with chromate dusts and adding to the comparison group those who worked less than 3 years in the plants under study). The authors reported a relative risk (RR) of 7.9 ($p < 0.001$) for lung cancer among the male underground gold miners; without the silicotics, the RR was 3.1 ($p < 0.02$). Surface workers had

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a nonsignificant RR of 1.6. No lung cancer deaths occurred among women during these years. No smoking data were presented for gold mine workers, although data presented for workers at a silica firebrick plant and an aluminosilicate brick plant indicated that two-thirds to three-fourths of the men smoked, whereas only 0 to 15 percent of the women did. There appeared to be an inverse gradient of the proportion of lung cancers by stage of silicosis or silicotuberculosis (although no standard classification such as that of International Labour Office (1980) is given).

Armstrong and colleagues (1979) followed 1,974 Kalgoorlie gold miners from Western Australia (whose smoking habits were measured between 1960 and 1962) for silicosis incidence and mortality through 1975. Expected death rates were obtained from the age-specific death rates of Western Australia during 1963–1967, 1968–1972, and 1972–1976. There were significant ($p<0.01$) mortality excesses for respiratory cancer (SMR 140) and for pneumoconoisis and silicosis (SMR 640). The authors compared the cancer risk of the underground miners and the surface miners and also the association between silicosis, smoking, and lung cancer. They observed a 40 percent excess of lung cancer among underground workers and a 13 percent excess risk of pulmonary cancer among silicotics (both nonsignificant). In 1961–1962, the Kalgoorlie miners had a greater prevalence of smoking (66.3 percent) than either the coal miners (58.7 percent) or the male residents of Busselton, Australia, in 1966 (53.2 percent) and tended to smoke more cigarettes per day. The authors stated that the lung cancer risk was probably a function of the heavier cigarette smoking habits of the miners and that there was little evidence to link experience underground (and thus exposure to silica) to lung cancer risk.

Costello (1982) conducted a followup study of 12,258 white "metal ore" miners who were part of a 1958–1961 U.S. Public Health Service (US PHS) survey of silicosis and the metal mining industry. SMRs were calculated using as expected values the 1968 through 1970 white male mortality rates in the 16 States where the mines were located. The results showed that the cohort as a whole had an all-causes SMR of 105.9 ($p<0.01$); the SMR for cancer of the trachea, bronchus, and lung was 126.6 ($p<0.001$), and the SMR for pneumoconiosis (mostly silicosis) was 343.6 ($p<0.001$). Both digestive tract cancers and hypertensive heart disease were significantly reduced. Costello presented several cause-specific and ore-specific SMRs that were all significant at $p<0.05$. Respiratory cancer SMRs were 130.0 among lead zinc miners, 354.6 for mercury miners, and 346.5 for chromium miners. Highly statistically significant SMRs for pneumoconiosis were obtained among copper, lead zinc, molybdenum, and gold or silver ore miners. In the US PHS 1958–1961 survey, 14.5 percent of the metal miners were nonsmokers, 10.9 percent were ex-

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smokers, 70.5 percent were current smokers, and 37 percent were pipe and cigar smokers. The smoking status of 0.4 percent was unknown. Costello argued that on the basis of a relationship between lung function tests and lung cancer, cigarette smoking was the major predictor of excess lung cancer in these metal ore miners.

Steel Industry

Gibson and colleagues (1977) conducted a retrospective cohort study of the Dofasco steel mill workers in Hamilton, Ontario, Canada, from 1967 to 1976. The authors compared foundry workers with nonfoundry workers and reported a lung cancer SMR of 250 ($p < 0.0005$). They used metropolitan Toronto male mortality rates to calculate expected values. The authors noted that the finishing area had the highest mean level of total suspended particulates (much of it silica), respirable particulates, and benzene-soluble fraction of total suspended particulates. The molding and furnace work areas had similar industrial hygiene characteristics. No smoking histories were available for the cohort as a whole. However, 22 of the 24 men with lung cancers were cigarette smokers. The authors proposed that smoking and particulate exposure (containing adsorbed organic material) might be an explanation for the excess lung cancers.

Blot and colleagues (1983) conducted a case–control study of lung cancer among white men in eastern Pennsylvania to assess the association with employment in the steel industry. Interviews with next of kin provided information about residential, occupational, and smoking histories. The authors demonstrated a smoking-adjusted odds ratio of 2.2 for usual employment in the steel industry (95 percent confidence interval, 1.5 to 3.3). The odds ratio for lung cancer was also calculated by smoking category and was significantly elevated for light smokers and heavy smokers but not for nonsmokers or for moderate smokers.

Workplaces With Exposure to Silica Only

In contrast with workers in the foundry and mining industries, where silica exposure is most likely to be "contaminated" by combination with organic foundry fumes or asbestiform materials, or radon in the case of mining, some workers are exposed to "pure" silica. These workers are found in several industries, including ceramics or firebrick manufacture, granite quarrying, or tunnel digging.

Katsnelson and Mokronosova (1979) examined lung cancer at two aluminosilicate fireclay plants and at a silica firebrick plant. Although the firebricks and the fireclay dusts contain high levels of quartz, no dust samples were collected in the plants. The relative risk (RR) for lung cancer for the male workers was 4.0 ($p < 0.01$) and

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4.5, respectively, at the fireclay plants, and a nonsignificant SMR of 5.1 was reported for the female workers at the first plant. At the firebrick plants the RR was 2.0 ($p < 0.05$) for male workers and 0.8 for the female workers.

Vermont granite workers are exposed to quartz dust with a concentration of approximately 30 percent free silica. Davis and colleagues (1983) conducted a proportional morbidity rate (PMR) study of 969 deceased white granite workers whose x rays were on file at the Vermont Division of Industrial Hygiene and who had died between 1952 and 1978. The authors developed a dust exposure index for the purpose of assessing exposure profiles for their study subjects. They analyzed the data, excluding tuberculosis and silicosis after both of these causes of death showed powerful excess disease risks. Slight excesses for digestive tract, lung, larynx, and prostate cancers were reported, including a PMR of 1.3 for general respiratory cancer (95 percent confidence intervals, 1.0 to 1.6). No apparent trends emerged relating dust exposure categories with either digestive cancer, respiratory diseases, or lung cancer. Smoking data were not available for the subjects.

Costello and Graham (1985) conducted a cohort study of 5,414 Vermont granite workers from 1950 to 1982. The authors used the personnel information on file in the Occupational Hygiene Division of the Vermont State Health Department to ascertain date of hire and date of death. Significant overall excess mortality was observed for silicosis (SMR 586.6) and tuberculosis (SMR 473.8), but the excesses were confined to workers hired before 1940. However, no increased risks were observed for either respiratory system cancer or lung cancer. The latency time may have been too short to determine the lung cancer risk among granite workers hired after 1940. Information was lacking on smoking and dust exposure, and the Vermont records regarding employees at risk were incomplete.

Selikoff (1978) examined a 932-man cohort of unionized New York City tunnel workers from 1955 to 1972. These men were exposed to silicious dusts containing sizable amounts of quartz, schists, and gneises, but there was little likelihood of exposure to asbestos. There was an SMR of 495 for pulmonary tuberculosis, an SMR of 160 for lung cancer, and a gradient in the risk of respiratory cancer according to the number of years worked. No smoking data were available, and it is possible that this elevated risk may be a reflection only of long-term smoking habits and not of silica exposure.

Followup of Silicotics

Westerholm (1980) conducted a followup study from 1931 to 1969 of silicotics from the Swedish Pneumoconiosis Register. For those whose silicosis arose from employment in mining, quarrying, or tunneling (MQT) and whose silicosis was diagnosed between 1931

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and 1948, the lung cancer PMR was 590 ($p<0.01$); for MQT workers whose silicosis was diagnosed between 1949 and 1969, the PMR was 380 ($p<0.01$). The other significant finding was among workers in the steel and iron industry (SII) whose silicosis occurred between 1949 and 1969; their PMR was 220 ($p<0.05$). Westerholm and colleagues (1985) extended the study from 1961 to 1980 to follow up 712 silicosis cases and 810 noncases from the Swedish silica exposure registry, matched for age, industry, and occupation. For MQT workers, the SMR was 538 ($p<0.05$) and for SII workers, 385 ($p<0.05$). Smoking was not adjusted in the first study, and in the second, it was indirectly accounted for by the selection of controls from the same cohort as the silicosis cases.

Finkelstein and colleagues (1982) studied 1,190 Ontario, Canada, silicotic miners diagnosed between 1940 and 1975. The authors reported an overall SMR of 198 ($p<0.01$), with SMRs of 303 ($p<0.01$) and 195 ($p<0.05$) for silicotics diagnosed between 1940 and 1949 and between 1950 and 1959, respectively. No smoking data were collected.

Schuller and Ruttner (1985) examined the mortality from 1960 to 1978 of 2,399 cases of silicosis in Switzerland. To account for the sequelae of silicosis (such as tuberculosis and cor pulmonale), the authors calculated age- and period-specific mortality odds ratios (MOR). The lung cancer MORs by industry were as follows: miners 229 ($p<0.01$); stone workers 118 ($p<0.6$); foundrymen 327 ($p<0.001$); others plus ceramic workers 237 ($p<0.05$); and ceramic workers 205 ($p=0.25$). The overall MOR for all Swiss silicotics was 223 ($p<0.05$). The authors noted that smoking is a major cofactor because smokers have more chest symptoms, thus making silicosis more easily detected, and because a high proportion of workers in silica-exposed jobs are smokers, ranging from 60 percent to 85 percent. Because of the lack of significant lung cancer risk among stone workers with silicosis (having less confounding exposure to polycyclic aromatic hydrocarbons than workers in foundries), the authors argued against silica being a carcinogen, but postulated an interaction of occupation and smoking. The authors cited the need for cohort studies of workers in these industries with silica exposure, including detailed smoking information. An additional question is the relation of lung cancer risk by degree of silicosis.

Neuberger and colleagues (1985) examined the relative risk for lung cancer among Austrian silicotics from 1955 to 1979. The overall risk adjusted for age and sex was 1.4 ($p<0.05$). The lung cancer relative risk increased from 1.31 in the 1955 to 1959 period to 1.42 in the 1975 to 1979 period. No information was provided on smoking, on industry-specific risks, or on possible silica exposure levels.

Kurppa and colleagues (1985) examined the subsequent mortality of 961 cases of silicosis diagnosed in Finland between 1935 and 1977.

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Using the Finnish male population as a comparison group, they observed 80 lung cancer deaths instead of the age-adjusted expected number of 25.6, a SMR of 312 (99 percent confidence interval, 230 to 414). The authors also found SMRs of over 700 for pulmonary disease and tuberculosis. When the lung cancer risk was examined by industry, the SMR results were as follows: mining 436 ($p<0.01$); stone industry 271 ($p<0.01$); steel casting 184; iron foundries 225; and other industries 343 ($p<0.01$). The authors demonstrated that the SMRs for each industry showed a 40 percent or more risk increase (despite small numbers) regardless of whether the silicosis was diagnosed between 1935 and 1959 or between 1960 and 1977. The authors did not have smoking data.

Zambon and colleagues (1985) examined a cohort of 1,234 silicotics from the Veneto region of Italy who were diagnosed from 1959 to 1963, and followed them through 1980. Complete occupational and smoking histories were available. Overall, the cohort had striking excesses of infectious disease (tuberculosis) and respiratory disease (silicosis) mortality, with SMRs of 1,960 and 741, respectively. There was a significant ($p<0.05$) lung cancer SMR of 228 and a nonsignificant SMR of 206 for cancer of the larynx (based on only seven cases). There was a gradient of lung cancer risk using years since first silica exposure as a surrogate for dose (risk did not begin to rise until 20 years after the first exposure). The gradient was maintained across mining and tunneling industries; tunneling and quarrying industries had significant overall SMRs of 239 and 569, respectively. The authors reported that only 13.2 percent of the cohort were nonsmokers and only 3 of 49 deaths occurred in this group; thus, they believed that the excess mortality was very likely due to smoking.

Research Recommendations

1. Further prospective dose–response studies on chronic bronchitis and airways obstruction assessing silica concentration, smoking, and airway reactivity should be undertaken.
2. Systematic, well-controlled studies of lung tissue from silica-exposed workers to assess the pathology and associated impairment of small airways disease should be undertaken.
3. Experimental studies of the interaction of cigarette smoke and silica dust on the pathogenesis of small airways disease should be undertaken.
4. The potential for silica to act as a carcinogen alone or in combination with other exposures should be investigated in carefully controlled studies that include a detailed examination of the smoking habits of the participants.
5. Priority should be given to compliance with the current silica permissible exposure limit.

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6. Systematic surveillance of silica-exposed populations to document silica dose and silica-associated health effects should be extended by government agencies, unions, and industry.

Summary and Conclusions

1. Silicosis, acute silicosis, mixed-dust silicosis, silicotuberculosis, and diatomaceous earth pneumoconiosis are causally related to silica exposure as a sole or principal etiological agent.
2. Epidemiological evidence, based on both cross-sectional and prospective studies, demonstrates that silica dust is associated with chronic bronchitis and chronic airways obstruction. Silica dust and smoking are major risk factors and appear to be additive in producing chronic bronchitis and chronic airways obstruction. Most studies indicate that the smoking effect is stronger than the silica dust effect.
3. Pathological studies describe mineral dust airways disease, which is morphologically similar to the small airways lesions caused by cigarette smoking.
4. A number of studies have demonstrated an increased risk of lung cancer in workers exposed to silica, but few of these studies have adequately controlled for smoking. Therefore, while the increased standardized mortality ratios for lung cancer in these populations suggest the need for further investigation of a potential carcinogenic effect of silica exposure (particularly in a combined exposure with other possible carcinogens), the evidence does not currently establish whether silica exposure increases the risk of developing lung cancer in man.
5. Smoking control efforts should be an important concomitant of efforts to reduce the burden of silica-related illness in working populations.

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CHAPTER 9

OCCUPATIONAL EXPOSURES TO PETROCHEMICALS, AROMATIC AMINES, AND PESTICIDES

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Introduction

Workers employed in industries that produce or use petrochemicals, aromatic amines, and pesticides can be exposed to chemicals that threaten their health. Substantial proportions of these workers smoke tobacco. It is possible that the hazards of smoking and occupation have independent damaging effects on health, but it is also possible that the two exposures act synergistically. It is the purpose of this chapter to review the available evidence bearing on the hazards of working in industries where petrochemicals, aromatic amines, and pesticides are produced or utilized, and to explore the likelihood that smoking and chemical exposures interact to enhance the risk of various cancers and chronic obstructive lung disease. Unfortunately, there are very limited data on such potential interactions.

Petrochemical, Aromatic Amine, and Pesticide Workplace Exposures

The word "petrochemical" means any substance derived from petroleum or natural gas. By this definition, petrochemicals are pervasive in modern industry and agriculture, and worker exposure might logically include almost the entire workforce. Historically, however, concern about adverse effects on human health has focused mainly on industries where petroleum is separated into its many valuable components (refineries) or where the various products of that separation are used in such a way that workers are substantially exposed (manufacture of rubber and processing of leather, for example). Workers exposed to the products of inefficient hydrocarbon combustion (vehicle exhaust, coke production) are also objects of concern because they inhale unburned hydrocarbons and also the many reactive substances generated by pyrolysis.

A number of aromatic amines, such as betanaphthylamine and benzidine, are used in the manufacture of dyes for the textile and garment industries. Industrial exposure to some of these chemicals has been reduced because of the known carcinogenicity of betanaphthylamine and similar compounds. However, naphthylamines are sometimes used as antioxidants in the manufacture of rubber products, and significant numbers of workers are still exposed to benzidine, 4-aminobiphenyl, and other hazardous aromatic amine products. The groups of interest with regard to exposure are, therefore, rubber workers and people employed in the manufacture of aromatic amine dyes.

Workers exposed to pesticides include manufacturers, formulators, custom applicators, and end-users, principally farmers. Farming, as an occupational category, has been included in some epidemiologic studies. Degrees of pesticide exposure on the part of farmers vary enormously both qualitatively and quantitatively; therefore, the

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assumption that the health status of farmers is a reflection of pesticide toxicity is, at best, dubious. This chapter focuses on the few studies of the health status of workers engaged in pesticide manufacture, formulation, or application.

Prevalence of Smoking in the Petrochemical, Aromatic Amine, and Pesticide Industries

Information on smoking habits has been very limited in occupational epidemiologic studies; there are no published reports that specifically describe the smoking habits of workers in the petrochemical, aromatic amine, and pesticide industries. A number of surveys have demonstrated the tremendous variability in smoking prevalence between occupational groups. The variation in smoking prevalence between occupational groups, discussed in chapter 2 in this Report, indicates that operatives and laborers have a higher prevalence of smoking and earlier ages of initiation.

Because levels of exposure to hazardous and potentially hazardous substances in the workplace are also greater in operatives and laborers, smoking can potentially confound attempts to relate workplace exposures to the development of certain diseases known to be related to cigarette smoking, such as lung and bladder cancer and chronic obstructive lung disease. The independent contributions of occupation and smoking to disease risk cannot be determined, nor can interactions be evaluated, without adequate measures of both exposures. Assumptions of equal smoking exposure within and between occupational cohorts are often tenuous. Few of the studies reviewed in this chapter measured occupational or tobacco exposure adequately.

Interactions of Workplace Exposure and Cigarette Smoking

A synergistic effect of two factors is one that exceeds the expected effects of the two factors acting additively. Reif (1984) has defined synergy quantitatively and unambiguously. Essentially, if the risk ratio for workers in a given occupational setting significantly exceeds the expected additive effects of two exposures acting separately, potentiation, or synergy, of the two factors is inferred. When the combined action equals the sum of the effects of the two agents working independently, the factors are additive. Similarly, if two factors work independently, but their dual effect is less than the sum of their independent effects, antagonism exists. Weiss (1980) reported that the risk of developing lung cancer after exposure to chloromethyl ethers (CME) was greater in nonsmokers and ex-smokers than in current smokers. This example of possible antagonism leads to speculation that the excess mucus that blankets the airways of smokers might diminish the carcinogenic effect of CME.

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This may result because chloromethyl ethers are direct-acting carcinogens that hydrolyze in water.

To the extent possible, interactions between workplace exposure and cigarette smoking are discussed in terms of Reif's definitions.

Studies of Workers Exposed to Petrochemicals

Refinery, Coke Oven, and Gas Workers

The Bureau of Labor Statistics (US DOL 1984) reported that 83,200 workers were employed in petroleum refining in September 1984. These workers are exposed in varying degrees to crude petroleum and to various fractions produced in the refining process, including polycyclic aromatic hydrocarbons (PAH). Many of these substances have been shown to produce lung and kidney cancer in animals (IARC 1972).

Because of exposure to known carcinogens, a number of cohorts of refinery workers have been investigated. The results of these cohort mortality studies, summarized in Table 1, were not consistent regarding cancer risk, but were consistent in their lack of well-defined chemical exposures and the absence of information on smoking habits of individuals within the cohort. Some of these investigations suggested an increased risk of death for specific cancer types; others suggested a decreased risk.

Hanis and colleagues (1979) showed statistically significant increases in risk of death due to esophageal and stomach cancer combined and due to lung cancer. Combined mortality due to bladder and kidney cancer was also slightly greater than expected. Smoking could not be ruled out as a contributor to the increased risk in this group of refinery workers.

Thomas and colleagues (1982) observed increased proportionate mortality ratios for stomach and pancreatic cancer in their study of 2,500 refinery workers. Risks of death due to leukemia, prostatic cancer, brain neoplasia, and skin cancer also appeared to be elevated. The role that smoking might play in relation to the findings for stomach and pancreatic cancer was not discussed.

Hanis and colleagues (1982) demonstrated elevated risks of death due to pancreatic and kidney cancer in a cohort of refinery and chemical workers. Pancreatic and kidney cancer mortality was greater than expected by approximately 50 percent, but these elevations in observed deaths were not statistically significant. Although smoking information was not available for the entire cohort, 17 of the 24 pancreatic cancer deaths occurred in men who smoked (15 smoked cigarettes, 2 smoked cigars). Wen and colleagues (1983) also showed a slight, but nonsignificant, increase in pancreatic cancer in a cohort of refinery workers.

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TABLE 1.—Epidemiologic studies of mortality among petrochemical industry workers and workers in related industries

Study	Type of population	Study design	Major findings
Hanis et al. (1979)	15,032 male petrochemical workers	Historical prospective mortality	Compared with nonexposed workers, men working in refineries had a relative risk of 3.25*, 1.89*, and 1.08 for dying of esophagus/stomach, lung, and bladder/kidney cancer, respectively[1]
Theriault and Goulet (1979)	1,205 male refinery workers	Historical prospective mortality	Three primary brain cancer deaths in this small cohort, less than one expected; fewer than expected lung cancer and respiratory disease deaths[1]
Rushton and Alderson (1981)	34,708 male petrochemical workers	Historical prospective mortality	Fewer than expected deaths due to lung cancer (SMR 0.78*), bladder cancer (SMR 0.77), and bronchitis (SMR 0.64*)[1]
Thomas et al. (1982)	2,509 oil refinery workers	Proportionate mortality	Proportionate mortality ratios (PMRs) 1.42* for pancreatic cancer, 1.14 for lung cancer, and 0.57 for respiratory disease, compared with U.S. men; PMRs elevated for stomach (1.52), prostate (1.38), skin (1.81), and lymphatic cancers (1.61) and leukemia (1.83)[1]
Hanis et al. (1982)	8,666 refinery and chemical plant workers	Historical prospective mortality	SMRs 0.92, 0.99, 1.53, 1.55 for death due to lung, pancreatic, bladder, and kidney cancer, respectively; medical records inadequate to control for smoking; of deaths due to pancreatic cancer, 71 percent (17/24) were in men with a history of tobacco smoking[2]
Waxweiler et al. (1983)	7,595 petrochemical plant men	Historical prospective mortality	SMR 1.98 for mortality due to "total brain tumors"; SMR 0.78 for lung cancer and 0.64 for bladder cancer in hourly petrochemical workers; SMR 0.57* for nonmalignant respiratory disease deaths in white hourly workers[1]

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TABLE 1.—Continued

Study	Type of population	Study design	Major findings
Austin and Schnatter (1983)	6,588 white male petrochemical workers	Historical prospective mortality	Essentially same cohort as Waxweiler et al. (1983); similar results[1]
Wen et al. (1983)	16,888 refinery workers	Historical prospective mortality	Fewer than expected deaths due to lung cancer (SMR 0.99), bladder cancer (SMR 0.46*), and nonmalignant respiratory diseases (SMR 0.68*); SMR 1.09 for cancer of pancreas; SMR 2.28* for bone cancer[1]
McCraw et al. (1985)	3,976 refinery workers	Historical prospective mortality	Fewer than expected deaths due to all cancers (SMR 0.91) and all respiratory tract diseases (SMR 0.44*); SMR 2.13* for leukemia[1]
Hanis et al. (1985a, b)	21,698 petrochemical workers	Historical prospective mortality	Small but significant increases in all cause and circulatory disease mortality in workers exposed to petrochemicals, differences not explained by smoking; small, statistically insignificant increases in all malignancy deaths and prostate and lung cancer deaths; compared with U.S. mortality rates, no significant increase in mortality for any cause in this cohort[1]
Redmond et al. (1972)	3,530 coke oven workers, subgroup of 59,000 steelworkers	Historical prospective mortality	Male coke oven workers had relative risks of 2.85* and 2.05* for dying of lung cancer and bladder cancer, respectively; relative risk 1.11 for other respiratory diseases[1]
Doll et al. (1972)	3,028 gas workers	Historical prospective mortality	Compared with unexposed workers, coal carbonization process workers had a relative risk of 2.40*, 2.35*, and 1.83* for dying of lung cancer, bladder cancer, and bronchitis, respectively[1]

*SCM significantly different from 1.00 at $p < .05$.

[1] Smoking history not considered.

[2] Smoking history considered.

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Hanis and colleagues (1985a) expanded their previous work to include current employees and retirees of two additional U.S. refineries and chemical plants. They analyzed 3,198 deaths from 1970 through 1977 in an exposed population of 21,698 workers; standardized mortality ratios (SMRs) were calculated, using for comparison U.S. population mortality rates specific to age, sex, race, calendar year, and cause. Ninety-one percent of deaths in the refinery and chemical workers occurred among retirees. Although this study identified some causes of death that appeared to be either unusually frequent or infrequent in one or another of the three chemical plants studied, no statistically significant excesses or deficits of cause-specific mortalities were found for the cohort as a whole, relative to the general U.S. population. Specifically, neither brain tumors nor gastrointestinal cancers nor lymphopoietic malignancies were found to be unusually common in the full worker cohort, as previous studies of chemical plant workers had suggested. At one of the three plants, deaths caused by malignant neoplasms in general and by digestive organ cancers in particular were significantly in excess, but this result was counterbalanced by the unusually low mortality experience from these causes at the other two plants. The authors were impressed that certain subgroups of digestive and urinary organ cancers were increased. They speculate that smoking could have played a significant role in these findings.

In a second report on the same cohort, Hanis and colleagues (1985b) used direct standardization of mortality rates. This report categorized workers into nine occupational groups, of which five had "potential exposure" to petrochemicals in their work (process operators, mechanical workers, laborers, service workers, and laboratory technicians and field workers), and four had "no exposure" (officials and managers, professionals, technicians, and office and clerical workers), and compared mortality experience between these groupings. Comparisons used age, sex, race, and calendar-year adjusted rates. In the aggregate, all-cause mortality was higher for the potentially exposed workers (236.1 deaths/10,000/year) than for the nonexposed workers (189.1 deaths/10,000/year). This increase resulted from more circulatory system deaths (145.6 deaths/10,000/year versus 106.6 deaths/10,000/year) and malignant neoplasms (49.8 deaths/10,000/year versus 41.0 deaths/10,000/year) among the potentially exposed workers. The mortality rate for respiratory system diseases excluding lung cancer was lower for the potentially exposed workers (10.8 deaths/10,000/year versus 14.7 deaths/10,000/year). Smoking histories (ever smoked or never smoked) were available for 70 percent of the cohort. As a group, workers who had ever smoked had significantly elevated mortality rate ratios (relative risks) for all causes (1.9), all malignant neo-

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plasms (2.3), circulatory diseases (1.7), respiratory diseases (3.5), and diseases of the digestive system (2.2).

Among workers who had ever smoked, all-cause mortality and diseases of the circulatory system were increased in the subgroup of potentially exposed workers compared with the nonexposed workers (risk ratios 1.2 and 1.4, respectively). Rates for the potentially exposed groups who had never smoked were not elevated compared with the rates for the nonexposed who had never smoked. The number of deaths in these groups was small, so power for these comparisons is low. The analysis did not specifically test for an interaction between smoking and petrochemical exposure. Additional followup of this particular cohort may permit a more powerful analysis, including examination of the interaction of smoking and petrochemical exposure for specific cancer sites.

Certain epidemiologic studies have been directed at the hazards of specific tasks performed in the course of petroleum refining. The refining of lubrication oils involves exposure to unique solvents (benzene, hexane, methylethylketone, xylene, and toluene) and to the oils themselves, which have some carcinogenic potential. A recent study (Wen et al. 1985) focused on mortality among 1,008 male refinery workers engaged in the lubricating-dewaxing process at any time between 1935 and 1978; 210 observed deaths were analyzed by cause. Standardized mortality ratios were calculated, using for comparison rates specific for age, sex, race, and cause, based on the U.S. population at 5-year intervals from 1935 to 1975. Recently measured air concentrations of solvents were far below regulatory workplace standards. The standardized mortality ratio for all causes was 0.70 (significantly less than 1.0, $p=0.01$) and for malignant disease, 0.86 (not significantly different from 1.0). Of the site-specific cancer mortality ratios, only that for bone cancer was significantly elevated (SMR 10.3), but the elevation was based on only three cases, and subsequent investigation showed that only one of these was truly a mesenchymal tumor of bone origin. The other two represented metastatic cancers, one from a lung tumor and the other from a glial (brain) malignancy. Eight prostate cancer deaths were identified; the corresponding SMR of 1.82 was not significant. No deaths from cancer of the mouth or pharynx were observed, thus failing to confirm a previously reported association of these cancers with lubricating oil refining. No significant excess of leukemia deaths was found (SMR 1.67). No data on smoking habits were collected.

The other studies of refinery workers summarized in Table 1 showed an average or a decreased risk for lung and bladder cancer. Most showed a decreased risk for nonmalignant respiratory disease deaths, leading one group of researchers (Waxweiler et al. 1983) to speculate that strict enforcement of antismoking policies might be

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responsible for the reduced risk of smoking-related diseases in refinery workers.

Cohort mortality studies in industries with similar environmental exposures are also described in Table 1. Redmond and colleagues (1972) described the increased risk of lung cancer and bladder cancer mortality in coke oven workers. The risk appears to result from exposure to PAH emitted in the exhaust created during the coking process. Unfortunately, smoking information was not collected in this classic study.

Doll and colleagues (1972) showed comparable results in their cohort study of gas workers. Coal carbonization workers who are exposed to PAH emitted by retort ovens had significant increases in mortality resulting from lung cancer, bladder cancer, and bronchitis. Smoking histories on a 10 percent random sample in this cohort showed that the smoking habits of gas workers in the retort houses did not differ from the habits of other gas workers. The authors concluded, therefore, that differences in smoking prevalence did not explain the mortality excess experienced by gas workers in retort houses. They commented that the sample size was too small to tell whether there was any interaction between smoking habits and the occupational hazard.

Rubber Workers

Workers engaged in the manufacture of rubber products have long been of concern to occupational health professionals because their work environments are commonly contaminated with dusts and the fumes of hundreds of industrial chemicals, including hydrocarbon solvents. The carcinogenic potential of a number of materials used in rubber manufacture—benzene, betanaphthylamine, and other amine and nitroso derivatives of hydrocarbons—is well documented in man, laboratory animals, or both. Worker exposure to some of the most likely carcinogens has been described (Mancuso and Brennan 1970; Monson and Fine 1978). In addition, exposure to talc, carbon black, and the dust from the milling and grinding processes represents a continuing hazard to the respiratory tract.

The feedstocks and solvents used in this industry are chemically diverse, and the mix of chemical exposures changes from one year to the next. Worker exposures are so different from one plant to another and from one time to another that it is questionable whether rubber manufacturing should be considered an "industry." Divergent findings from the many studies since Case and colleagues (1954) first attributed an excess of bladder cancer in rubber workers to their occupational exposure may well result from the diversity and evolution of pollutants in this unique work environment.

Production workers employed in manufacture, fabrication, and reclamation of rubber in September 1984 totaled 188,000 (US DOL

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1984). There are no current estimates of the frequency or intensity of smoking in this specific segment of the workforce. Because of smoking restrictions at some worksites where explosion hazards exist, smoking may not be quite as pervasive among rubber workers as it is in other blue-collar populations who work where similar restrictions are not in effect.

Epidemiologic studies aimed at determining the risk of cancer attributable to employment in the rubber industry are summarized in Table 2. All of these studies are surveys of mortality experience over the last several decades. All but two were of the historical prospective design. In none was smoking taken into consideration as a factor contributing to cancer mortality. Direct information regarding the smoking habits of decedents was probably difficult, or impossible, to obtain. Also, with the exception of bladder cancer, the forms of malignancy most often identified as possibly excessive (brain, hematopoietic, lymphatic) are not commonly regarded as smoking-related cancers.

An early analysis of proportionate mortality in Akron, Ohio, rubber workers suggested excess rates of cancer affecting the respiratory, genitourinary, and central nervous systems (Mancuso et al. 1968). A subsequent historical prospective study (McMichael et al. 1974) analyzed 1,783 deaths by cause in a cohort of 6,678 male workers employed from January 1964 and compared cause-specific SMRs with rates based on the U.S. male population and on previously published rates for steelworkers. Elevated ratios suggested excess risks of malignant disease of the stomach, prostate, and lymphatic and hematopoietic systems. There was no indication of excess risk of cancer of the lung or bladder at one Akron plant, and only slight risk elevations at five other plants. No attempt was made to assess the impact of smoking. A followup study (McMichael et al. 1975) tended to associate leukemia deaths with job assignments involving solvent exposure.

In a prospective mortality study of rubber workers, Fox and colleagues (1974) demonstrated an increased risk of mortality due to all cancers combined and to bladder cancer specifically. In subsamples of this cohort, specifically workers in the tire sector and the hose rubber sector, significant increases in lung cancer mortality were observed. These sectors of the workforce had known exposures to asbestos. Smoking histories were not available in this study, although deaths due to bronchitis and emphysema were fewer than expected in tire workers.

A study of mortality and morbidity among Akron rubber workers included a cohort of 13,570 workers (Monson and Nakano 1976; Monson and Fine 1978). Information was assembled from death certificates, and incidence data were also collected from local hospital tumor registries. Comparisons were made between the

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TABLE 2.—Epidemiologic studies of mortality among rubber workers

Study	Type of population	Study design	Controls	Disease status studied	Major findings
Mancuso et al. (1968)	1,877 rubber workers; 463 deaths	Historical prospective mortality	Office workers in rubber industry	All causes	Apparent excess mortalities from various malignancies among "nonoffice" workers, including cancers of the gastrointestinal tract, lung, and hematopoietic tissues; mortality from nonmalignant diseases of the circulatory and respiratory systems also apparently elevated; not tested statistically
Mancuso and Brennan (1970)	1,877 rubber workers	Historical prospective mortality	Office workers in rubber industry	Cancer of gallbladder, ducts, salivary glands	Apparent excess mortalities in particular plants and jobs from cancer of the gallbladder, bile ducts, and salivary glands; not tested statistically
Fox et al. (1974)	40,867 cablemakers	Historical prospective mortality	U.K. male population	All diseases	Elevated SMR for all neoplasms and bladder cancer mortality; greater than expected lung cancer mortality in tire makers and hoserubber sector; fewer than expected deaths from bronchitis
McMichael et al. (1974)	6,678 male rubber workers	Historical prospective mortality	U.S. male population	All diseases	Elevated SMRs for neoplasms of gastrointestinal tract and lymphatic and hematopoietic systems; no excess of lung or bladder cancer or chronic pulmonary disease
McMichael et al. (1975)	6,678 male rubber workers; 8 leukemia deaths	Case–control	Other deceased rubber workers (matched)	Leukemia	Significant excess of mortality from lymphatic leukemia associated with past exposure to solvents

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TABLE 2.—Continued

Study	Type of population	Study design	Controls	Disease status studied	Major findings
Monson and Nakano (1976)	13,571 white male rubber workers	Historical prospective mortality	White U.S. men	All causes	Excess deaths from specific cancers at specific work sites: gastrointestinal/processing, lung/tire curing, bladder/all workers, brain and lymphatic/tire building, leukemia/all workers
Monson and Fine (1978)	13,750 rubber workers; 1,359 deaths	Historical prospective mortality, morbidity	U.S. men, and within-plant comparisons	Cancer	Excess rates of cancer of gastrointestinal tract, lung, bladder, skin, brain, and hematopoietic tissues in specific jobs
Arp et al. (1983)	15 cases of lymphatic leukemia	Case–control	Other deceased employees, matched	Lymphocytic leukemia	Cases more likely than controls to have had exposure to benzene and other coal-tar-based solvents

NOTE: Smoking history was not considered in any of these studies.

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cohort and the general male U.S. population, and also between cancer incidence in specific departments and incidence in all other departments combined. There appeared to be increased risks of various malignancies associated with certain work areas, notably cancers of the gastrointestinal tract, lung, bladder, skin, and brain, as well as lymphomas and leukemia. Interestingly, bladder cancer was not found to be in excess among workers presumably exposed to betanaphthylamine, and lung cancer did not occur with unusual frequency in work areas where operators had previously been found to exhibit respiratory morbidity. Lung cancer was found in excess among workers engaged in tire curing and molding and in deicing and fuel cell operations. No effort was made to take into account the role of smoking as a factor causing cancer in this worker cohort.

Studies of Workers Exposed to Aromatic Amines

Since the work of Rehn (1895), there has been increasing evidence that exposure to aromatic amines used in the dye-making industry is an important cause of bladder cancer. Case series reported in the United States (Evans 1937) and in the United Kingdom (Case et al. 1954) added evidence that naphthylamines and benzidine were the likely carcinogens accounting for the high incidence of bladder cancer in exposed chemical workers. Other studies of bladder cancer risk and exposure to aromatic amines have been reviewed recently (Clayson 1981; Johnson 1983). In addition, Melick and colleagues (1971) demonstrated that 4-aminobiphenyl is a bladder carcinogen, and there is concern that benzidine-derived dyes may also be carcinogenic (Johnson 1983).

Approximately 83,700 workers were employed in the manufacture of industrial organic chemicals in September 1984 (US DOL 1984). Some unknown fraction of these workers is exposed to aromatic amines. The National Institute for Occupational Safety and Health (NIOSH) (1979) estimated that 79,000 workers in various categories are exposed to benzidine and related chemicals. Since many of the aromatic amines are regulated as carcinogens and because new methods are available for synthesis of dyestuffs, exposure to aromatic amines has decreased (Johnson 1983). However, benzidine derivatives are still commonly used and have not been studied as extensively as other aromatic amines. Benzidine derivatives are known to be excreted as free benzidine in the urine of rhesus monkeys (Rinde and Troll 1975).

Mancuso and El-Attar (1967) conducted a retrospective cohort mortality study of 639 men who manufactured betanaphthylamine and benzidine. Fourteen deaths due to bladder cancer and one due to kidney cancer were observed, although less than one case was expected on the basis of the rates for Ohio residents. Six deaths due

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to pancreatic cancer were also observed. Smoking histories were not obtained.

Zavon and colleagues (1973) identified a small cohort of workers involved in the manufacture of benzidine. These workers averaged 13 years of exposure to benzidine. Of the 25 workers, 13 developed bladder tumors and 4 developed kidney tumors. Smoking histories were not reported, so the possibility of interaction cannot be addressed.

A risk assessment of a cohort exposed to aromatic amines has recently been reported (Schulte et al. 1985). Thirteen confirmed cases of bladder cancer occurred in a cohort of 1,385 workers in a plant where betanaphthylamine and benzidine were manufactured and used intermittently from 1940 to 1972. Cases were identified from an ongoing mortality survey, from a bladder cancer screening clinic, and from a survey of local urologists. Incidence rates were calculated on the basis of person-years of exposure, and were compared with the Surveillance, Epidemiology, and End Results (SEER) program's incidence rates for the entire United States. Overall, bladder cancer incidence in the cohort was 3.9 times the incidence in the U.S. general population. The incidence rate increased dramatically with duration of employment; this increase was independent of age. Peak incidence occurred with people younger than most bladder cancer victims in the general population. Smoking histories were evaluated; no significant differences in smoking patterns were found between cases and controls.

The relationship between exposure to aromatic amines and bladder cancer has also been explored in case–control studies. These studies are reviewed later in this chapter.

Investigation of the carcinogenicity of betanaphthylamine and other aromatic amines has provided important insights into the nature of chemical carcinogenesis in general. Decades ago, it was realized that bladder carcinogenesis was a species-specific phenomenon: betanaphthylamine induced bladder tumors in dogs but not in rats or mice (Scott 1962). Carcinogenic potential apparently depends on the pathway of biotransformation of the amine compound and the efficiency of urinary excretion. This differs markedly in various species. Because the oxidation products formed are dependent on activities of various oxidizing enzymes (mainly hepatic), substances capable of modifying these enzyme activities (induction or inhibition) could influence the carcinogenicity of the aromatic amines. There is, therefore, a rational biochemical basis for xenobiotic interactions. It is now known that aromatic amines are capable of causing tumors in many organs and tissues of laboratory animals in addition to the urinary bladder. The distribution of cancers induced is again remarkably different among species (Clayson 1981). Finally, it is noteworthy that tobacco smoke contains measurable amounts of

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carcinogenic aromatic amines (Wynder and Stellman 1981), and that betanaphthylamine and an oxidation product thereof have been identified in the urine of a cigarette smoker (Connor et al. 1983).

Studies of Workers Exposed to Pesticides

The Bureau of Labor Statistics (US DOL 1984) estimated that 36,700 workers were involved in the manufacture of agricultural chemicals in September 1984. This estimate does not, of course, include the much larger number of people exposed while using these chemicals, such as farmers and gardeners. These end-users exposed to pesticides could easily number over 1 million individuals.

A mortality survey of workers in pesticide application analyzed 311 deaths (Wang and MacMahon 1979a), comparing mortality rates for various causes with rates characteristic of the general U.S. population. Elevated SMRs were found for cancer of the lung, skin, and bladder, but only the elevated ratio for bladder (R 277) was statistically significant. The ratio did not correspond to the intensity of exposure, being much higher in those applications with minimal exposure. No attempt was made to assess the role of smoking as a factor accounting for the excess cancer mortalities. In a similar companion analysis of 113 deaths among workers engaged in the manufacture of chlordane and heptachlor (Wang and MacMahon 1979b), the investigators found a different pattern of mortality: there was no indication of excess cancer mortality at any study site. Smoking effects could not be taken into account. As is usual in occupational mortality surveys, overall mortality was substantially lower among the employed than in the general U.S. population (McMichael 1976).

Barthel (1981) surveyed 1,658 German male pesticide applicators in a retrospective cohort study, of whom 169 developed malignant tumors that resulted in death. These workers had applied a variety of fungicides, insecticides, and herbicides, usually in dust form. This report tabulated the specific pesticides that were used and included the period of time the cohort was likely to have been exposed to each specific pesticide. Compared with the male population of East Germany, this cohort had a 1.8-fold greater than expected mortality from bronchogenic carcinoma. Those individuals with the longest exposure to pesticide had the greatest risk of lung cancer mortality, e.g., a threefold increase in men exposed to pesticides for more than 19 years. Smoking was measured in a subsample of exposed workers and compared with age- and sex-matched controls selected at random from people receiving a chest x ray at a clinic for the general public. This source of controls can be criticized as being biased for people with chest disease and, therefore, smoking prevalence. Nonetheless, the pesticide-exposed workers and the controls had

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similar smoking habits: 49.7 percent of the pesticide applicators were smokers versus 49.1 percent of the controls from the screening clinic. Lifetime tobacco exposures were also similar for the two groups.

Barthel speculated that the increased risk of lung cancer death could be partly attributed to arsenicals used prior to 1955 and possibly to asbestos present in the carrier substances (talcum, kaolin, and bentonite) used in pesticide dust formulations.

Mortality surveys were conducted (Ott et al. 1974) to detect excess cause-specific death rates among workers engaged in the manufacture of arsenical pesticides. Proportionate mortality ratios were calculated for the arsenic-exposed workers (173 decedents) and were compared with ratios derived from the mortality experience among approximately 1,800 nonexposed workers at the same company. Arsenic exposure was found to pose an average 3.5-fold increased risk of lung cancer, the magnitude depending on the estimated intensity (airborne arsenic concentrations) and duration of arsenic exposure. An elevated risk ratio was also found for lymphatic and hematopoietic malignancies (3.9), but this was based on just five cases (1.3 expected). There was no evident increase in risk for any other malignant disease. A cross-sectional review of smoking histories of the arsenic-exposed workers showed no differences from the employee population in general, and no relationship to arsenic dosage estimates.

A subsequent study examined causes of death among 1,393 persons (male and female) over several decades at a pesticide manufacturing plant in Baltimore, Maryland, where several hundred workers had been exposed to airborne arsenical compounds, mainly in the 1940s and 1950s (Mabuchi et al. 1979). Additional workers had been exposed to various other pesticides, including organochlorines and carbamates. Those who had left employment were traced. The mortality experience of the white population of the city of Baltimore was used for comparison, allowing the calculation of SMRs for the target population. As in the study by Ott and colleagues (1980), significantly and substantially elevated ratios were found for lung cancer among male workers exposed to arsenicals specifically. The ratios increased with the duration of employment in arsenical manufacture, suggesting a dose–response relationship. Two cases of anemia were identified, one pernicious and the other aplastic. No excess of lymphatic cancer was identified. Among workers involved in the manufacture of nonarsenical pesticides, the mortality pattern was essentially the same as that of the Baltimore city white population. Although the smoking habits of decedents were not determined, the authors offered cogent arguments in support of an occupational rather than a smoking causality: (1) SMRs for smoking-related causes of death other than lung cancer were not elevated in the arsenic-exposed group, and (2) the strong dose–response relation-

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ship between arsenic exposure and lung cancer would not be expected to be paralleled by a concomitant increase in smoking risk, when no such relationship was found among workers engaged in the manufacture of nonarsenical pesticides.

Mortality among workers engaged in the manufacture of 2,4,5-T has been examined (Ott et al. 1980). These workers were presumably exposed to chlorodioxins. Mortality occurring among 204 workers from 1950 to 1971 was compared with that recently tabulated for all U.S. men. Of 11 deaths, only 1 was due to cancer; this was a respiratory tract malignancy in a 63-year-old retiree who had been exposed to the 2,4,5-T manufacturing process for 8 years and who smoked up to two packs of cigarettes daily.

As with the petrochemical worker mortality studies, the few studies of workers exposed to pesticides lack specific information from which to measure the contribution of smoking to the increased risk of cancer. Because cohorts of workers manufacturing pesticides are not large, it is unlikely that epidemiologic studies will be done to address specific questions regarding smoking and pesticide interactions.

Occupational Exposures and Smoking as Causal Factors in Specific Diseases

Several investigations have examined the role of occupational exposures as risk factors in the development of specific diseases. The case–control design has the disadvantage of being nonspecific and sometimes unreliable in identifying exposure that occurred in the workplace. The main advantage of this approach is the opportunity to collect information on other risk factors, specifically smoking, together with the greater statistical power that results from studying a larger number of cases than might occur in a specific industrial cohort. In this section, epidemiologic studies of various cancer types and chronic lung disease are reviewed.

All Cancers

Dubrow and Wegman (1984) examined the occupational characteristics of 16,629 cancer victims who died in Massachusetts between 1971 and 1973. They calculated the age-standardized mortality odds ratios for various types of cancer within 321 occupational categories, relying on death certificate indication of the "usual occupation" of the decedent, and attempted to adjust for social class. To limit the confounding effect of smoking on cancer incidence, they used adjustment factors based on published estimates of smoking frequency in major occupational groupings, together with lung cancer risk ratios for smokers and ex-smokers. The estimates of smoking frequency within occupational groups were based on a 1970 National

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Health Interview Survey of 75,827 American men and women reported by Sterling and Weinkam (1976). The authors not only reported their own findings, but also compared their results with those from 11 other large-scale mortality surveys.

In this study a large number of occupations wherein death caused by particular forms of cancer appeared to be excessive was identified. Certain associations, such as lung cancer in shipyard workers, have been confirmed by other studies; the associations are plausible in terms of well-known exposures, especially exposure to asbestos. Significant excesses of bladder cancer were found among chemical workers and engineers, cosmetologists, leather workers, and garage mechanics, again generally in accord with the view that particular occupational exposures pose carcinogenic risks. High rates of certain cancers in schoolteachers, clergymen, administrators, judges, and lawyers are much more difficult to understand in environmental terms.

To the extent that the adjustment for smoking effects used in this analysis can be relied upon, the study would appear to show that certain occupations are, in fact, associated with excess risk of cancer, quite apart from the risk of smoking. It is not possible to estimate the relative magnitudes of the two risk factors, or the existence of interaction between them.

Data from the Third National Cancer Survey (TNCS) Interview Study of 7,518 incident cases were used to seek associations between various occupations and types of cancer (Williams et al. 1977). Data assembled on each case included a synopsis of lifetime employment, education, residential location, and use of tobacco and alcohol, as well as age, sex, race, and socioeconomic status. The large number of cases and the detailed information available made possible a number of adjustments and comparisons not possible in other studies. The main analytical strategy was to compare, serially, the proportions of specific main lifetime industries and occupations among patients with cancer at one site with proportions of patients having cancers at other sites combined as a control group (intercancer comparisons). The advantages and limitations of this approach were discussed by the authors. Even when smoking was controlled for statistically, people engaged in trucking were found to be at excess risk of lung cancer, a finding supported by the Massachusetts cancer mortality survey (Dubrow and Wegman 1984). Other transport, service, manufacturing, and construction workers were also at excess risk of lung cancer. As often happens, some associations were discovered that are difficult to understand mechanistically: excess leukemia and multiple myeloma in salespeople and malignant melanoma in schoolteachers, for example. The study does not present relative risk ratios for smoking within occupational categories from which the relative importance of the two factors might be assessed. As in the

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Massachusetts mortality survey (Dubrow and Wegman 1984), it must be concluded that to the extent smoking effects were adequately controlled by statistical design, certain occupations appear to be associated with significant risks of cancer, independent of the role of smoking. Unavoidably, the occupational classes used for this kind of study are broad: the actual exposure circumstances within these classes that might be conducive to cancer can only be speculated.

Viadana and colleagues (1976) studied 11,591 white male cancer patients and controls who were hospitalized at Roswell Park Memorial Institute between 1956 and 1965. They used occupational histories to classify cases and controls as being exposed to "chemicals" and "combustion products," and into specific groups within these broad classifications, e.g., operatives in the chemical industry or bus, cab, or taxi drivers. Operatives in the chemical industry had an increased relative risk of having cancer of the stomach (RR 4.25, $p<0.05$). The relative risks for lung and laryngeal cancer were slightly, but not significantly, increased.

Relative risks for larynx (RR 3.63, $p<0.05$), pharynx (RR 3.38, $p<0.05$), and bladder (RR 6.77, $p<0.05$) cancers were significantly elevated for operatives in the leather industry. Relative risks were altered after controlling for smoking, but the risks associated with occupation appeared to be independent of smoking. The influence of smoking on the risks associated with occupation were difficult to assess, because the relative risks adjusted for age and smoking were not tabulated. Instead, these results were discussed selectively. Although the information needed to investigate the interaction between smoking and occupation was available, this report did not discuss this issue.

Lung Cancer

Stayner and Wegman (1983) used a case–control design to study the relationship between smoking, lung cancer, and occupation, based on a portion of the data from the Third National Cancer Survey. The analysis was limited to men aged 30 to 84 when diagnosed as having lung cancer who had responded to an interview that included occupational and smoking histories. Occupation was coded in broad categories defined for the 1970 census. Cases and controls were grouped as "ever" or "never" users of tobacco to control for smoking exposure. Controls were selected from survey participants with other types of cancer, excluding those individuals with the types of cancer that have been associated with occupation or smoking (e.g., lip, mouth, pharynx, larynx, esophagus, pancreas, bladder, liver, skin, brain, and blood and bone marrow). These exclusions left 900 controls to be compared with 420 cases. Blue-collar workers had an odds ratio (OR) of 1.24 ($p<0.05$) for developing lung cancer after adjustment for smoking status and age. This

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difference was due in part to the increased odds for developing squamous cell carcinoma (OR 2.11, $p < 0.05$) compared with average odds for developing adenocarcinoma (OR 0.97) and small cell carcinoma (OR 1.22). When the data were analyzed using more narrowly defined occupational groups, no statistically significant associations were found. However, when histologic types were considered separately, laborers had higher odds ratios for small-cell carcinoma (OR 2.47, $p < 0.05$) and squamous cell carcinoma (OR 1.97, $p < 0.05$) after adjustment for smoking.

Stayner and Wegman reported positive associations between smoking and all three histologic types of lung cancer. They did not consider the potential interactions between smoking and occupation in discussing their data. Their report did illustrate the importance of considering histologic type when conducting etiologic studies of lung cancer.

Few studies of occupational risk focus on women. Leung (1977) reported an association between cooking with a kerosene stove and lung cancer in Chinese women living in Hong Kong. This case–control study was conducted to identify factors that might account for the relatively high mortality rates for lung cancer experienced by women in Hong Kong. In 260 consecutive cases of histologically proven lung cancer, 92 percent (166/180) of the men and 56 percent (45/80) of the women smoked cigarettes compared with 59 percent of the male smokers and 11 percent of the female smokers in a "nonrandom" population sample. In a second series of 44 lung cancer cases in women, 91 percent (40/44) used a kerosene stove daily for over 2 years compared with 36 percent of the families sampled in seven areas of Hong Kong.

The sampling schemes used in this study could easily produce biased results. Smoking prevalence in the community was based on a convenience sample and might have underestimated the prevalence of smoking by women. Kerosene stove usage could be associated with many other environmental exposures that might be related to lung cancer. Nevertheless, strong associations between smoking and kerosene stove use and lung cancer were found among women. The author concluded that the question of synergy between stove usage and smoking requires further study.

In a case–control study of lung cancer, Pastorino and colleagues (1984) estimated the proportions of lung cancer attributable to smoking and occupational exposure to known or suspected carcinogens. Lung cancer cases were drawn from a well-defined geographic area in northern Italy where a large proportion (74 percent) of employed men work in industry. In this area, 240 incident cases of lung cancer in men occurred between 1976 and 1979. Twenty-nine cases were excluded because diagnostic criteria were not met and 7 cases could not be reached for interview, leaving 204 cases (85

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percent of total) for analysis. Controls were selected at random from the electoral rolls of men living in the same region and matched with cases for age within 2 years. Of the 366 controls enrolled, 15 could not be reached for interview. Interviews were conducted by two occupational physicians and two public health nurses. Occupational histories focused on specific exposure to asbestos, tars and mineral oil, chromium, nickel, arsenic, bis-chloromethyl ether, chloromethyl methyl ether, vinyl chloride, and polycyclic aromatic hydrocarbons as contained in soot. "No exposure" was defined strictly as a work situation where the subject could not have been exposed to these materials. "Possible" and "probable" exposures were defined on the basis of descriptions of specific job tasks. Ten percent of the control interviews and 50 percent of the case interviews were with next of kin.

The relative risk for lung cancer was strongly related to cigarette smoking in a dose-related way. Relative risk ranged from 2.3 for smokers of 1 to 9 cigarettes per day to 9.0 for smokers of 30 or more cigarettes per day. Occupational exposures were also positively associated with lung cancer. The relative risk for possible exposure was 1.6, and for probable exposure, 2.7. The authors estimated that 81 percent of lung cancers could be attributed to smoking (95 percent confidence interval, 69 to 93) and that 33 percent could be attributed to occupational exposure to known carcinogens (95 percent confidence interval, 19 to 47).

Pastorino and colleagues (1984) illustrated how relative risk varies positively with occupational exposure and cigarette smoking. The relative risk increased in men without occupational exposure from 1.0 in nonsmokers to 2.7, 6.2, 9, and 11 in men who smoked 1 to 9, 10 to 19, 20 to 29, and 30 or more cigarettes per day, respectively. In men with possible and probable occupational exposure, the relative risk increased from 2.5 in nonsmokers to 3.8, 14, 19, and 20 in men who smoked 1 to 9, 10 to 19, 20 to 29, and 30 or more cigarettes a day, respectively. Occupational exposure was subcategorized by exposure to asbestos and PAH, the most common occupational exposures in this study. Both were independently associated with lung cancer risk. The relative risks associated with asbestos and PAH exposures in combination with smoking were more consistent with additive effects, but a specific analysis of the possible interactions was not discussed.

Bladder Cancer

In the last 15 years, many case–control studies and analyses of mortality statistics have been used to examine relationships between occupation and bladder cancer. In only a few has enough historical information been aggregated in detail sufficient to permit exploration of interactive effects between occupation and smoking.

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A case–control study of bladder cancer patients in the hospitals of Leeds, England, failed to show that smoking was a risk factor for bladder cancer, but did indicate that the prognosis was worse in patients who continued to smoke (Anthony and Thomas 1970a). Controls for this study were lung cancer patients and surgical cases interviewed 5 years previously at the same hospital. They were not matched to cases by age. In an expansion of this study, Anthony and Thomas (1970b) matched cases to controls (again using previously interviewed patients) with respect to age, sex, residence, and smoking habit (never smoked, greatest amount ever smoked, cessation of smoking). They then calculated risk ratios for aggregates of cases according to their "predominant occupations" and "employment in suspect environments." They identified significantly elevated risks of bladder cancer among workers in the chemical dye industry, textile workers, tailors, engineering workers, and hairdressers. Because cases and controls were matched for smoking habit, risks were presumably attributable only to occupation.

In an extensive case–control study of bladder cancer in the Boston–Brockton, Massachusetts, area in 1967–1968, Cole and colleagues (1971, 1972) examined occupation and smoking information obtained by interviewing 470 incident cases and 500 age- and sex-matched controls. Controls were selected at random from published "resident lists." Smoking was taken into account with respect to intensity (cigarettes per day) and also estimated total dose (pack-years). Thirteen occupational exposure categories were used in classifying patients and controls: dyestuffs, rubber, leather, printing, paint, petroleum, other organic chemicals, other chemicals, fumes and dust, manufacturing (not elsewhere classified), farming, service, and office. From this study the authors calculated mean relative risk ratios of 1.89 and 2.00 for bladder cancer in male and female smokers, respectively, and demonstrated gradients of risk in both sexes, based on numbers of cigarettes smoked per day. The maximum mean relative risk ratio (3.8) was for women who smoked more than one and one-half packs per day. Standardization by occupational categories did not alter the relative risk estimates for smoking.

When risks were analyzed by occupational categories (ever employed), significantly elevated ratios were found in only two categories: those working with rubber and rubber products (1.57) and those working with leather and leather products (2.00). People exposed to dyestuffs, paint, and other organic chemicals exhibited apparent elevations of risk, but the number of cases available for study was too small to yield statistically significant increases. Relative risks were very similar whether or not controlled for smoking. Examined in terms of "usual occupation" instead of "ever employed," risk associations with occupation tended to be weaker, but rubber and leather industries were again identified as those most likely to

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involve an occupational hazard of bladder cancer, even when controlled for smoking. Risk attributable to hazardous occupation (work in industries involving exposure to chemicals) was estimated to be 7 to 18 percent of the total bladder cancer risk, depending on the basis used for specifying occupation. Relative risk ratios ranged from 1.21 to 1.75.

The epidemiology of bladder cancer with respect to beverage habits as well as smoking and occupation was addressed in three Canadian studies. Miller (1977) conducted a case–control study of 349 bladder cancer cases from British Columbia, Nova Scotia, and Newfoundland, matching each case to controls by age, sex, and residence (but not by smoking). Control subjects were recruited from the residential neighborhoods of the subjects. Questionnaires administered in the homes inquired into the occupations of the respondents, as well as their smoking and coffee-consuming habits. Significant relative risk ratios (2.0 to 10.5) were found for cigarette smoking, and showed a substantial dependence on estimated lifetime consumption of cigarettes. Occupational risks were evaluated only with respect to seven categories: chemical, rubber, photography, spray painting, petroleum, medicine, and "other." Risk ratios were 2.0 or more in all categories, and were statistically significant in two: "chemical" (12.0) and "other" (2.1). No details of the nature of chemical exposures were offered, and no analysis of smoking habit within occupational categories was presented. The number of case–control pairs within the six specific categories was small (total 78), and no occupation-based risk ratios for nonsmokers were stated explicitly. Population-attributable risk percentages calculated by the authors for men were occupation (known and suspect), 35 percent; cigarette smoking, 56 percent; coffee drinking, 27 percent; and total, 118 percent. For women the percentages were 1, 29, and 13 percent, respectively; the total was 43 percent.

An extension of this study on bladder cancer published in 1980 (Howe et al. 1980) included 632 case–control pairs from the same Canadian provinces. Strong relative risks for smoking were confirmed in men and women, the magnitudes depending on daily usage, duration, and estimated lifetime consumption. Associated with significantly elevated bladder cancer risk in men were workers in the chemical, rubber, petroleum, welding, and railroad industries, guards and watchmen, nurserymen, metal machinists, material recorders, and military personnel. Risk ratios for military personnel and clerical workers declined when smoking was controlled for; other risk ratios reportedly did not. This analysis was based on responses to a query as to whether subjects had ever worked in the specified jobs, not on usual occupation. Despite the size of the study, the number of discordant matched pairs was relatively small: fewer than 50 in all occupational categories except agriculture, military,

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and mechanics. No excess risk was indicated for people engaged in the dyeing of cloth or tanning, but the number of pairs available for analysis was not sufficient to provide reliable estimates. Discordant pair ratios of 4/3 and 5/1 were recorded for past contacts with benzidine and bis-chloromethyl ether, respectively, on the part of male respondents. The numbers were too small to permit an examination for the confounding effects of smoking. Very few women were employed in the suspect industries, and no significant risk elevations associated with occupation were identified among women.

Miller and colleagues (1978) matched each of 265 incident bladder tumor patients diagnosed at the Ottawa Civic Hospital Urology Clinic to two control patients treated at the clinic who did not have bladder tumors. Administered questionnaires inquired into previous disease in self and family, occupational exposures, use of coffee, tobacco, and sweeteners, exposure to radiation, and prior treatment with antituberculosis drugs. Relative risk calculations and discriminant analysis identified the following significant risks, in apparent order of importance: in men, a family history of allergy (1.8), occupational exposure to radiation (1.6), occupational exposure to chemicals (1.5), cigarette smoking (1.6), and a history of gout (1.7). In women, coffee drinking (1.6) and a history of tuberculosis (2.0) were identified as risks; a history of allergy in the patient appeared to be protective (0.3). Chemical exposures were identified tentatively as paints, varnishes, lacquers, gum and wood chemicals, and industrial chemicals. Risk ratios derived from this study are uniformly low, and those for factors traditionally regarded as important for bladder cancer (smoking and occupation) are lower than a risk ratio having no previously recognized association with the disease (family history of allergy, in men only). This aspect of the findings casts a degree of doubt on the soundness of the study design, particularly the use of patients with urologic disease other than bladder cancer as controls. Discriminant function analysis presumably identified both smoking and occupational exposure to chemicals and radiation as independent risk factors for bladder cancer. No data were offered from which to determine whether these risks are additive or synergistic.

Calculating proportionate incidence ratios for bladder cancer within broad occupational categories used by the Los Angeles County/University of Southern California Cancer Surveillance Program, Weinberg and colleagues (1983) examined incidence data for Los Angeles County over the period 1972–1976. They found higher relative risks of bladder cancer among managers and salesmen (high on the socioeconomic scale) than among service workers, laborers, and transportation workers (low on the socioeconomic scale). The latter group have been reported to be the heavier smokers (CDC 1976; Bonham and Leaverton 1976). The authors argued that, at

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least in the Los Angeles area, the occurrence of bladder cancer in relation to social class corresponds more closely with coffee-drinking habits (greater in the upper classes) than with smoking or occupation. The social class distribution of bladder cancer incidence in Los Angeles contrasts sharply with the report of Adelstein (1980) in England, who found from analysis of death certificate and census data for 1970–1972 that cancer in general and bladder cancer in particular were afflictions primarily of the lower socioeconomic classes. The discrepant relationships to social class categories may be attributable to the different parameters used in the two studies (incidence versus mortality), to the disparate cultural and economic circumstances of the populations examined, or specifically, to different spectra of environmental carcinogens in the two regions. Interestingly, the two studies are in essential agreement with respect to lung cancer but not bladder cancer.

Glashan and Cartwright (1981) and colleagues (Cartwright et al. 1981), in a case–control study, matched 991 incident cases of bladder cancer treated at three West Yorkshire clinics over 3 years to age- and sex-matched controls "without malignant disease." The source of the controls was not mentioned, but presumably they were clinic patients. Elevated relative risk ratios for smoking (not quantitatively defined) were found in men (1.8) and women (1.6). Significantly elevated relative risks were found for chemical industry workers and printers, but not for leather workers, hairdressers, or dye users. Nonsmoking dye manufacture process workers experienced an apparent increase in risk of bladder cancer (RR 1.9, not statistically significant), but dye process workers who smoked were at highly significant risk (RR 4.6). A similar relationship was found among printers. The risk ratios for nonsmokers were admittedly based on few subjects. Risk ratios for dye process workers increased strikingly with duration of employment (>29 years, RR 10.5). The chemical nature of the dyes to which workers were actually exposed was not discussed.

A case–control study of 212 cases of bladder cancer in rural Denmark drew upon general population controls matched to cases by sex, age, and region of residence (Mommsen et al. 1982, 1983). Multivariate logistic regression was used to identify factors (evaluated by questionnaire) associated statistically with the malignancy. Significant relative risk ratios were found for tobacco use (1.6–2.1), work with petroleum, asphalt, oil, or gasoline (2.9–3.8), industrial work (2.2), work with chemical materials (2.0), alcohol use (2.3), and previous venereal disease (2.9). Farmers, who were presumably exposed to pesticides, were at less than average risk of developing bladder cancer. The report did not explore the interactive effects of occupation and tobacco use.

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A case–control study in the greater New Orleans area, wherein 82 patients with bladder cancer and 169 matched general population controls were interviewed by telephone, was used to identify smoking of filter cigarettes (but not of unfiltered cigarettes or other tobacco products) as a risk factor for bladder cancer (Sullivan 1982). Matching criteria were not specified. A large number of employment categories and chemical exposures appeared to involve risks, most prominently mechanical engineers and people exposed to paint thinners, coal, petroleum, metals, welding materials, office supplies, and industrial equipment.

In a study in northern New Jersey (Najem et al. 1982), 75 cases were compared with 150 patient controls, matched by age, sex, race, place of birth (in New Jersey or elsewhere), current residence, and the clinic providing care. Occupations were recorded only when job tenure was more than 1 year. Smoking habits were characterized as never smoked, former smoker, or current smoker. Several criteria were used to test the significance of associations, and significant risks were analyzed to test for the confounding effects of smoking. Significant risk ratios were identified for cigarette smoking (2.0) and work in dye (3.1), petroleum (2.5), and plastics (3.4) industries, but not for employment in rubber, textile, printing, rodenticide, or cable industries, although some ratios did exceed 1. When the significant occupational risk ratios were analyzed within the three strata of smoking status, ratios for current smokers were essentially the same as those calculated without controlling for smoking. Curiously, the occupational risk ratios for nonsmokers in the dye, plastics, and petroleum industries consistently exceeded the ratios for current smokers, but the ratios for ex-smokers were consistently lower (1.3 to 1.5). Some ratios were based on only a single case in a smoking–occupation cell.

In a recently reported case–control study at Turin, Italy, 512 male bladder cancer patients diagnosed from 1978 to 1983 were compared with 596 patient controls (225 urologic, 371 surgical) (Vineis et al. 1984). Smoking and occupational information was assembled by interview. Highly significant relative risk ratios were found for cigarette smoking, the magnitude depending on smoking intensity, on age when smoking started, and possibly on brand of cigarettes smoked. Occupational risk analysis was based on 64 patients classified as "exposed": 14 cases and 2 controls employed more than 6 months in dye production (said to include exposure to benzidine and betanaphthylamine), plus 28 cases and 20 controls employed in the rubber industry. From this, the authors calculated risk ratios strongly suggesting interactive effects of occupational exposure and smoking, most striking in workers less than 50 years of age, and dependent on smoking intensity (relative risk was 144.0 for hazardously employed workers who smoked). The relative risk for

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hazardous occupation among nonsmokers of all ages (there were only five chemically exposed: two cases, three controls) was 3.7. The relative risk for smoking among the nonexposed of all ages was 5.2. The risk for the occupationally exposed who smoked was 11.6 relative to nonexposed nonsmokers. The risk ratio relationships based on all age groups are more suggestive of an additive overall effect than of synergy. The small number of occupationally exposed nonsmokers in the study limits the confidence that can be placed in the analysis.

Smith and colleagues (1985) recently examined relationships of occupational solvent exposure and smoking to incident cases of bladder cancer in regions of the United States served by the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program and included in the National Bladder Cancer Study (NBCS) of 1978. Controls selected from the NBCS study were frequency-matched to the cases by age and sex. Among nonsmokers reporting at least 6 month's exposure to chlorinated and simple hydrocarbon solvents used in dry cleaning and in other industries, the relative risk of bladder cancer was significantly elevated only in women (RR 1.38), and this was not significantly related to duration of exposure. In both men and women chemically exposed, however, the risk of bladder cancer increased progressively and significantly from nonsmokers to former smokers to current smokers. There was no evidence of interaction between the effects of occupation and smoking. The evidence of a smoking effect was consistent and substantial in this study (highest RR 4.68), but indications of a solvent exposure effect were weak and of borderline statistical significance.

Inhalation of combustion effluents is thought to pose a risk of cancer at various sites, including the bladder. For a case–control study of 81 male bladder cancer patients in Quebec (1970–1975), age- and sex-matched individuals living in the patients' neighborhoods were recruited to serve as controls (Theriault et al. 1981). Detailed histories were taken covering lifetime employment and residence, medications, personal habits, and water supply. Smoking habit was characterized qualitatively and quantitatively. Information on deceased cases was received from next of kin. These authors calculated a mean relative risk of bladder cancer of 5.70 among currently smoking workers in the electrolysis department of an aluminum reduction plant. Relative risk for smoking among other workers was 1.82, and risk associated with electrolysis department employment alone was 1.90. (It was necessary to base the latter estimate on ex-smokers because there were no nonsmokers so employed.) The independent risk ratios are not statistically significant, but the range of values for electrolysis workers who smoked extended from 2.0 to 12.30. To the extent that the ratio estimates can be relied

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upon, they suggest a strong interaction between smoking and occupational exposure.

Silverman and colleagues (1983), in a population-based case–control study of 303 white male bladder cancer cases in Detroit (1977–1978), explored occupational, dietary, and personal habit associations. Controls under 65 years of age were chosen from the Detroit population by random digit dialing, operating with a pool of 2,110 households. Controls of retirement age were selected at random from Health Care Financing Administration lists. A total of 296 controls were recruited for home interviews. Analysis of occupational associations relied on an "ever employed" query, and responses were classified according to the industry identified and by occupation. An apparent strong interaction involved truck driving as an occupation and cigarette smoking. Among people who had never been truck drivers, smoking one or two packs of cigarettes per day increased the risk of bladder cancer by a factor of 1.6; smoking more than two packs increased the risk ratio to 2.1. The ratio for truck drivers smoking less than one pack per day was 1.3; for smokers of one or two packs per day, the ratio was 6.8. The risk ratio for heavy smokers could not be calculated because none of the controls reported smoking more than two packs per day. A relationship with the inhalation of diesel exhaust was suspected, but could not be confirmed from the data.

Not unexpectedly, the case–control studies used to test a relationship of pesticide exposure to urinary tract cancer are inconclusive. Pesticides are chemically and toxicologically diverse; worker exposures to them are equally varied. It is unlikely that in epidemiologic studies based on broad occupational categories carcinogenic risk would be detected, if indeed it exists. Several case–control studies of bladder cancer have indicated that as an occupational group, people "working in agriculture" are at no more than average risk of urinary tract cancer, or are actually at less than average risk (Anthony and Thomas 1970b; Cole et al. 1972; Howe et al. 1980). In some studies of exposures to pesticides, specifically, nonsignificantly elevated risk ratios have been shown (Najem et al. 1982; McLaughlin et al. 1983). In Canada, bladder cancer was found to be significantly associated with crop spraying and nursery work as occupations (Howe et al. 1980). These associations were said to be unaffected by controlling for smoking.

Other Specific Cancer Sites

Cancer of the kidney and upper urinary tract has received less attention than bladder cancer. In a nationwide case–control study of 202 patients with renal adenocarcinoma (Wynder et al. 1974), the past personal and occupational histories of the patients were examined in relation to histories from other hospitalized patients.

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Relative risk among heavy smokers (more than one pack per day) under 50 years of age was 8.0, but only 2.1 in patients over age 50. Moderate smokers (up to one pack per day) were at intermediate risk. Except for a tentative identification of employment in textiles as a risk factor, no associations with occupational exposures to metals, dyes, or other organic chemicals were found.

In the Boston area, 43 cases of cancer of the renal pelvis and ureter were studied in relation to bladder cancer cases and randomly chosen general population controls (Schmauz and Cole 1974). Only among smokers of more than two and one-half packs of cigarettes per day did a significant risk appear (RR 10.0). Of the occupational categories identified, only leather working exhibited a suspect relationship to cancer at these sites.

Occurrences of renal cell carcinoma (495) and cancer of the renal pelvis (74) in the Minneapolis–St. Paul area from 1974 to 1979 were studied for heritable and environmental risk factors (McLaughlin et al. 1983, 1984). Controls were chosen randomly from the metropolitan area population. Because half of the cases were already deceased, background data had to be obtained through next-of-kin interviews. With respect to cancer of the renal pelvis, the risk of disease increased steadily in both men and women in relation to smoking intensity (maximum RR 10.7 in men, 11.1 in women). The only links to occupation appeared in relation to exposures to hydrocarbons: coal, natural gas, and mineral and cutting oils. There were not enough cases to permit analyses for smoking risk within occupations. Renal cell carcinoma also appeared to be related to cigarette smoking, but relative risk ratios were much lower (2.3 in male, 2.1 in female heavy smokers), and the dose–response relationship was not as consistent as in the case of renal pelvis or bladder cancer. Analysis for "usual industry of employment" failed to identify any significant occupational associations.

Musicco and colleagues (1982), in a case–control study of brain neoplasms in Italy, sought to associate the occurrence of gliomas (various types and grades) with occupations of victims prior to diagnosis during 1979 and 1980. Forty-two cases were matched with nonglioma patients at the Neurological Institute C. Besta of Milan. The controls were matched by age, sex, and area of residence. They suffered from a variety of chronic diseases, some probably characterized by physical and or mental disability from a relatively early age. Smoking was defined as a minimum 1-year usage, and total lifetime usage was estimated. More than 20 pack-years was considered heavy smoking. The authors found a significantly elevated risk ratio (5.0) for "agricultural work after 1960" when the data were analyzed without stratification. When stratified by sex, age, and residence, the ratio was 1.9 (not significant). The relative risk was 1.3 for smoking and 1.5 for heavy smoking, neither statistically significant. No

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occupational risk ratios for nonsmokers were calculated. Particularly with respect to occupational risk calculations, the appropriateness of neurologically afflicted patients as controls must be questioned. Nonetheless, the authors were inclined to indict modern pesticides and fertilizers as causal factors for gliomas.

Austin and Schnatter (1983), in a followup case–control study of 21 patients dying from a brain tumor in a Texas petrochemical worker cohort, indicated that the tumors were of several different types. Efforts to identify unique past chemical exposures of brain tumor victims were not successful.

Using case–control methodology in reviewing 142 cases of pancreatic adenocarcinoma in several large U.S. clinical centers, Wynder and colleagues (1973) demonstrated that cigarette smokers were at increased risk of developing this disease. Risk ratios increased progressively with the number of cigarettes smoked per day. Controls for this study were patients in the same hospitals who had been interviewed for other epidemiologic studies. Controls did not include patients suffering from tobacco-related cancers (mouth, larynx, lung, esophagus, bladder, kidney) or other tobacco-related diseases (bronchitis, emphysema, coronary heart disease). Fifteen male cancer patients reported having been occupationally exposed to "dyes, chemicals, metal dust, saw dust, grease, oil, or gas fumes," but there was no difference between cases and controls with respect to the frequency with which this exposure was reported.

A case–control study in New Jersey (Stemhagen et al. 1983) of 265 victims of primary liver cancer occurring from 1975 to 1980 was conducted by interview of family members. Controls were selected from hospital records and death certificates, and were matched by age, sex, race, and county of residence. No evidence was adduced to indict smoking as a factor in causing this disease. Significantly elevated risk ratios were derived for farm laborers but not for farm owners or farm managers or for people engaged in manufacturing pesticides. Other people apparently at risk were gasoline service station employees, those employed at eating and drinking establishments, and those providing laundry and dry cleaning services. It was not possible to identify specific past chemical exposures that might have contributed to the risk.

A recent study of 102 cases of primary liver cancer in Sweden utilized controls matched by age, sex, race, year of death, and municipality where the decedent had lived (Hardell et al. 1984). No association with smoking history was found. Occupational exposure to solvents appeared to double the risk of liver cancer. No other occupations or chemical exposures were identified as risk factors, although a strong association with alcoholism was indicated.

Investigation of 207 cases of large bowel cancer in a Quebec community explored several risk factors in cases and controls, the

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latter selected from the communities where the cases resided, and matched by age and sex (Vobecky et al. 1983). Smoking was not identified as a significant risk factor, although a slightly elevated risk ratio (1.2) for smoking (alone) was calculated. Industrial exposure at a local synthetic fiber factory did appear to be a significant association (RR 2.2). When the risk of industrial exposure and smoking were considered in combination, a higher risk was evident (2.8), at a stronger level of significance. A moderate degree of smoking–occupation interaction is suggested.

Chronic Lung Disease

The likelihood that exposure to dusts and fumes in rubber product manufacture plays a causative role in the chronic obstructive lung disease encountered in this industry was examined in two studies. Fine and Peters (1976) assessed symptomatology and pulmonary function in 65 white male workers engaged an average of 7 years in rubber processing at three Akron tire plants. Air sampling showed 1 to 3 mg/m^3 of respirable dust in the work environments. Smoking habits were classified as never smoker, former smoker, current cigarette smoker, and current and former pipe and cigar smoker. Controls (189) were chosen from plant workers not exposed to polluted air. Processing workers reported a much higher prevalence of cough and phlegm than controls; this was true among nonsmokers as well as smokers in the various categories. Smoking nearly doubled the frequency of this symptom complex in the processing workers. However, dyspnea and wheeze, generally considered indicative of chronic obstructive lung disease, were no more prevalent among processing workers than among controls. Reported frequencies of bronchitis, pneumonia, asthma, and winter colds were not significantly greater among these workers than among controls. Pulmonary function testing yielded important findings. In comparing all workers with all controls, only the ratio of forced expiratory volume in 1 second to forced vital capacity (FEV_1/FVC) was significantly lower in the particulate-exposed workers. However, the exposed group and the control group were subdivided according to whether they had been employed in their respective jobs for more or less than 10 years. Although the long-term processing workers were older and had smoked longer than the controls, decrements in flow rates and FEV_1/FVC were not significantly correlated with years of cigarette smoking. Using appropriate adjustments for age, the long-term-exposed employees exhibited significant deficits in FEV_1, FEV_1/FVC, and flow rates at 50 and 25 percent of FVC. Multiple regression analysis confirmed that duration of employment in rubber processing was a significant predictor of reduced FEV_1 and FVC. Employment for more than 10 years appeared to cause a significant decline in FEV_1/FVC and the FVC-standardized flow rate

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at 50 percent FVC. These results were independent of smoking variables, ethnicity, socioeconomic status, and age. The absence of a correlation between decrement in lung function and cigarette smoking and the small number of workers in this study raise questions about the generalizability of the data in this study.

Lednar and colleagues (1977) examined the work history and smoking habit backgrounds of 73 former rubber workers who were retired prematurely between 1964 and 1973 with medically documented, disabling pulmonary disease. They were members of a cohort of 4,302 workers employed in 1964 at an Akron plant. Thirty-nine were retired with emphysema, 10 with lung cancer, 8 with asthma, and 16 with other pulmonary conditions. Work background and likely exposure to dusts and fumes were determined from company records; smoking histories were obtained from questionnaires mailed to retirees or relatives. The investigators utilized two control groups, the first consisting of disabled employees retired because of diseases other than pulmonary (disabled controls) and the second of currently employed workers and early retirees free of acknowledged pulmonary disease (nondisabled controls). Relative risk ratios were calculated for smoking and for occupational exposures to dusts and fumes. Relative risks for pulmonary disability retirement in relation to smoking and various occupational titles were also calculated. Risk ratios for smoking alone (based on smokers and nonsmokers at worksites not otherwise contaminated) were consistently greater than 1.0, but they were significant only in the case of maintenance workers. For all workers combined, the smoking risk ratio was 2.95 ($p<0.05$). Ratios for occupational exposure alone were remarkably elevated in some job classifications, but none were significant. When the combination of smoking and occupational exposure was considered, however, substantially and significantly elevated risk ratios were found for workers engaged in extrusion (15.8), finishing and inspection (7.8), curing (6.7), and other tasks. Furthermore, combined exposure to dust and cigarette smoke appeared to increase by tenfold to twelvefold the risk of pulmonary disability. The data suggested interactive effects between smoking and occupational pollutants, more in the range of potentiation than simple addition.

Another suggestion of enhanced adverse effects from cigarette smoke and irritating air pollutants has come from examination of workers exposed to airborne contaminants from the milling of rubber (Sparks et al. 1982). For the factory worker population as a whole, productive cough was definitely more common among current smokers than among nonsmokers: 35.5 percent of the smokers versus 6.5 percent of the nonsmokers in parts of the plant where dust concentrations were minimal. Among workers exposed to irritating dust, 8 percent of the nonsmokers experienced a productive cough

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and 42.5 percent of the smokers were so affected. In a work area where dust concentrations were highest, but did not generate complaints of upper respiratory tract irritation, 3.3 of the nonsmokers and 29.3 of the smokers reported productive cough. The combination of irritating fumes or particles with cigarette smoke may stimulate bronchial mucus secretion more than either factor acting alone.

In a recent longitudinal study of 3,799 male coke oven workers, Madison and colleagues (1984) examined relationships between a series of risk variables (age, current smoking status, job location) and indices of pulmonary function (FEV_1, FVC, and detailed exfoliative cytology of sputum). Covariance and multiple logistic regression analyses were done to identify the principal factors predicting FEV_1 and FEV_1/FVC. Measurements were done in 1978 and in 1982. Appropriate adjustments were made for height, weight, and years at the coke oven. Data from Caucasians and blacks were analyzed separately. Both smoking and job location (six categories) had significant detrimental effects on FEV_1 and FEV_1/FVC in Caucasian workers. In blacks, smoking adversely affected FEV_1 and FEV_1/FVC but job location did not.

Sputum cytology included examination for various cells (reactive bronchial epithelial cells, metaplastic epithelium, histiocytes, polymorphonuclear leukocytes); prominence in each specimen was graded on a scale of 0 to 4, and atypical metaplasia was rated as mild, moderate, or severe. The investigators found excessive prominence of certain exfoliated cells well correlated with reduced FEV_1 and FEV_1/FVC, a result apparently not caused by smoking, because the percentage of workers showing cells was equivalent in both smoking categories. Multiple logistic regression was done to identify factors principally responsible for metaplasia in Caucasians: age and smoking were the strongest predictors, but job location was also a significant factor. Among blacks, only smoking and age were significantly predictive.

Madison and colleagues (1984) believe that their use of data from two examinations, plus sputum cytology, identified work-related pulmonary injury not demonstrated in earlier cross-sectional studies and that the findings may portend pulmonary disability in some workers. The interval between examinations was not considered long enough to permit time trend analysis. These authors reported no measurement of airborne particulate or fumes at the six job locations.

Research Recommendations

1. Efforts to minimize workplace exposure to known and suspected carcinogens should continue and not be delayed in anticipa-

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tion of definitive evidence of hazard from occupational or environmental studies in humans.

2. Efforts to assist smokers in their efforts to quit smoking must continue in all sectors of the population. Blue-collar workers have a higher prevalence of smoking and a higher exposure to materials that might interact with cigarette smoke to increase disease risk. Because of these dual exposures, an intensive effort should be made to reduce the smoking rates of these workers.
3. Epidemiologic studies to assess the health impacts of smoking or work exposures to noxious substances should take both factors into account as potentially causative. Additionally, the possibility of interaction should be kept in mind, and whenever possible, tested for.
4. Laboratory animal studies designed to explore the health-damaging effects of tobacco smoke should include experiments capable of identifying interactions with major industrial pollutants.
5. There should be continuing research aimed at identifying the principal constituents of common industrial pollutants that act as cancer initiators and promoters. There should also be continuing efforts to demonstrate the mechanism of tissue damage caused by cigarette smoke and various industrial pollutants, alone and in combination.
6. Modern tissue culture techniques employed to identify carcinogens should be exploited as test systems for interactive effects between tobacco smoke constituents and industrial pollutants.

Summary and Conclusions

1. The biotransformation of industrial toxicants can be modified at least to some extent by the constituents of tobacco smoke through enzyme induction or possibly inhibition. Both tobacco smoke and some industrial pollutants contain substances capable of initiating and promoting cancer and damaging the airways and lung parenchyma. There is, therefore, an ample biologic basis for suspecting that important interactive effects between some workplace pollutants and tobacco smoke exist.
2. In mortality studies of coke oven workers and gas workers, convincing evidence has indicated that work exposures to oven effluents are causing an excess risk of lung cancer in spite of the lack of adequate information on smoking. Other mortality studies that suggest small increases in smoking-related diseases, such as pancreatic cancer in refinery workers, cannot be interpreted without more information on smoking.

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3. For bladder cancer, the interactions between smoking and occupational exposure are unclear, with both additive and antagonistic interactions having been demonstrated.
4. The risk of pulmonary disability in rubber workers was increased when smoking and occupational exposure to particulates were combined. There are few empirical animal experiments that demonstrate interactive effects between cigarette smoking and various industrial chemicals for lung disease.

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CHAPTER 10

COTTON DUST EXPOSURE AND CIGARETTE SMOKING

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Introduction

Exposures to cotton, hemp, and flax dust have been associated with two acute pulmonary responses: irritant (industrial) bronchitis and chest tightness (byssinosis). These symptoms, often accompanied by reduction in lung function, have occurred in 2 to 30 percent of cotton textile workers within hours of resuming exposure following a weekend or holiday (Schilling 1956; Morgan et al. 1982). These elements of the acute cotton dust pulmonary response may not occur together, and may represent responses of distinct pulmonary mechanisms. The exposure variables or host characteristics that lead to cough rather than to bronchoconstriction are currently under careful study (Hogg and Eggleston 1984). The effects of cigarette smoking upon these different responses is also incompletely understood.

In the manufacture of cotton textiles, cotton dust exposure occurs most intensely when the tightly packed bale is opened and when abrasive crushing and carding remove the "trash" (plant bracts and other parts, dirt, bacteria, and fungi) and align the fibers for spinning (Gideon and Johnson 1978). Normally, as the cotton fibers are spun, twisted, and woven into cloth, progressively less dust is generated. By the time cotton cloth is processed, the procedure is practically free of cotton dust (Kilburn 1983).

Cross-sectional studies have shown that byssinosis prevalence is greatest among cotton textile workers in the dusty preparation jobs (e.g., carder, stripper, or grinder) (Figure 1). Byssinosis prevalence has been related to the duration of cotton dust exposure, to the quality of the raw cotton, and to the levels of lint-free cotton dust (Molyneux and Tombleson 1970; Merchant, Lumsden, Kilburn, O'Fallon et al. 1973b; Kamat et al. 1981). At a cotton dust level of 0.2 mg/m^3 (lint-free dust of approximately 15 μm or less), approximately 15 percent of the cotton textile workers have some grade of byssinosis (Merchant, Lumsden, Kilburn, O'Fallon et al. 1973b). While a small sex-specific effect (male disadvantage) has been noted (Berry et al. 1974), no age effect has been shown after adjustment for exposure (Merchant, Lumsden, Kilburn, O'Fallon et al. 1973b; Berry et al. 1974). Cigarette smoke interacts with cotton dust exposure in cotton textile workers and has been associated with increased byssinosis prevalence and severity (Berry et al. 1974). The frequency of byssinosis has been closely correlated with the presence of chronic bronchitis, and both symptoms have been associated with ventilatory impairment (Imbus and Suh 1973). Cross-sectional studies have correlated cotton dust exposure with two components of ventilatory impairment: reduction in the baseline level of forced expiration and reversible loss of function across a work shift. The relationship of byssinosis and bronchitis with ventilatory impairment and its

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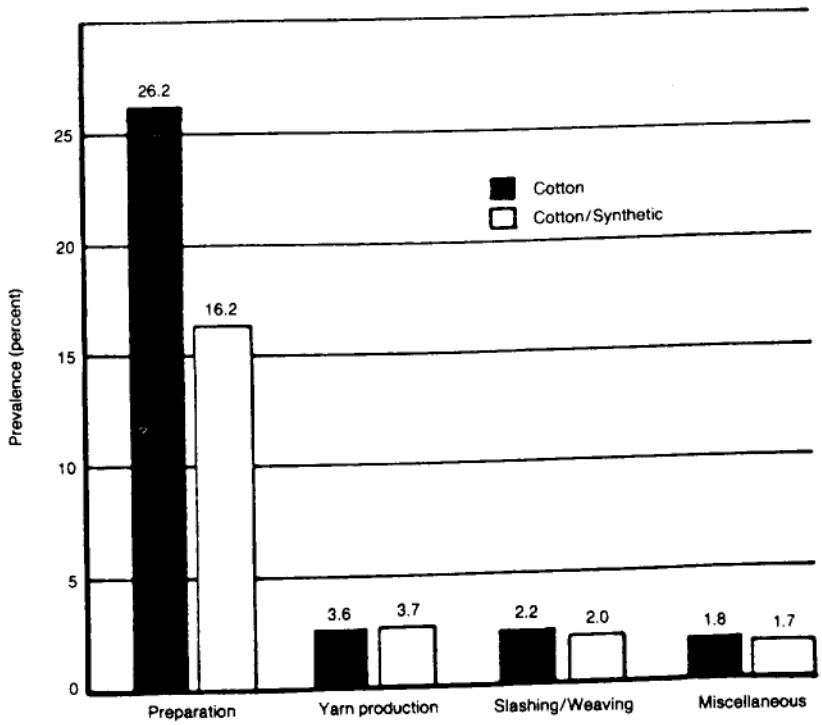


FIGURE 1.—Byssinosis prevalence by work area and raw material use

NOTE: Average prevalence: cotton, 5.2 percent; cotton/synthetic, 4.4 percent.
SOURCE: Imbus and Suh (1973).

relationship to cigarette smoking is discussed in greater detail later in this chapter.

Influence of Cigarette Smoking on the Natural History of Byssinosis

Cigarette Smoking Patterns Among Workers Exposed to Cotton Dust

The smoking patterns of cotton dust exposed workers have been reported by a number of authors and are presented in Table 1.

In summary, current studies show that male cotton workers tend to smoke to a greater degree than do female cotton workers. Male textile workers in Western Europe and in Canada smoke with

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TABLE 1.—Prevalence of smoking in studies of cotton workers

Study	Number and type of population	Smoking characteristics (percent)				Comments
Schrag and Gullett (1970)	509 cotton textile workers		SM 38	EX/NS		Percent smoking <1 pack/day not available
Kari-Koskinen and Hirvonen (1970)	987 female cotton workers, Finland		16.9	83.1		>53% began smoking at 15–19 years of age
		Age				
		17–29	39.8			
		30–39	14.1			
		40–49	9.0			
		50–60	5.0			
Merchant, Kilburn, et al. (1972)	435 cotton-synthetic blend workers, North Carolina		SM 54.7	EX 12.0	NS 33.3	
Kilburn, Kilburn et al. (1973)	1,046 female textile workers, North Carolina		SM			
		Syn. wool workers	45.2			
		Cottonmill workers	35.8			
Szymczykiewicz et al. (1970)	637 men, 2,530 women	Men	80.5			
		Women	8.9			
Fox et al. (1973)	Cotton workers, 35 mills, Great Britain		SM 62	NS 31.6	EX 6.3	
		Cigs/day				
		1–14	38.2			
		15–24	21			
		>24	2.8			

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TABLE 1.—Continued

Study	Number and type of population	Smoking characteristics (percent)			Comments
Imbus and Suh (1973)	10,133 cotton workers, North Carolina		Men	78	Smokers include ever smoked 1 cig/day for 1 year
			Women	43	
Berry et al. (1974)	14 cotton and 2 manmade fiber mills, Great Britain		Men	75.6	Former smokers not reported
			Women	56.5	
Zuskin et al. (1976)	Wool workers and controls	Workers	Men	47	
			Women	0	
		Controls	Men	55	
			Women	0	
Khogali (1976)	271 ginnery workers, Sudan			SM 36.5	Almost 1/2 smokers said smoked <5 cigs/day
Jones et al. (1977)	153 cottonmill workers, southeast United States			SM/EX 70	
Bouhuys et al. (1977)	Card and weave room workers, South Carolina			SM	
			Men	18–41	
			Women	15–25	

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TABLE 1.—Continued

Study	Number and type of population	Smoking characteristics (percent)				Comments
Palmer et al. (1978)	203 gin workers		SM	EX	NS	*( )=mean pack-years (1 pk/day/year)
		Ginners	51.1 (16.0)*	25.5 (9.6)	23.4	
		Pressmen	57.1 (7.3)	19.1 (4.1)	23.8	
		Others	45.5 (15.3)	15.1 (8.0)	39.4	
		Controls	52.3 (11.4)	19.2 (9.1)	28.5	
Bouhuys et al. (1979)	Textile workers, aged ≥45, South Carolina	Women	SM	EX	NS	
		Carding	18	14	68	
		Spinning	20	10	70	
		Preparing	17	14	69	
		Weaving	20	10	69	
		Others*	15	11	74	*Includes cloth room workers and miscellaneous job categories
		Men				
		Carding	26	44	26	
		Spinning	37	45	18	
		Preparing	50	42	8	
		Weaving	38	37	18	
		Others*	20	35	30	
Jones et al. (1979)	Cotton and wool/synthetic mill workers		SM*	NS		*Smokers include ex-smokers
		Mill 1	52.8	47.2		
		Mill 2	66.9	33.1		
		Mill 3	64.8	35.2		
		Mill 4	38.0	62.0		

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TABLE 1.—Continued

Study	Number and type of population	Smoking characteristics (percent)			Comments
			SM	EX	
Barman (1979)	70 cottonmill workers	Men	44	28	
		Women	58		
Sparks and Peters (1980)	Cotton dust-exposed workers	Men	44	28	
		Women	55	—	
Grimard and Adams (1981)	Textile workers, Canada	Men	76.6		
		Women	60.4		
Beck et al. (1982)	118 male and 162 female cotton textile workers	Men			
		Workers	27		
		Controls	16		
		Women			
		Workers	31		
		Controls	43		

NOTE: SM = Smoker; EX = Ex-smoker; NS = Nonsmoker.

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greater frequency than do American workers, with many studies showing the proportion of smokers to be well over 70 percent.

Acute Effects of Smoking and Cotton Dust Exposure on Respiratory Symptoms

The symptoms of Monday chest tightness begin gradually, 3 or 4 hours after the cotton textile worker returns to work. A dry cough and shortness of breath on exertion frequently accompany the sensation of chest tightness. However, the physiologic reaction associated with Monday chest tightness is not confined to the chest. A low grade temperature, a 20 to 30 percent increase in the peripheral white blood cell (polymorphonuclear leukocyte) count, and a general malaise have been frequently reported. These systemic symptoms suggest the presence of a host inflammatory response; however, the relationship between these systemic symptoms and the symptom of chest tightness is not well defined.

By 1936, an association had been recognized between Monday chest tightness and detectable loss of ventilatory capacity and increased breathlessness (Prausnitz 1936). Recognition that in susceptible cotton mill workers, Monday chest tightness may be followed by permanent respiratory disability led to the evolution of a standard byssinosis case definition. Schilling and colleagues (1955) developed specific questions concerning Monday chest tightness for the British Medical Research Council's respiratory symptom survey questionnaire (*British Medical Journal* 1960). A positive response to the standardized questions regarding Monday chest tightness defined the presence of byssinosis.

Molyneux and Tombleson (1970) conducted one of the first prospective studies of byssinosis. At the initial examination, these investigators interviewed 1,359 workers from 14 cotton spinning mills and 227 workers from 2 manmade fiber spinning mills in Lancashire, United Kingdom. Followup examinations were conducted at 6-month intervals over 3 years, from 1963 to 1966. Byssinosis and bronchitis prevalence were determined by the use of the Medical Research Council's questionnaire on respiratory symptoms (*British Medical Journal* 1960), to which the Roach and Schilling (1960) questions on chest tightness were added. Byssinosis was graded as follows (Molyneux and Tombleson 1970):[1]

Grade 0: No evidence of chest tightness or breathing difficulty on the first day of the workweek

Grade 1/2: Occasional chest tightness on Mondays

[1] Note: Other investigators have used grade [illegible] to indicate the presence of chronic obstructive pulmonary disease (COPD). Rooney et al. 1969. However, this category would also include the chronic obstructive pulmonary disease that occurs secondary to cigarette smoking among cotton workers since COPD occurs frequently [illegible] is not specific for disease related to cotton dust exposure.

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Grade 1: Chest tightness or difficulty in breathing on Mondays only

Grade 2: Chest tightness or difficulty in breathing on Monday and other days

Age, length of exposure to cotton dust, and smoking habit were determined by questionnaire. Individuals were considered smokers if they regularly smoked one or more cigarettes per day. Hexlet and total dust air samplers were used to measure the mass concentration of the respirable, medium, and fly components of the total airborne dust.

Byssinosis prevalence (adjusted for age, sex, and mill type) showed a progressive increase with increasing duration of cotton dust exposure (Table 2) (Molyneux and Tombleson 1970). A rearrangement of the data from this Lancashire mill workers study and calculation of the Mantel-Haenszel (weighted) odds ratios (Mantel 1963) shows an interesting relationship between smoking, byssinosis, bronchitis, and sex. A similar relationship is demonstrated by data from studies of American cotton mill workers (Merchant et al. 1972; Imbus and Suh 1973). Cigarette smoking was associated with an overall 2.21-fold excess risk of bronchitis in the Lancashire cotton mill workers (Table 3). Cotton mill workers of both sexes who smoked had a consistently greater prevalence of bronchitis than did nonsmokers. The magnitude of the smoking effect was similar for men (2.28-fold) and women (2.16-fold). The presence of bronchitis conferred an approximately twofold excess risk of developing byssinosis (Table 4). This risk was significant for men and for women, for smokers as well as for nonsmokers. Once the presence of bronchitis had been controlled for, however (Table 5), cigarette smoking did not add significant additional risk for developing byssinosis.

One may interpret these observations to show that among cotton mill workers both cotton dust exposure and cigarette smoking produced the symptoms of bronchitis. Bronchitis, in turn, seemed to confer additional risk for the development of acute chest tightness (byssinosis). Cigarette smoking, therefore, seems to facilitate the development of byssinosis in smokers exposed to cotton dust, perhaps by the prior induction of bronchitis. Applying an additive logit model (6 dust levels x 3 lengths of exposure x 4 combinations of sex and smoking habit) to these data, Berry and colleagues (1974) found that cigarette smokers had a modest (1.4-fold) increase in the adjusted prevalence of byssinosis when compared with nonsmokers and ex-smokers. Two years after the initial questionnaire survey, these investigators were able to reinterview about half of the original population (669 cotton workers and 127 manmade fiber workers). Incidence and remission rates were tabulated for byssinosis and bronchitis by length of exposure, sex, and smoking status. The incidence of both bronchitis and byssinosis was greater among

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TABLE 2.—Prevalence (percent) of byssinosis in nine exposure groups

Exposure (yr)	Number in group	Observed prevalence	Prevalence adjusted for age	Prevalence adjusted for age, mill type, and sex
0–4	305	5.2	8.8	8.0
5–9	155	23.3	20.5	19.2
10–14	168	28.0	22.3	21.0
15–19	187	35.8	29.5	27.5
20–24	117	36.8	30.9	31.1
25–29	115	43.5	40.2	42.4
30–34	94	30.9	30.2	35.1
35–39	99	35.4	36.5	41.4
≥40	119	33.6	37.7	41.8

SOURCE: Molyneux and Tombleson (1970).

TABLE 3.—Age-adjusted association of bronchitis and smoking, by byssinosis status and sex

Smoker	Bronchitis with byssinosis N	Present	Absent	Bronchitis without byssinosis N	Present	Absent	Chi square and odds ratio for the association of smoking/bronchitis[1]
				Men			
Yes	127	55%	45%	301	46%	54%	$X^2=15.20$
No	33	55%	45%	105	21%	79%	OR=2.28
							($p<0.0001$)
				Women			
Yes	125	48%	52%	322	31%	69%	$X^2=21.10$
No	78	33%	67%	268	16%	84%	OR=2.16
							($p<0.0001$)
Chi Square[2]:		$X^2=2.83$			$X^2=36.8$		
Odds Ratio[2]:		OR=1.49			OR=2.63		
		($p=0.09$)			($p<0.0001$)		
Chi Square[3]:							$X^2=36.3$
Odds Ratio[3]:							OR=2.21
							($p<0.0001$)

[1] Weighted by Mantel-Haenszel technique for byssinosis frequency.
[2] Weighted by Mantel-Haenszel technique for sex distribution.
[3] Weighted by Mantel-Haenszel technique for frequency of both byssinosis and sex.
SOURCE: Molyneux and Tombleson (1970).

smokers than among nonsmokers or ex-smokers of both sexes; however, these differences were not statistically significant (Berry et al. 1974).

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TABLE 4.—Age-adjusted association of bronchitis and byssinosis by smoking status and sex

Association of byssinosis and bronchitis	Odds ratio	p-Value
Men and women combined		
Cigarette smoker	1.73	0.0002
Nonsmoker	3.13	<0.0001
Combined smoking status		
Men	1.80	0.001
Women	2.25	<0.0001
Combined overall	2.02	<0.0001

SOURCE: Data from Molyneux and Tombleson (1970).

TABLE 5.—Age-adjusted association of byssinosis and smoking by bronchitis status and sex

Association of byssinosis and smoking	Odds ratio	p-Value
Men and women combined		
Bronchitis present	0.82	0.39
Bronchitis absent	1.44	0.03
Combined bronchitis status		
Men	1.19	0.45
Women	1.17	0.36
Combined overall	1.18	0.23

SOURCE: Data from Molyneux and Tombleson (1970).

More than 10,000 Burlington Industries textile employees (95 percent of the workforce) from 19 plants participated in a 1970 survey conducted by Duke University with the cooperation of Burlington Industries and the North Carolina State Board of Health (Imbus and Suh 1973). Each participant received the modified British Medical Research Council Respiratory Questionnaire for determining the prevalence of byssinosis and bronchitis. Byssinosis was graded according to the classification of Roach and Schilling (1960). Chronic bronchitis was defined as grade 0, no evidence of sputum production; grade 1, simple chronic bronchitis; and grade 2, chronic bronchitis with an exacerbation (Imbus and Suh 1973). Smokers were defined as those regularly smoking one or more cigarettes per day (Molyneux and Tombleson 1970). Forced expiration was measured in all participants before the beginning of the work shift on the first day of the workweek. Approximately 80

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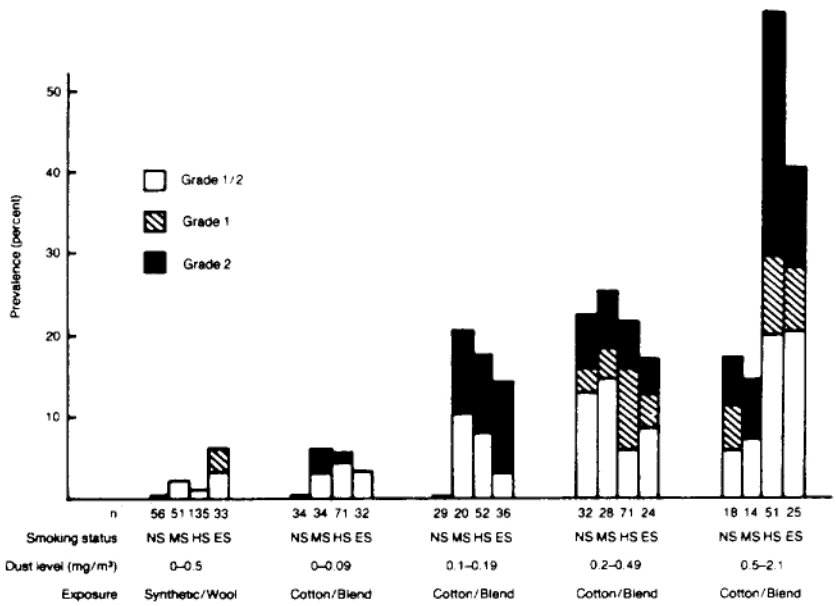


FIGURE 2.—Byssinosis prevalence by grade, smoking status, and dust level among men working in synthetic/wool mills and cotton/blend mills, North Carolina, 1970–1971

SOURCE: Merchant, Lumsden, Kilburn, O'Fallon et al. (1973a)

percent underwent spirometry again 6 hours into the work shift (Imbus and Suh 1973).

Like Molyneux and Tombleson (1970) in their study of the Lancashire mill workers, the North Carolina investigators found that smoking was responsible for a doubling of the bronchitis risk and that the presence of bronchitis was strongly associated with byssinosis. After controlling for the effect of bronchitis, there was no additional significant smoking effect on the risk of chest tightness at the observed dust levels. Cigarette smoking seemed to play a greater role in byssinosis prevalence as cotton dust levels rose (smoking–cotton dust interaction). Figure 2 shows no cigarette smoking effect on byssinosis prevalence at low dust levels. However, at the highest dust levels, cigarette smoking was found to interact with cotton dust exposure to substantially increase the acute symptom prevalence (Merchant et al. 1972; Merchant, Lumsden, Kilburn, O'Fallon et al. 1973a).

No "safe" level of cotton dust exposure has been identified for cigarette smokers (Merchant, Lumsden, Kilburn, O'Fallon et al. 1973b). However, among nonsmokers, these investigators found no case of byssinosis below a cotton dust level of 0.2 mg/m^3. An

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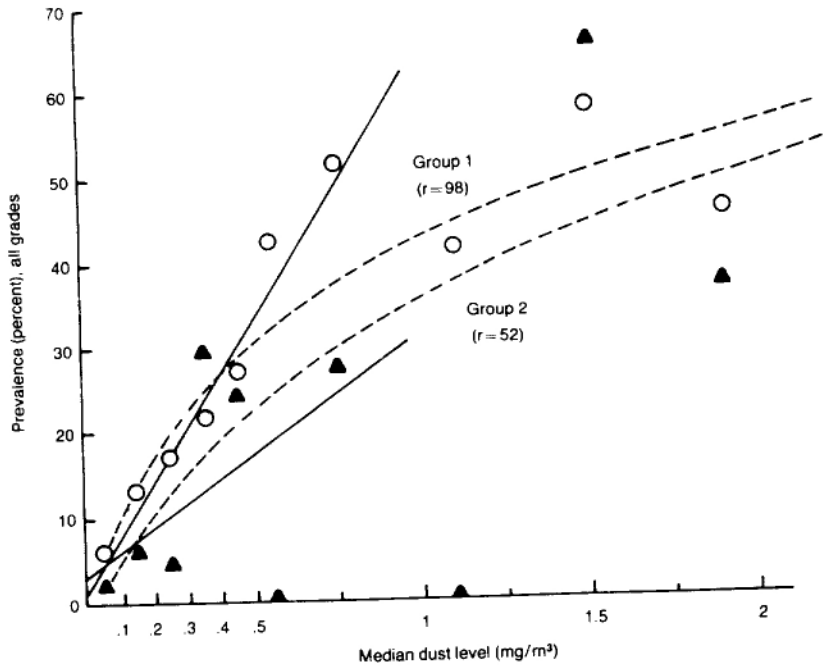


FIGURE 3.—Byssinosis prevalence by median dust level among current smokers and those who never smoked, preparation and yarn area workers, linear regressions and fitted profit dose–response curves

NOTE: Group 1 (○), smokers, group 2 (△), nonsmokers.
SOURCE: Merchant, Lumsden, Kilburn, O'Fallon et al. (1973b).

examination of a large population found one case in a nonsmoker below this level (Figure 3). Workers with byssinosis who stopped smoking but did not change their work area lost their byssinosis symptoms (Merchant et al. 1972). These observations suggest that there may be a "safe" level of cotton dust in the absence of other inhaled irritants. Cigarette smoking seems to lower this threshold of susceptibility to chest tightness below the present limits of cotton dust detection. At least in some individuals, this threshold may be restored by smoking cessation.

The repeated demonstration of a linear dose–response relationship of symptoms with cotton dust levels led to the development of cotton dust exposure standards to protect the majority of the workforce (Roach and Schilling 1960; McKerrow et al. 1962; Merchant et al. 1972; Merchant, Lumsden, Kilburn, O'Fallon et al. 1973b). The

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American Congress of Government Industrial Hygienists' (ACGIH) early cotton dust standard was based upon the work of Roach and Schilling (1960), which concluded that 1 mg/m^3 gross (total) dust was a safe level for occupational exposure. Further study, however, found that the biologic activity of cotton dust resided primarily in the respirable dust fraction (McKerrow et al. 1962). The use of total dust as the only measure of exposure has sometimes resulted in a misleading lack of association between cotton dust level and byssinosis symptoms (McKerrow et al. 1962; Molyneux and Tomblesson 1970; Merchant et al. 1972).

High correlations between byssinosis symptoms and respirable dust levels were observed, using the vertical elutriator to sample dust of an aerodynamic diameter of 15 μm and less (Merchant, Lumsden, Kilburn, O'Fallon et al. 1973b). In Figure 3, cigarette smokers are shown to have a slightly higher prevalence of byssinosis symptoms than nonsmokers at each measured dust level. A linear dose–response model fits the data at low dust levels. At respirable dust levels from 0.1 to 0.75 mg/m^3, the byssinosis prevalence in nonsmokers rose from 5 to 24 percent, and in smokers, from 8 to 53 percent. The tapering of the dose–response curve at higher dust levels has been attributed to self-selection by less susceptible cotton workers (Kilburn 1983).

To minimize the acute symptoms and to inhibit possible chronic consequences, the Occupational Safety and Health Administration (OSHA) (US DOL 1981) has modified the permissible exposure limits to acknowledge the importance of the respirable fraction of cotton dust (approximately 15 μm or less aerodynamic equivalent diameter). The OSHA standard specifies that employees engaged in yarn manufacturing may not be exposed to respirable cotton dust levels greater than 0.200 mg/m^3 over an 8-hour average, and employees assigned to the slashing/weaving processes can be exposed to no more than an 8-hour average of 0.750 mg/m^3 of cotton dust (US DOL 1981). No specific accommodation has been made to recognize the increased byssinosis susceptibility of cigarette smokers.

Effects of Smoking and Cotton Dust Exposure on Pulmonary Function Tests

In a cross-sectional study of 61 textile workers on carding machines, Zuskin and colleagues (1975) found a rough correlation between the grade of byssinosis and the 1-second forced expiratory volume (FEV_1) before dust exposure. These observations confirm those of Merchant, Halprin and colleagues (1974) (Figure 4). It is suggested that those with byssinosis symptoms start the workweek with a lower FEV_1 than those without symptoms (age, height, sex, race unaccounted for), and at least for the individuals with byssinosis grade 1/2, that overnight exposure cessation is insufficient for

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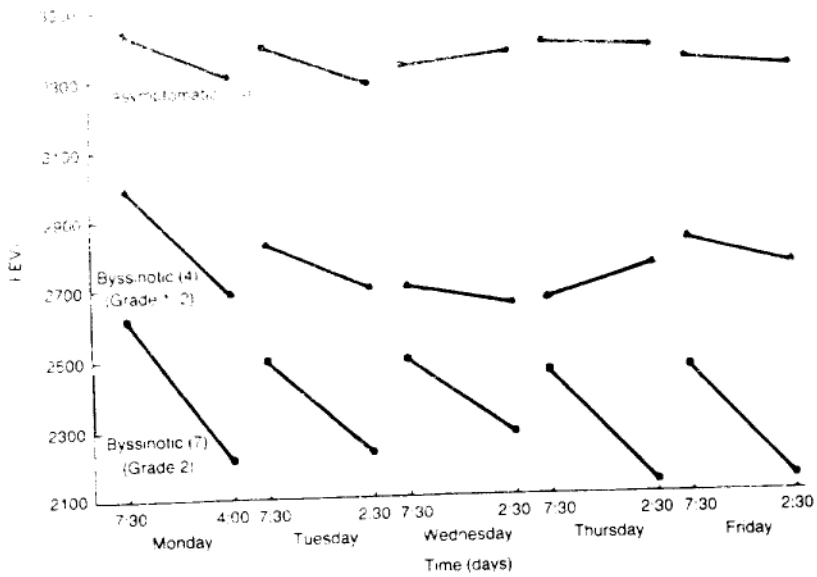


FIGURE 4.—FEV_1 during 5-day exposure of 25 carders
SOURCE: Merchant, Halprin et al. (1974).

complete respiratory recovery and that a longer abstinence period (a weekend, for example) is necessary to restore preexposure levels of ventilatory function (Merchant, Halprin et al. 1974).

The baseline (initial) ventilatory function, measured as percent of predicted FEV_1 and forced vital capacity (FVC), showed that among nonsmokers (Table 6), a mild decrease was noted in those with bronchitis alone (without byssinosis) and a more marked decrease was observed in those with byssinosis alone (without bronchitis). In men, the lowest value was observed among bronchitics with byssinosis. Smoking further reduced the baseline ventilatory function in every category (except nonbronchitic, byssinotic women). (The authors pointed out that the small sample size may have made the slightly higher ventilatory function value among this group of women somewhat uncertain.) There was also an interaction of the effects of cigarette smoking with cotton dust exposure upon baseline forced expiration, similar to that found for symptoms of chest tightness (Merchant, Lumsden, Kilburn, O'Fallon et al. 1973b).

Studies of pulmonary function among 61 textile workers showed that cotton dust exerts its acute effect primarily upon the conducting airways rather than upon the gas-exchanging parenchyma (Zuskin et al. 1975). Zuskin and colleagues observed a significant reduction

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TABLE 6.—Average percentage of predicted FEV_1 in smokers and nonsmokers with and without byssinosis and bronchitis

Subjects	Average percent of predicted FEV_1 (sample size)	
	Nonbyssinotic	Byssinotic
Male nonsmokers		
Nonbronchitic	89.4 (993)	84.5 (28)
Bronchitic	88.2 (59)	80.1 (16)
Male smokers		
Nonbronchitic	85.9 (3,172)	81.5 (157)
Bronchitic	81.2 (434)	73.7 (109)
Female nonsmokers		
Nonbronchitic	85.7 (1,729)	76.6 (47)
Bronchitic	82.9 (68)	78.4 (11)
Female smokers		
Nonbronchitic	82.6 (1,213)	77.0 (30)
Bronchitic	81.3 (93)	73.5 (15)

SOURCE: Imbus and Suh (1973).

across a workshift in FEV_1 and midexpiratory flow at 50 percent ($MEF_{50\%}$) and a statistically significant increase in residual volume. In contrast, plethysmographically determined total lung capacity (a measure of alveolar volume) and the single-breath diffusing capacity (a measure of gas diffusion) were unchanged.

In Figures 5 and 6 are shown the effects of byssinosis, bronchitis, and smoking on FEV_1 measured before and after 6 hours' work, adjusted to a base age of 40 years. People with bronchitis alone (without byssinosis) and people with byssinosis alone (without bronchitis) experience a decline in FEV_1 during the workday. People with a combination of both conditions, however, show the greatest decrement. Although forced expiration change across a work shift also shows a strong association with dust levels (Merchant, Lumsden, Kilburn, O'Fallon et al. 1973b), the relationship of cigarette smoking to the cross-shift decline in function is less clear. Merchant, Lumsden, Kilburn, O'Fallon, and colleagues (1973a) found no smoking effect on acute ventilatory function change within any dust level, over all dust levels, or as part of a dust times smoking interaction (Merchant, Lumsden, Kilburn, O'Fallon et al. 1973a). Zuskin and colleagues (1969) and Jones and colleagues (1979) reported similar observations. However, Haglind and Rylander

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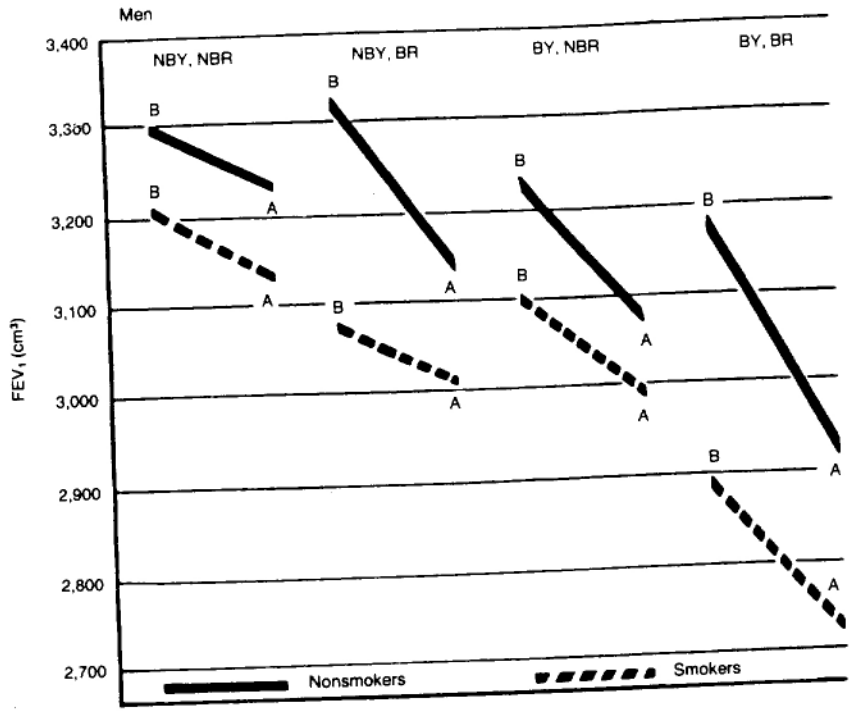


FIGURE 5.—Byssinosis, bronchitis, and smoking effects on FEV_1 in men before and after 6 hours' work, adjusted to base age 40 years

NOTE: B, before work; A, after 6 hours' work.
SOURCE: Imbus and Suh (1973).

(1984) found that cigarette smokers seemed to have a lower effect threshold. Among cigarette smokers, the threshold for a 5 percent decrease in FEV_1 was 0.58 mg dust/m^3, compared with a threshold in nonsmokers nearly threefold greater (1.63 mg/m^3). These results confirmed the findings of Merchant and colleagues (1975) among a group of 12 cotton workers in an exposure chamber. In addition to the lower threshold, Haglind and Rylander (1984) reported a larger FEV_1 decrease among smokers than among nonsmokers at the same exposure levels. These findings and the others previously mentioned suggest that cigarette smoke may enhance the airways reaction to cotton dust.

Cross-shift change in ventilatory function has been shown to depend upon the type of cotton dust as well as the level (Table 7)

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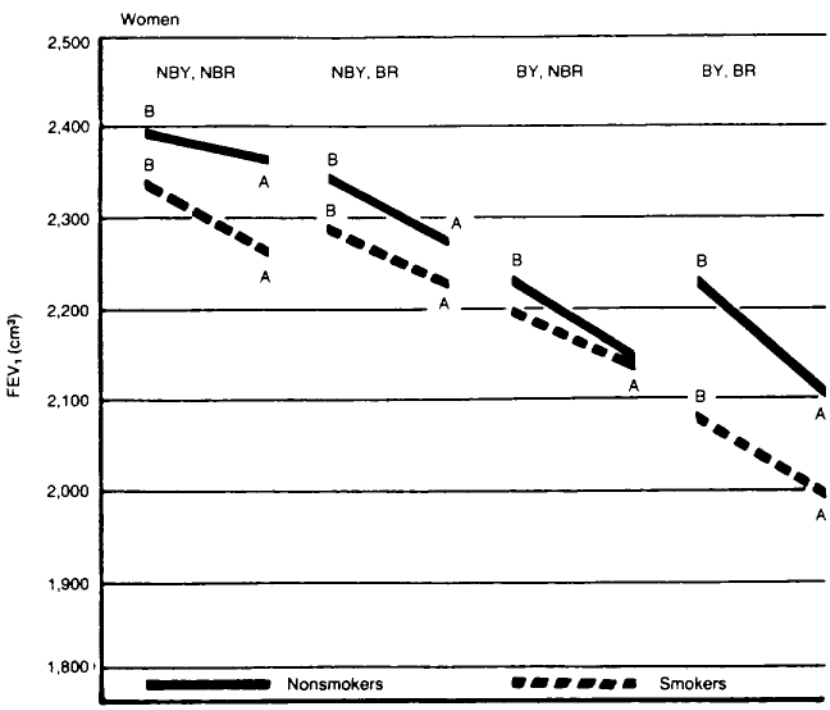


FIGURE 6.—Byssinosis, bronchitis, and smoking effects on FEV_1 in women before and after 6 hours' work, adjusted to base age 40 years

NOTE: B, before work; A, after 6 hours' work.
SOURCE: Imbus and Suh (1973).

(Schilling 1956; Roach and Schilling 1960; Merchant, Lumsden, Kilburn, O'Fallon et al. 1973b; Merchant et al. 1975; Castellan et al. 1984). Under the conditions of an experimental card room (using carding machines under typical commercial production conditions), concentrations of gravimetric elutriated cotton dust and the corresponding acute FEV_1 change were measured (Table 7). In Figure 7 is shown the significant association of dust concentration and ventilatory response found by Castellan and colleagues (1984). Bacterial endotoxin, a contaminate of cotton dust, was found in this study to correlate even more closely with a decline in ventilatory function, but Diem and colleagues (1984) found that the across-shift decline was more closely correlated with the log dust level than with the number of gram negative rods or log endotoxin level.

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TABLE 7.—Slopes of dose–response regressions for individual cottons, using vertically elutriated gravimetric dust as an exposure index

Cotton type	Change (percentage per mg/m³ of dust)		
	FVC	FEV_1	$FEF_{75\%}$
California strict middling	−0.9[1]	−0.4[1]	+4.0[1]
California strict low middling	−2.3[2]	−3.4[3]	−18.0[3]
California strict low middling spotted	−2.7[3]	−3.1[3]	−13.2[2]
Texas strict low middling	−2.3[3]	−2.9[3]	−18.4[3]
Texas strict low middling spotted	−3.6[3]	−6.2[3]	−27.3[3]
Mississippi strict low middling	−3.1[3]	−3.5[3]	−20.1[3]
Mississippi strict low middling spotted	−15.9[3]	−24.4[3]	−88.6[3]

NOTE: Regressions based on spirometric responses of 54 persons. FVC = forced vital capacity; FEV_1 = forced expiratory volume in 1 second; $FEF_{75\%}$ = maximal flow at 75 percent of expired vital capacity.

[1] p = not significant.

[2] $p < 0.01$.

[3] $p < 0.0001$.

SOURCE: Castellan et al. (1984).

Chronic Clinical Effects of Cotton Dust Exposure

Nonreversible reduction in forced expiration is usually caused by an increase in airways resistance (particularly in the small airways), a reduction in elastic recoil (emphysema), or both (Bates et al. 1971). Chronic cough and sputum production may be a nonspecific irritant reaction to particle deposition in the conducting airways. Similar reactions have been seen in cigarette smokers and workers exposed in dusty trades including mining (coal and metal), manufacturing (cement and plastics), and foundry work (Morgan and Seaton 1975; Hankinson et al. 1977; Morgan 1978; Kilburn 1983).

Chronic airflow obstruction is associated with increased age-adjusted total mortality and respiratory disease mortality. However, once adjustment has been made for airflow obstruction, cough and chronic mucus hypersecretion (the symptoms of chronic bronchitis) have little additional predictive value for chronic obstructive lung disease (COLD) mortality (Peto et al. 1983). Since there are both significant morbidity and mortality consequences associated with the development of chronic obstruction but not with simple bronchitis, it is important to determine whether the acute symptoms of bronchitis and chest tightness associated with cotton dust exposure are associated with chronic airflow obstruction to a greater extent than could be explained by cigarette smoking alone.

The contribution of the acute byssinotic symptoms (grades 1/2 and 1) to the subsequent development of airflow obstruction and the chronic forms (grades 2 and 3) of byssinosis is not well documented (Douglas et al. 1984). The term "byssinosis" is often applied to the acute response to inhalation of cotton dust as well as to the

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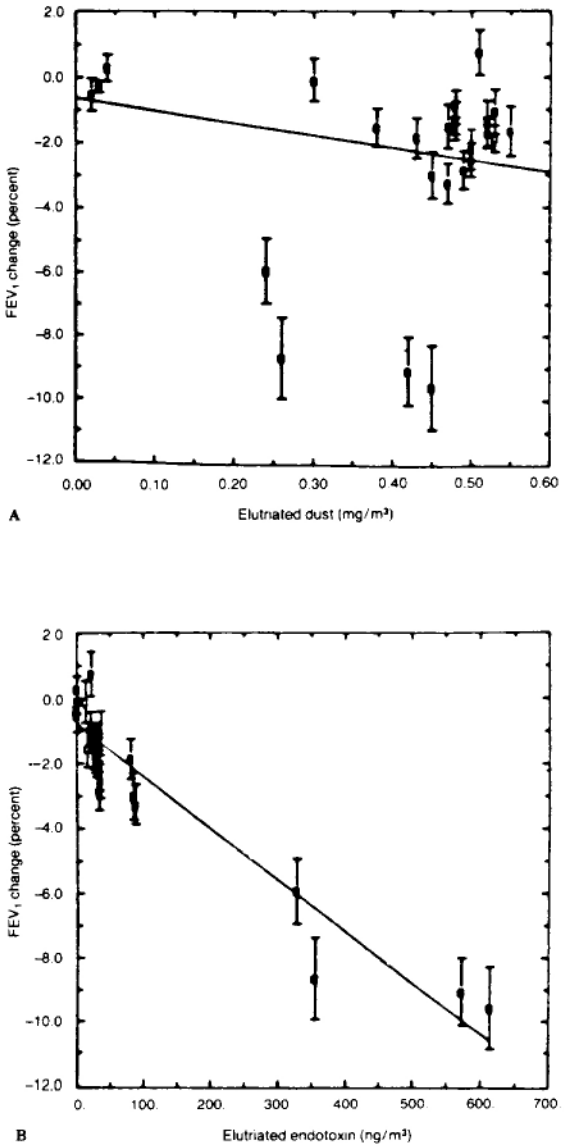


FIGURE 7.—Percentage of change in forced expiratory volume in 1 second (FEV_1) (mean±SE) for each subgroup of people exposed for 6 hours to a clean room and to dust from various cottons (54 persons in two equal-sized subgroups; seven different cottons)

NOTE: A. Plot of change in FEV_1 (percent) versus vertically elutriated airborne gravimetric dust concentration (mg/m^3); B. Plot of change in FEV_1 (percent) versus vertically elutriated airborne endotoxin concentration ($ng \cdot m^3$).
SOURCE: Castellan et al. (1984).

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permanent dyspnea with impaired function. Although a link of pathogenesis between the two has been assumed, and is supported by finding impairment in textile workers without other exposures, no longitudinal study has been done that documents this transition (Kilburn 1983).

Nevertheless, chronic airflow obstruction has been found more frequently in cotton textile workers than in control populations (Bouhuys et al. 1977; Wegman et al. 1983). Obstruction has been found particularly among the older, cigarette-smoking cotton textile workers (Merchant, Lumsden, Kilburn, O'Fallon et al. 1973a; Beck, Maunder, and Schachter 1984). Whether cotton textile workers are compared with a control population of synthetic fiber and wool workers (Merchant, Lumsden, Kilburn, O'Fallon et al. 1973a), with farmers and workers from other industries (Bouhuys et al. 1969), or with the population of a rural town (Beck, Schachter, and Maunder 1984), there is a cross-sectional correlation between occupational exposure to cotton dust and impaired ventilatory function.

Followup studies that document a greater fall in ventilatory function among those with byssinosis help to establish the transition between acute and chronic effect (Bouhuys and Zuskin 1976). Beck, Schachter, and Maunder (1984) have compared the frequency of pulmonary function abnormality among South Carolina cotton textile workers with the pulmonary function survey results among residents of a Connecticut community. These researchers report that both byssinosis and smoking were associated with subsequent impairment of age- and height-adjusted respiratory function. They found that even asymptomatic cotton textile workers had significant lung function impairment compared with controls. In general, cotton textile workers had lower lung function among smokers and nonsmokers, for both men and women and among those with and without symptoms, but these differences were only statistically significant for the nonsmoking asymptomatic female subgroup (the subgroup with the largest number of individuals). Smokers also had lower FEV_1 than nonsmokers in each of the subgroups. However, in the absence of cotton dust measurements, nonoccupational factors related to control selection may be postulated to have contributed to these findings (Tockman and Baser 1984).

Other followup studies of cotton textile workers provide inconsistent support for the importance of byssinosis to subsequent ventilatory impairment. Zuskin and Valic (1975) reported on a 10-year followup of selected members of a worker cohort exposed to coarse cotton dust. These investigators found both an increased prevalence of byssinosis on followup examination and approximately twice the rate of mean annual decline in FEV_1 among men who had byssinosis initially, compared with those who later developed it or to those who did not report this symptom. Smoking was not found to contribute

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significantly to the development of byssinosis. Contrasting results were reported by Berry and colleagues (1973), who examined cotton textile workers at several plants and found that the cotton textile workers had a 54 mL per year decline in FEV_1 compared with 32 mL per year in workers in the synthetic textile mill; however, most of this excess decline could be attributed to workers in only one mill. FEV_1 declined 19 mL per year faster in smokers than in nonsmokers. However, despite these differences between the cotton workers and the control group, no difference in annual FEV_1 decline was found between the subjects with and without byssinosis symptoms. Cotton textile workers with acute (grades 0 or 1) byssinosis symptoms and those with bronchitis following cotton dust exposure may be a subset of the population at risk of further ventilatory deterioration. The sensitivity and specificity of these symptoms for subsequent lung injury is yet to be established by cohort studies.

Followup studies of cotton textile workers have been weakened by several sources of bias. Self-selection of workers for continued employment in dusty environments introduces bias into studies that examine only the currently available workforce, who may be healthier than workers who have left the industry. Berry and colleagues (1973) reported that less than half of the subjects were available sufficiently often to calculate an annual FEV decline. Merchant, Lumsden, Kilburn, O'Fallon, and colleagues (1973b) reported substantial evidence of selection away from dust exposure in the cotton textile industry, which results in the presence of relatively resistant workers in dustier areas at the time of cross-sectional surveys. As Beck, Schachter, and Maunder (1984) have shown, it is feasible to survey the retired workforce in addition to those currently active in order to account for workers who retire prematurely because of poor respiratory health. To finally determine the magnitude of the cotton dust effect on chronic lung function of cotton textile workers, studies must carefully distinguish the separate indices of cotton dust lung injury, and impairment rates must be tabulated over the entire population at risk. However, documentation of the association between exposure and lung injury will become increasingly difficult as industrial hygiene control reduces the levels of occupational cotton dust exposure.

Mechanisms of Cotton Dust Lung Injury

Epidemiologic observations have suggested that cigarette smoking and cotton dust have complementary effects on the airways. A discussion of the mechanisms of cotton dust lung injury may facilitate an understanding of this interaction.

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Inflammation (Bronchitis)

Considerable effort has been devoted to the search for specific agents responsible for the symptoms and changes in lung function associated with cotton dust exposure. These investigations have focused upon water-soluble extracts found in the cotton bract. An animal model has been developed that partly reflects the sequence of clinical findings seen in cotton textile workers. Hamster inhalation of condensed vegetable tannins from card room floor sweepings stimulated the recruitment of leukocytes to the trachea, bronchi, and small bronchioles, with a time course similar to that of byssinosis symptoms in humans (Kilburn, Lynn et al. 1973). Tannins isolated from cotton bract have been shown to cause pneumocyte lysis (Ayars et al. 1984). Other agents in cotton dust have also been found to have pharmacologic activity (Hitchcock 1974; Ainsworth et al. 1979). Compounds that have been identified in cotton bract extract in significant concentrations include tannin, 5-hydroxytryptamine, endotoxin, and histamine (Rylander 1981; Bouhuys and Lindell 1961; Rohrbach et al. 1984; Russell et al. 1982).

Pharmacologic activity has also been isolated from the components of bacteria and fungi found in cotton bract. Studies by Cinkotai and colleagues (1977) have demonstrated a close relationship between the prevalence of byssinotic symptoms and the airborne concentration of gram-negative (endoagar) bacteria. In Figure 8 are shown a close correlation between byssinotic symptoms and levels of gram-negative bacteria, a more variable relationship with gram-positive (nutrient agar) bacteria, and no relationship with fungi or with airborne dust. Human exposure to airborne gram-negative bacteria may result in symptoms related to the presence of endotoxin lipopolysaccharide within the bacterial cell walls (Rylander 1982). This material could activate complement (Wilson et al. 1980) with subsequent generation of anaphylatoxins, release of histamine and leukotactic substances, and induction of an inflammatory response.

Cotton bales from different geographic areas may be contaminated with different levels of gram-negative bacteria. Cottons grown in dry areas with irrigation were found to have smaller amounts of gram-negative bacteria (Rylander et al. 1985). The culturing of viable organisms was found to be a misleading index of byssinosis potency, however, because endotoxin activity persists after bacterial death (Rylander et al. 1985). Airborne endotoxin levels correlated with byssinosis symptoms, blood neutrophil levels, and airways response (Rylander et al. 1985). Castellan and colleagues (1984) have reported a high correlation between endotoxin exposure and ventilatory fall in experimental exposures (part B of Figure 7). Their data show no evidence for an endotoxin exposure threshold, but this conclusion depends on the validity of the four outlying observations presented in the figure. In an experimental card room, Haglind and Rylander

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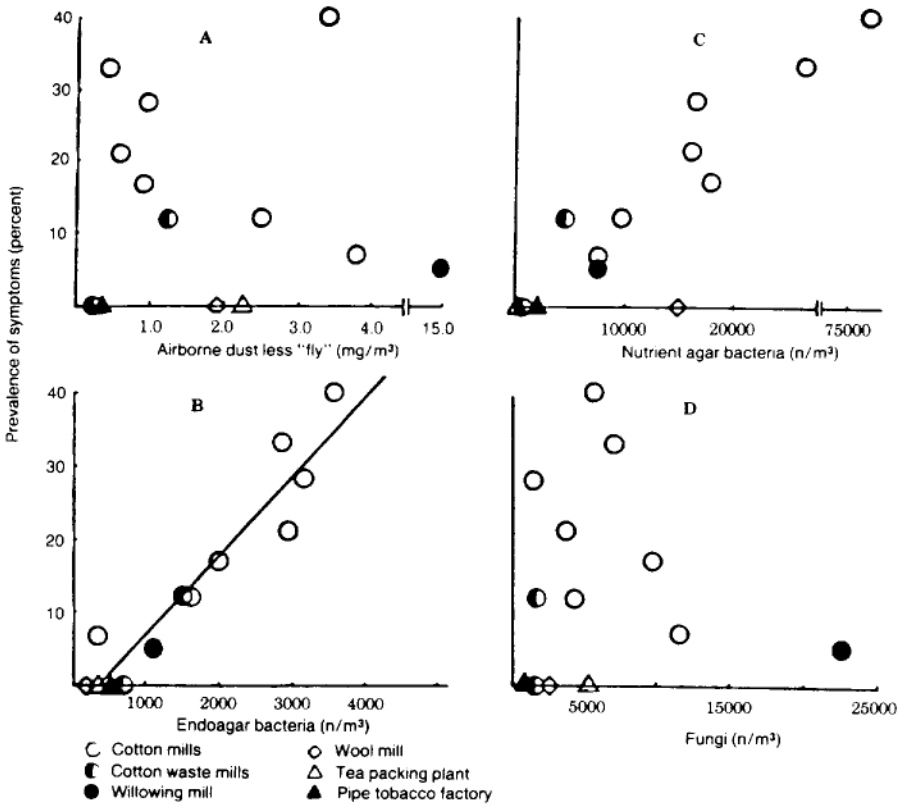


FIGURE 8.—Concentration of endotoxins in airborne dust correlated with the prevalence of byssinotic symptoms

SOURCE: Cinkotai et al. (1977).

(1984) found a dose–response relationship between the average FEV_1 decrement across a work shift and the amount of airborne dust or endotoxin. These data have been used to suggest that endotoxin contamination of cotton, rather than the plant dust itself, is responsible for the byssinosis syndrome. However, Buck and colleagues (1984) have reported that cotton bract extract contains a bronchoconstricting agent or agents distinct from endotoxin and have suggested that an interaction may exist between the effects of endotoxin and these other agents; Diem and colleagues (1984) have

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shown a closer correlation in across-shift decline in lung function with log cotton dust levels than with log endotoxin levels or the number of gram negative bacteria.

Cloutier and colleagues (1984) noted that many of the hypothesized mechanisms of byssinosis, including bacterial endotoxin effects (Rylander et al. 1979, 1985; Rylander 1981, 1982), nonallergic histamine release (Bouhuys and Lindell 1961; Ainsworth et al. 1979; Noweir et al. 1984), and airways smooth muscle contraction by a 5-hydroxytryptamine (5-HT), receptor agonist (Russell et al. 1982), require that the byssinotic agent cross the airway epithelium. Normally the respiratory epithelium bars inhaled substances from access to the interstitium, to airway smooth muscle, or to the bloodstream (Cloutier et al. 1984). The application of aqueous cotton bract extract to canine trachea has been found to disrupt this barrier by inhibition of transepithelial ion flux (Cloutier et al. 1984). Alteration in the active ion transport may result in an altered osmotic balance in the airway. Although the components of cotton bract extract responsible for the altered ion flux are unknown, Cloutier and colleagues (1984) consider tannin and 5-HT to be likely causes, endotoxin to be a possible cause, and histamine to be an unlikely cause. Other components of the cotton bract, including lacinilene C-7 methyl ether, have also been mentioned as possible etiologic agents (Kilburn 1980).

Inhalation of cigarette smoke can also induce alteration of active ion transport by the airway epithelium (Welsh and Karp 1983). Inhalation of the smoke from one cigarette decreased the electrical potential difference across the tracheal epithelium owing to an inhibition of the rate of chloride ion secretion. Active ion transport by the airway epithelium plays an important role in the regulation of the volume and composition of the respiratory tract fluid. Inhibition of transepithelial ion flux by cotton dust (Cloutier et al. 1984) and by cigarette smoke (Welsh and Karp 1983; Kennedy et al. 1984) may produce the symptoms of acute bronchitis, and each could conceivably have an additive effect upon the other.

Alteration of the osmolarity and the ion concentration of inhaled aerosols can produce both cough and bronchoconstriction (Eschenbacher et al. 1984). These investigators found that in asthmatics, the stimuli for cough could be distinguished from those for bronchoconstriction. They suggest that afferent airway nerve depolarization may occur as a result of anion flux imbalance (outward anionic flux cannot be balanced owing to the inhibition of inward anion movement) and that cough is the reflex response (Eschenbacher et al. 1984). Alternatively, Hogg and Eggleston (1984), noting that disruption of epithelial tight junctions has resulted from transtracheal osmotic gradients, propose a mechanism whereby the vagal irritant reflex receptors located close to the tight junction might be

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deformed by this osmotic disruption. In addition, epithelial injury and sensory receptor sensitization account for increased susceptibility to cough following airways irritation in asthmatic subjects (Empey et al. 1976). It is possible that acute bronchitis in cotton workers may be caused, in part, by similar mechanisms.

Airways Constriction

Cotton dust exposure may induce airways narrowing in atopic individuals (Jones et al. 1980; Parkes 1982). Skin test atopy identifies those at risk of acute bronchoconstriction (cross-shift FEV_1 change) following exposure to high concentrations of cotton dust (elevated levels of both total and respirable dust) (Jones et al. 1980). These results do not necessarily imply that a specific immunoglobulin E (IgE) response is triggered or that elevated levels of IgE (beyond those found in atopic individuals) must be detected in serum (Pepys et al. 1973). The cotton dust bronchoconstrictor response seen in atopics may be nonspecific. Agents extracted from cotton dust have been documented to produce lung injury and physiologic response in previously unexposed volunteers. The presence of an airways response in individuals not previously exposed suggests a pharmacologic or irritant mechanism rather than an idiosyncratic (allergic) one (Buck and Bouhuys 1981; Wegman et al. 1983; Douglas et al. 1984; Haglind and Rylander 1984; Schachter et al. 1985). The nonimmunologic character of the cotton dust lung response is supported by the failure to find precipitating antibodies in the sera of cotton textile workers to extracts of cotton bract, carpels, stems, leaves, cotton lint, or card room cotton dust (Kutz et al. 1981).

Release of bronchoconstricting mediators from the mast cells beneath the bronchial epithelium does not require development of immune hypersensitivity (Dosman et al. 1981; Findlay et al. 1981). The nonspecific reaction induced by cotton dust contrasts with the specific hypersensitivity reactions due to inhaled organic dusts such as complete allergens, e.g., grain dust (Dosman 1977); incomplete haptens, e.g., penicillin (Davies et al. 1974); simple but very reactive copolymerizing compounds, e.g., isocyanate (Butcher et al. 1977); or wood dusts (Chan-Yeung et al. 1973). These specific hypersensitivity reactions are found in relatively few of the exposed individuals, even after a suitable period of exposure (Dosman et al. 1981), and atopy is not required for mediator release (Lam et al. 1979; Bryant and Burns 1976; Boushey et al. 1980).

Nonspecific hyperreactivity may be acquired as a result of chronic exposure to inhaled occupational irritants (Lam et al. 1979). One mechanism for triggering mast cell degranulation and subsequent smooth muscle contraction may result from PGF release from macrophages activated by cotton dust. An aqueous extract of cotton plant "trash" has caused in vitro elaboration of prostaglandins (PGF,

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PGE, and PGA) from rabbit alveolar macrophages (Fowler et al. 1981). Bronchoconstriction also may result from changes in airway osmolarity through stimulation of airway mast cells (Findlay et al. 1981) or vagal afferents (Empey et al. 1976; Orehek et al. 1976; Golden et al. 1978; Boushey 1982).

Epithelial injury similar to that observed following a viral upper respiratory infection might expose and stimulate the rapidly adapting sensory receptors of the airway and result in reflex (vagal) bronchoconstriction (Empey et al. 1976). The rapidly adapting sensory receptors extending between the airway epithelial mucosal cells are believed to be involved in ozone-induced hyperreactivity (Golden et al. 1978). Controlled exposures to other agents such as nitrogen dioxide (Orehek et al. 1976) and sulfur dioxide (Boushey 1982) have also resulted in hyperreactivity, possibly owing to vagal sensory fiber stimulation. In addition, byssinosis-like symptoms of cough, chest tightness, substernal soreness, and shortness of breath have been reported by healthy subjects after a controlled 2-hour exposure to ozone at 0.5 to 0.6 ppm (ambient air-pollution concentrations) (Golden et al. 1978). Epithelial injury and sensory receptor sensitization may contribute, therefore, to both cough (bronchitis) and airways constriction (byssinosis).

Barter and Campbell (1976) showed that the rate of deterioration in FEV_1 correlated with methacholine reactivity, independent of the effect of cigarette smoking. Hyperreactivity may therefore indicate the individuals at risk of subsequent loss of function. Although atopic individuals may have an increased susceptibility to bronchoconstriction, at present there is no evidence that atopics are at greater risk of lung disease associated with cotton dust exposure. Perhaps the recent development of an assay for the pharmacologic activity of cotton dust (Douglas et al. 1984) will provide a sufficiently sensitive measure of cotton dust exposure to determine the role of the cholinergic bronchial response in textile workers.

It is possible that the hyperreactivity model for chronic obstructive lung disease may help explain a greater risk of accelerated ventilatory deterioration in cotton textile workers. Van der Lende and colleagues (1970) suggested that airways hyperreactivity might be an underlying factor that led to irreversible obstruction among those exposed to airways irritants. Barter and Campbell (1976) demonstrated an accelerated rate of longitudinal ventilatory function decline in those with hyperreactivity.

Chronic Inflammatory Lung Destruction

Emphysema has been demonstrated post mortem in the lungs of cotton workers (Edwards et al. 1975; Pratt et al. 1980). A significant degree of emphysema, as measured by a reduction of lung elastic

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recoil pressure at total lung capacity, was found only in older (aged 56 to 69) hemp workers (smoking status unspecified) by Guyatt and colleagues (1973). These workers had at least 20 to 30 years of cotton dust exposure. The younger population (aged 31 to 51), studied with a variety of pulmonary function measurements by Zuskin and colleagues (1975), showed no emphysema as documented by normal values of the single breath carbon monoxide diffusing capacity. This finding of emphysematous changes only among older workers is consistent with the data for smokers in the general population, and therefore does not demonstrate a specific effect of cotton dust exposure. Kilburn (1981) reported the prevalence of radiographic changes consistent with emphysema (flattening of the diaphragms and radiolucent or avascular zones of lung) in 233 male cotton textile workers and found that these radiographic changes were present only in the smokers and former smokers in the population.

The data in Tables 8 and 9 are from the study of Pratt and colleagues (1980), who examined fixed, inflated lung specimens from unselected autopsies performed at the Durham (North Carolina) Veterans Administration Medical Center. The findings from the 565 cases with known smoking histories are presented. The mean percentages of centrilobular emphysema (CLE), mucous gland volume, goblet cell metaplasia, and pigmentation grouped by employment or nonemployment as a cotton worker and by smoking status are shown in Table 8. There were 44 cotton workers, 8 of whom were nonsmokers. The statistical results of covariance analyses performed on these data are shown in Table 9. Cotton dust exposure is significantly associated with mucous gland volume and peripheral goblet cell metaplasia in nonsmokers. Cigarette smoking and pipe smoking showed associations with centrilobular emphysema, but no association of emphysema was found with cotton dust exposure. Examination of the main lobar and segmental bronchi showed no morphologic differences between smokers and nonsmokers (Edwards et al. 1984). These data may be interpreted to show that airways inflammation (bronchitis) rather than parenchymal destruction (centrilobular emphysema) follows chronic cotton dust exposure.

Cotton Dust Exposure and Mortality From Respiratory Disease and Lung Cancer

Owing partly to the difficulty in following cohorts of cotton textile workers and partly to the lack of a smoking history among the recorded deaths, there have been few studies of mortality related to cotton dust exposure. In a mortality study of two cohorts of cotton textile workers, Henderson and Enterline (1973) found lower mortality rates overall (SMR 71.7 to 89.6), lower respiratory disease mortality (SMR 36.4 to 76.1) and lower lung cancer mortality (SMR

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TABLE 8.—Mean percentages of centrilobular emphysema, mucus glands, goblet cell metaplasia, and pigmentation

Group	N	Age	Mean percent CLE[1] (all cases)	Mean percent CLE (cases with CLE)	Gland volume (percent)	Goblet cells (percent)	Pigmentation (percent)
All	565	56.2	9.3	24.9	12.1	17.1	5.3
Noncotton	521	56.4	9.2	24.7	12.0	16.7	5.4
Cotton	44	57.6	10.4	26.9	13.0	21.6	4.5
All smokers	460	56.3	11.1	26.4	12.6	18.3	6.3
Smokers (noncotton)	424	56.1	11.0	26.2	12.6	18.0	6.8
Smokers (cotton)	36	57.9	12.6	28.4	12.0	20.4	4.7
Nonsmokers	105	57.3	1.0	6.7	9.8	12.0	2.6
Noncotton	97	57.4	1.1	6.9	9.3	10.7	2.5
Cotton	8	56.5	0.4	3.0	16.3	28.0	3.8
Cigarettes	427	55.6	11.6	26.6	12.6	18.8	6.7
Pipe/cigar	33	65.1	5.6	23.0	12.8	12.2	3.3

[1] CLE = centrilobular emphysema.

SOURCE: Pratt et al. (1980).

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TABLE 9.—Covariance model results (F-test probabilities)

Variable	Age	Cigarette smoker	Pipe smoker	Textile exposure	Cigarette textile
		Pipe smokers excluded			
CLE[1]	.002	.0001		NS[2]	NS
Pigment	NS	.0001		NS	NS
Mucus	NS	NS		NS	NS
Goblet	.02	NS		NS	.03
		Cigarette smokers excluded			
CLE	NS		.001	NS	
Pigment	.03		NS	NS	
Mucus	NS		NS	.02	
Goblet	NS		NS	.03	

[1] CLE = centrilobular emphysema.
[2] NS = not significant.
SOURCE: Pratt et al. (1980).

20.5 to 65.3) than expected from the mortality rates of Georgia white men. In a more recent study, Merchant and Ortmeyer (1981) found a doubling of respiratory disease mortality (SMR increased from 61 to 126) with increasing duration of cotton dust exposure from less than 20 to more than 30 years, although no overall mortality excess was observed. Berry and Molyneux (1981) also found no excess mortality associated with cotton dust exposure. Although consistent with previous studies, this last observation must be considered preliminary because less than 10 percent of the Lancashire cotton mill workers under study have died.

Two studies of cancer rates among North Carolina cotton textile employees showed no excess of lung cancer mortality (Heyden and Pratt 1980). Data from the Third National Cancer Survey contain a representative sample of incident cancer cases occurring over 3 years in a population of 21 million men and women who were interviewed to determine their occupation, socioeconomic status, and tobacco and alcohol consumption (Williams et al. 1977). These data indicated a slight (2.06), nonsignificant odds ratio excess risk for lung cancer among male cotton textile workers. While this observation is of interest because the odds ratio was adjusted for smoking, it depended upon only three cases of lung cancer. At this time, therefore, there is no evidence to suggest a lung cancer excess among cotton textile workers.

Control of Cotton Dust Exposure

The feasibility of controlling cotton dust exposure by preprocessing the cotton (heating, washing, or steaming) has been studied by Merchant, Lumsden, Kilburn, Germino, and colleagues (1973).

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Although washing the cotton removed detectable biologic effects, the cotton became difficult to spin. Steaming the cotton, while practical for the manufacturer, resulted in an unexpected consequence (Merchant, Lumsden et al. 1974); while it initially removed some of the cotton dust, the steaming process also bound dust to the cotton fiber. Although cotton steaming led to a lower dust level and a smaller fall in cross-shift ventilatory function in the preparation area, subsequent release of the bound dust during spinning resulted in increased dust levels and symptoms of byssinosis and bronchitis in the areas when these processes were performed (Merchant, Lumsden et al. 1974).

The inability to control cotton dust levels by treating the cotton has led to the imposition of Occupational Safety and Health Standards for containment of dust (US DOL 1981). Although these standards have resulted in substantial cost to the cotton textile industry, progress in reducing byssinosis has been made by the implementation of competent air hygiene practices (Kilburn 1983; Gideon and Johnson 1978) using commercially available lint and dust control systems (Barr et al. 1974).

Summary and Conclusions

1. Byssinosis prevalence and severity is increased in cotton textile workers who smoke in comparison with workers who do not smoke.
2. Cigarette smoking seems to facilitate the development of byssinosis in smokers exposed to cotton dust, perhaps by the prior induction of bronchitis. Cotton mill workers of both sexes who smoke have a consistently greater prevalence of bronchitis than nonsmokers.
3. The importance of cigarette smoking to byssinosis prevalence seems to grow with rising dust levels (a smoking–cotton dust interaction). At the highest dust levels, cigarette smoke was found to interact with cotton dust exposure to substantially increase the acute symptom prevalence.
4. Nonsmokers with byssinosis have lower preshift lung function and a greater cross-shift decline in lung function than asymptomatic workers, and those workers with bronchitis generally have lower preshift lung function than those without bronchitis. In general, smokers have lower lung function than nonsmokers among cotton workers, both in those with bronchitis and in those with byssinosis.
5. Although the average forced expiration values measured at the start of a shift are reduced among smokers, the cross-shift decline in function does not seem to be affected by smoking status.

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6. The contribution of the acute byssinotic symptoms (grades 1/2 and 1) to the subsequent development of what have been termed the chronic forms (grade 3) of byssinosis (which include airways obstruction) is not well documented; however, chronic airflow obstruction has been found more frequently in cotton textile workers than in control populations, and this lung function loss appears to be additive to that caused by cigarette smoking.
7. Cotton dust exposure is significantly associated with mucous gland volume and peripheral goblet cell metaplasia in nonsmokers, a pathology consistent with bronchitis. Among cigarette smokers, the interaction of cotton textile exposure and smoking is demonstrable for goblet cell hyperplasia. Centrilobular emphysema is found only in association with cigarette smoking and pipe smoking. There is no emphysema association found with cotton dust exposure.
8. The evidence does not currently suggest an excess risk of lung cancer among cotton textile workers.

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CHAPTER 11

IONIZING RADIATION AND LUNG CANCER

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Introduction

The major focus of this chapter is the interaction of cigarette smoking with radiation exposure; epidemiologic and experimental studies are reviewed. Radon is a noble gas that is created as a consequence of the radioactive decay of radium 226. Its half life is 3.8 days. Radon is of much less health concern than are its immediate decay products (Po-218, Pb-214, Bi-214, and Po-214), which have a collective half-life of approximately 30 minutes. Known collectively as radon daughters, they decay to lead 210, which has a half life of 22 years. Because there are small amounts of radium in all rocks and soils and in most building materials, radon is ubiquitous and is constantly being emanated from ground surfaces; when it diffuses into the atmosphere, it is rapidly diluted. Radon levels are enhanced whenever radon is emanated into an enclosed space rather than into the open air; therefore, radon levels in most underground mines are higher than in open air. There are elevated levels of radium in uranium and phosphate ores, so there are naturally enhanced levels of radon and its daughters in such underground mines (NCRP 1984a).

Human Exposure to Radiation From Radon Daughters

When radon in air decays, its daughters, being ionized metal atoms, tend to become attached to the nearest solid object, usually a dust particle. These dust particles and attached ions are inhaled by people breathing the air, and a fraction is deposited within the lungs. From the standpoint of radiation dose to the critical cells, the amount deposited on the tracheobronchial epithelium is important. Because radon daughters decay rapidly, they deliver their radiation before they can be removed by normal lung clearance mechanisms. Particles deposited by inertial forces (impaction) would also be present preferentially at bifurcations. Although alpha, beta, and gamma radiations are emitted by radon daughters, the alpha radiation delivers over 95 percent of the radiation dose to the epithelium. The beta and gamma contribution to dose is therefore generally disregarded (NCRP 1984b).

Exposures to radon daughters are generally measured in working levels (WL) or working level months (WLM). One WL is defined as a concentration of any combination of short-lived radon daughters in air that produces, from complete decay, 1.3 times 10^5 MeV (million electron volts) of alpha energy per liter. A person exposed while working for 1 working month (170 hours) in such an atmosphere would receive an exposure of 1 WLM. The maximum permissible exposure for underground miners is 4 WLM per year, which is approximately equivalent to an average monthly exposure of 0.3 WL for 12 working months per year. In the past, many miners in both

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uranium and nonuranium mines received cumulative exposures of between 10 and 10,000 WLM. It is primarily from the study of these groups that our information on the health hazards of radon daughters has come. Although inadequately studied, average levels of radon daughters in homes appear to be close to 0.004 WL in the United States (NCRP 1984a).

Use of the awkward WL is justified on the grounds that exposure to the alpha radiation from radon daughters cannot be readily converted to more universal measures of radiation such as "rad" or "rem." Many attempts to do so have been made, yielding values ranging from 0.1 to 10 rad per WLM. A further problem involves estimating the Quality Factor for the alpha radiation involved. Although use of 20 for this factor is recommended (ICRP 1981), the epidemiologic data indicate that from 10 to 15 may be appropriate (Radford 1984).

Smoking Habits of Exposed Miners

Although information on cigarette usage has not been obtained on all mining groups that have been studied for lung cancer, it has been obtained in many of them (Table 1). Cigarette smoking histories of U.S. uranium miners were obtained between 1950 and 1960, when they were admitted to a prospective study group (Lundin et al. 1971). It was found that white uranium miners in the United States smoked a little more heavily than comparable men in the U.S. population and that Navajo miners were extremely light smokers (Tables 2 and 3) (Archer et al. 1976). Swedish miners have a much lower smoking prevalence than U.S. miners (Cederlof et al. 1975; Radford and Renard 1984).

Risks of Lung Cancer Among Smoking and Nonsmoking Miners

Although the cancerous nature of the fatal lung disease of miners in the Joachimsthal and Schneeberg mining areas of central Europe was not noted until 1879 (Harting and Hesse 1879), the disease had been known for three centuries (Pirchan and Sikl 1932). Lung cancer may have resulted in the death of 40 percent or more of the miners (Arnstein 1913). It is now generally agreed that most of these lung cancer deaths may be attributed to radon daughters—and they were occurring at a high frequency prior to the introduction of cigarettes to Europe.

U.S. Uranium Miners

When the first lung cancer among nonsmoking underground U.S. uranium miners was observed in 1965, there had already been

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TABLE 1.—Epidemiological reports on interaction of smoking and cancer

Study	Group studied	Type of analysis	Cancer site	Results
Saccomanno et al. (1967)	U.S. uranium miners	Case collection	Lung	One cancer among nonsmokers vs. >60 among smokers
Lundin et al. (1969)	U.S. uranium miners	Cohort	Lung	Ten times more lung cancer in smokers than nonsmokers
Lundin et al. (1971)	U.S. uranium miners	Cohort	Lung	
Archer et al. (1973)	U.S. uranium miners	Case–control	Lung	Smoker I-L period shorter; histologic type distribution same in smokers and nonsmokers
Axelson and Sundell (1978)	Swedish lead–zinc miners	Case–control	Lung	Smoker I-L period much shorter
Archer et al. (1976)	U.S. uranium miners	Cohort	Lung	
Dahlgren (1979)	Swedish lead–arsenic–sulfide miners	Case–control	Lung	Smoking not large factor in excess lung cancers
Hornung and Samuels (1981)	U.S. uranium miners	Cohort, Cox regression	Lung	
Gottlieb and Husen (1982)	U.S. Navajo uranium miners	Case collection	Lung	Smoking little role in Navajo lung cancers
Damber and Larsson (1982)	Swedish miners	Case–control	Lung	Smoker I-L period shorter
Edling (1982); Edling and Axelson (1983)	Swedish iron miners	Case–control	Lung	Smoker I-L period shorter
Whittemore and McMillan (1983)	U.S. uranium miners	Nested case–control	Lung	
Radford and Renard (1984)	Swedish iron miners	Cohort	Lung	Smoker I-L periods slightly shorter

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TABLE 1.—Continued

Study	Group studied	Type of analysis	Cancer site	Results
Archer (1985)	U.S. uranium miners	Case–control	Lung	Smoker I-L period significantly shorter
Samet, Kutvirt et al. (1984)	U.S. Navajo uranium miners	Case–control	Lung	Smoking little role in Navajo lung cancers
Hinds et al. (1979)	Hospital patients	Case–control	Larynx	Prior dental x rays
Prentice et al. (1983)	A-bomb survivors	Cohort	Esophagus and lung	

TABLE 2.—Cigarette smoking habits of white U.S. uranium miners at study entry and of U.S. nonminer men

Smoking status	Uranium miners (percent)	Nonminers (percent)
Nonsmokers[1]	28.8	45.4
≤1 pack/day	54.2	39.8
>1 pack/day	16.9	14.8

[1] Includes smokers of pipes or cigars only and ex-smokers.
SOURCE: Adapted from Lundin et al. (1971).

TABLE 3.—Cigarette smoking habits of Navajos in U.S. uranium miner study group, at entry

Packs/day	Percentage smoking at entry	Percentage former smokers	Percentage never smoked
0.00	—	—	62.8
0.01–0.19	15.1	2.3	—
0.2–0.59	14.6	1.7	—
0.6–0.99	0.7	0.000	—
≥1.0	2.7	0.001	—

SOURCE: Adapted from Archer et al. (1976).

nearly 80 lung cancer deaths among cigarette-smoking U.S. uranium miners (Archer 1985). Because approximately one-third of the miners did not smoke cigarettes, the discrepancy was so striking that

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it led some observers to blame cigarette smoking for the entire problem and to conclude that if uranium miners did not smoke, they would rarely develop lung cancer.

A second lung cancer among nonsmoking uranium miners was observed in a mortality analysis of the U.S. uranium miner cohort published in 1969 (Lundin et al. 1969). These two cases represented a fourfold excess of lung cancers (only 0.5 case was expected among nonsmokers)—the same relative risk noted for cigarette smokers (15 expected versus 60 observed). Since the U.S uranium miners were known to smoke at a somewhat higher rate than other U.S. men (Table 2), in an analysis of how much extra cancer could be due to this extra smoking, Lundin and colleagues (1971) concluded that this extra smoking could account for no more than a 50 percent increase; a fivefold to tenfold increase had been observed. The discrepancy between smoker and nonsmoker lung cancer rates suggested an interaction between the two agents.

A later study of white U.S. uranium miners reported that the incidence of lung cancer varied both by cumulative amount of radiation exposure and by the intensity of cigarette smoking (Figure 1) (Archer et al. 1978). The mean exposure of these miners was about 870 WLM. Approximately 780 of the uranium miners in the U.S. study group were Navajo Indians. They had a much lower smoking prevalence than white miners (Table 3), but nevertheless had elevated lung cancer rates (Archer et al. 1976; Gottlieb and Husen 1982; Samet, Kutvirt et al. 1984). Many of those who developed lung cancer had smoked little or not at all (Table 4). Most of the lung cancers were therefore attributed to mining exposure (Samet, Kutvirt et al. 1984).

The role of other factors in the lung cancers of U.S. uranium miners was also studied. The induction-latent (I-L) period (time from start of mining to diagnosis of cancer) was shortened by increased age at the start of mining, by cigarette smoking, and by high exposure rates (Archer 1981). The attributable lung cancer risk tended to decline among miners who had reached the age of 65 and had 25 or more years of latency (Roscoe et al. 1983). An updated analysis of these data, using deaths occurring through 1982 and an adjustment of expected numbers of deaths for smoking habits, indicated that the drop in attributable risk appeared to occur mainly among the smokers, not the nonsmokers (Figure 2) (Roscoe et al., in press).

Because the I-L period is dependent on factors other than cigarette smoking (Archer 1981) and the smoking-related shortening of the I-L period was minimal in miners exposed to low radiation dose rates (Radford 1984), a more detailed case–control study was done of U.S. uranium miners (Archer 1985). There were 35 lung cancer cases among nonsmoking underground uranium miners (defined as smok-

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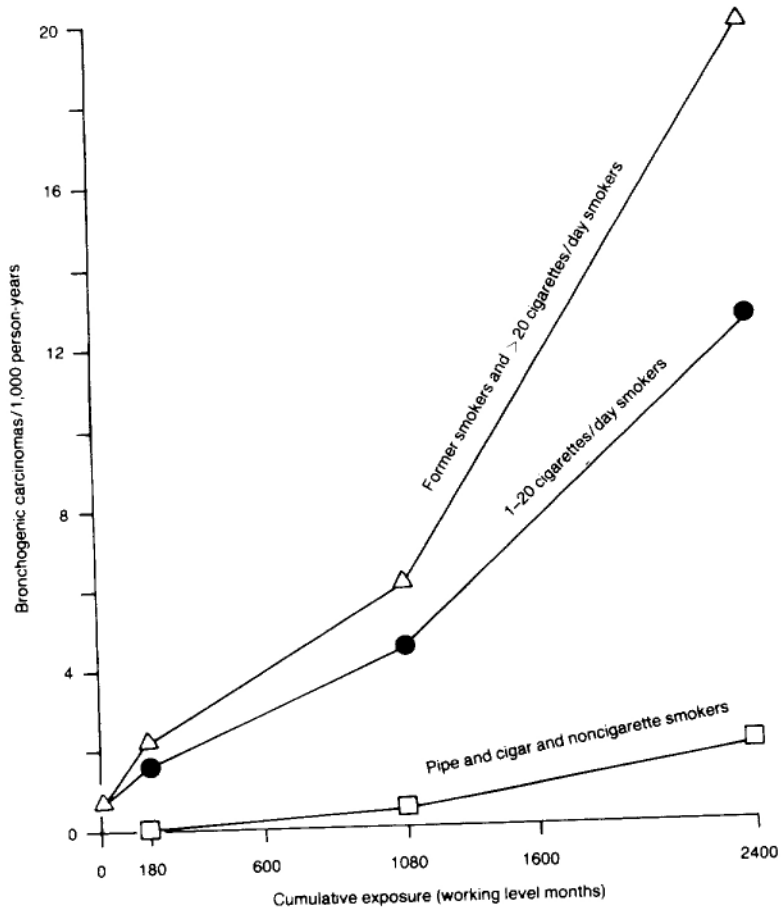


FIGURE 1.—Influence of cigarette smoking and radiation exposure on bronchogenic cancer incidence among U.S. uranium miners

SOURCE: Adapted from Archer et al. (1978).

ing a total of less than four pack-years of cigarettes and not smoking within 10 years of cancer diagnosis) whose lung cancer was diagnosed between January 1964 and January 1984. A few of them had smoked a pipe or cigars occasionally, but not regularly. Because not all of the lung cancer cases were members of the study group, supplemental smoking information was obtained from hospital records and relatives. Two controls were chosen for each case from among 334 smoking U.S. uranium miners. Controls were matched on

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TABLE 4.—Smoking habits of 21 Navajo uranium miners with lung cancer

Cigarettes/day	Number of men
0.0	8
<1	2
1–3	6
4–8	5

SOURCE: Adapted from Samet, Kutvirt et al. (1984).

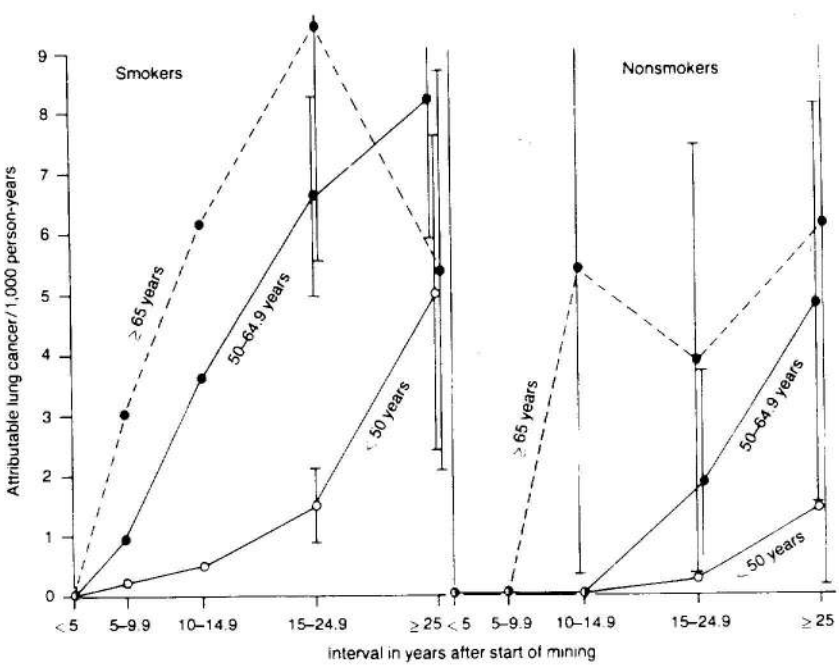


FIGURE 2.—Influence of age at observation and induction-latent period on attributable lung cancer deaths among U.S. uranium miners

NOTE: Error bars are 90 percent confidence intervals.
SOURCE: Adapted from Roscoe et al. (in press).

birthdate, on year when their mining started, and on the magnitude and rate of exposure to radon daughters. The mean I-L period was 23.8 and 18.5 years for nonsmokers and smokers, respectively

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($p < 0.001$). The mean age at death was 54.7 and 50.2 years, respectively ($p < 0.001$).

Two sophisticated analyses using Cox regression methods were done of the U.S. uranium miner cohort in an attempt to determine the relative contribution of various factors to the miners' lung cancers. One of the analyses used a cohort approach (Hornung and Samuels 1981); the other used a nested case–control approach (Whittemore and McMillan 1983). Both concluded that the interaction between smoking and radiation effects was multiplicative.

Swedish Miners

Axelson and Sundell (1978) conducted a case–control study of lung cancer patients in the area around two adjacent lead-zinc mines that had begun operating prior to 1920. Twenty-nine lung cancer cases were identified from parish death register data; the controls were the three individuals entered in the register just before and just after each lung cancer case, but who had not died of lung cancer. Of the 29 cases, 21 had underground mining exposure in comparison with only 19 of the 174 controls. The mean radon daughter exposure of the lung cancer cases was approximately 300 WLM. Smoking information was obtained for both groups (some from relatives). Data on the 21 lung cancer deaths of miners were collected over a 20-year period (1956–1976). The mean age at death was 70 and 59 years, respectively, for nonsmokers and smokers with lung cancer. The mean I-L period was 43 and 34 years, respectively, for nonsmokers and smokers with lung cancer. The nonsmokers contributed 47 percent of the lung cancers, whereas only 19 percent of the controls were nonsmokers.

Damber and Larsson (1982; Larsson and Damber 1982) performed a case–control study of 604 male lung cancer deaths in the three northernmost counties of Sweden. Two control groups were selected from among deceased and living populations. Decedent controls were drawn from the national registry for causes of death and matched for sex, year of death, and municipality to the lung cancer cases. Living controls were selected only for those lung cancer cases under the age of 80 (467 cases) and were drawn from the national population registry and matched for age, sex, and year of birth. Twenty-five of the cases and only 10 of the controls had underground mining exposure. The relative risks for smoking and underground mining exposure were these: nonsmoking individuals with no underground mining exposure, 1; nonsmokers with underground mining exposure (2.4 decedent controls, 7.0 living controls); smokers with no underground mining exposure (6.8 decedent, 7.4 living); and smoking miners (18.2 decedent and 16.1 living). The mean age at death was 69 and 63 years, respectively, for nonsmokers and smokers among the miners with lung cancer. The mean I-L period was 43 and 35 years,

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respectively, for nonsmokers and smokers among the miners with lung cancer. The mean exposure was not given, but was probably about 100 WLM, as many of the subjects were the individuals studied by Radford and Renard (1984). This difference was considered to represent a multiplicative effect of cigarettes and radon daughters, but it was not possible to rule out an additive effect.

Case–control studies were done with a different group of Swedish iron miners (Edling 1982; Edling and Axelson 1983). Cases were deaths from lung cancer, and controls were miners who died from nonmalignant causes, matched for birthdate, sex, and year of death. Mean exposures were about 100 WLM. There were 44 cases among miners, and a standardized mortality ratio (SMR) of 11.5 to 16.2 was calculated for lung cancer. Of these 44 cases, 38 were smokers and 6 were nonsmokers. The risk ratio was 1.5 to 2 times greater among smokers than among nonsmokers. The mean age at death was 67 and 61 for nonsmokers and heavy smokers, respectively. The mean I-L period was 40 and 37 for nonsmokers and heavy smokers, respectively. The authors concluded that the interaction was probably additive.

A retrospective cohort study was done of another group of workers from two iron mines, one worked since 1890, the other since 1920 (Radford and Renard 1984). Death data were collected for a 26-year period (1951–1976). There were 50 lung cancer deaths that occurred 10 or more years after start of mining. The mean exposure was about 94 WLM (84 WLM corrected for exposure immediately prior to death). Smoking information was obtained from relatives for all lung cancer deaths and by questionnaire from approximately half of those study members alive in 1973. Using general population data on smoking and mortality, a dose–response relationship for radon daughter exposure was demonstrated. There were 18 lung cancer deaths among nonsmokers versus 32 among smokers. The relative risk due to radon daughter exposure was 10 for nonsmokers and 2.9 for smokers ($p < 0.001$), and the radiation exposures were approximately equal for both groups. The absolute excess lung cancer risk attributable to radon daughter exposures was slightly higher for smokers than for nonsmokers. The mean I-L periods were 41.3 for nonsmokers and 38.8 years for smokers. The mean age at death from lung cancer was approximately 65 years, but was not calculated by smoking status. The authors concluded that the interaction was slightly more than additive.

Canadian Miners

In studies of a group of Canadian fluorspar miners there were only 2 lung cancer deaths among nonsmokers versus 76 among smokers (Wright and Couves 1977; Morrison et al. 1981). Smoking data were incomplete, but it was estimated that only 5 percent of the miners were nonsmokers. The mean exposure was approximately 600 WLM.

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The followup period was from 1933 to 1977, an interval of 44 years. The mean I-L period was 25 years and declined with increasing age at start of mining. The mean age at death was 52 years.

An analysis of sputum cytology results from 249 active Canadian uranium miners found that the frequency of atypical cells in sputum was related to both cigarette smoking and radiation exposure. Few atypias were seen among nonsmokers, and this was interpreted as a potentiation of the radiation effect by smoking (Band et al. 1980).

Other Epidemiological Studies Relating Radiation and Cancer

Because of the high cost of imported fuel, the Swedes were among the first to emphasize the closing of cracks and adding insulation to dwellings in order to conserve heating fuel. Sealing the indoor environment also resulted in an elevation in the radon levels in the indoor environment. These radon exposures have resulted in a substantial interest in Sweden in the role of radon as well as in the role of cigarette smoking on their lung cancer death rates.

A case–control study was conducted in rural areas of Sweden, limited to people who had lived at the same address for 30 years before death (Axelson 1983). Measurements of radon in different types of houses led the researchers to classify wooden houses without basements as low radon, and brick or concrete houses with basements (especially those built on alum shale or granite deposits) as high radon. Smoking histories were obtained on half of the cases from questionnaires completed by relatives. In the high exposure housing, smokers had a lung cancer crude risk ratio of 8.3; in the low exposure houses the ratio was only 2.0. There was no difference in smoking habits between inhabitants of the two types of houses. The researchers felt that this indicated a multiplicative or synergistic interaction. A second study of Swedish residents did not alter that conclusion (Axelson 1983; Edling et al. 1984).

In a case–control autopsy study of 204 Japanese A-bomb survivors with lung cancer who subsequently died, the relationship of smoking to radiation exposure was examined (Ishimaru et al. 1975). An increase in lung cancer risk was seen with increasing radiation exposure and increasing amount smoked, but no interaction could be discerned.

A cohort study of 40,000 A-bomb survivors studied the relationship of cigarette smoking and radiation exposure to cancer mortality (Prentice et al. 1983). Subjects were stratified by smoking and radiation categories, and multiplicative and additive models were examined. There were 281 lung cancers. The lung cancer risk rose with both increasing radiation and increasing smoking. Cancer of some sites showed an absence of or a negative correlation, but both esophageal and lung cancer risk rose with both increasing radiation

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TABLE 5.—Interaction of radiation and cigarette smoking among Japanese A-bomb survivors

Cancer site	Number of cancers	Relative risk estimates					
		Nonsmokers			Smokers		
		< 10 rad	10–99 rad	≥ 100 rad	< 10 rad	10–99 rad	≥ 100 rad
Stomach	658	1	1.2	1.4	1.3	1.0	1.3
Esophagus	58	1	3.2	6.5	5.6	6.6	7.8
Lung	281	1	1.1	2.3	2.4	2.4	3.6

SOURCE: Adapted from Prentice et al. (1983).

and increasing smoking (Table 5). The use of Cox regression analysis did not distinguish between an additive or a multiplicative interaction.

Preliminary findings from a case–control study among A-bomb survivors suggest that gamma radiation and cigarette smoking combine in an additive fashion to increase lung cancer risk (Blot et al. 1984).

Comment on Epidemiological Studies

With the exception of some of the U.S. studies with over 300 lung cancer cases, most of the human studies were of relatively small populations, with small numbers of lung cancers. Although confidence in the risk estimates and the mean I-L periods derived is decreased, there is no reason to suspect that the small population sizes provided any qualitative distortion of the smoking–radiation interaction. The studies varied in the quality of their radiation dose estimates and of their smoking information. Some of the smoking data was obtained by interview, some retrospectively from relatives, and some at entry into the study with no consideration given to subsequent changes in smoking habits. Because of the small numbers, pipe and cigar smokers and ex-smokers were sometimes combined with other groups or light smokers and heavy smokers were often combined. Some had smoking information on little more than half of the population. The observations of protective, additive, or multiplicative effects cannot be easily dismissed. These observed differences could all be correct for specific groups at specific times without violating any biological principles.

The mean I-L periods in the various studies differ considerably, as do the relationships between nonsmoker and smoker I-L periods. It should be noted that in all of the studies the I-L period was shorter among smokers than among nonsmokers, although in some studies

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the difference was small. In studies of radiation and cancer, it has frequently been noted that the observed latent period is strongly dependent on age at exposure and on the length of the followup period. That is, subjects who are young at first exposure and who are followed for most of their lives will exhibit a much longer mean latent period than will a group first exposed during middle age and followed for only 25 years. The intensity and magnitude of exposure may also have an influence on the I-L period (Archer et al. 1979). Longer I-L periods were noted among Europeans than among U.S. miners. Longer followup periods and higher radiation dose rates and doses are probably responsible for this difference.

Cigarette smoking habits may also influence the measured I-L period for developing lung cancer following onset of radon daughter exposure independent of any biologic interaction. Even without significant radon daughter exposure, a number of smoking miners would have developed lung cancer, and some may have done so prior to the latent period required for radiation-induced cancers. This phenomenon would be particularly important in those individuals whose radiation exposure (but not their smoking exposure) began late in life. The effect of this independent development of lung cancer due to cigarette smoking would be to shorten the I-L time calculated for radon daughter exposure in smokers compared with nonsmokers, and for workers who joined the workforce later in life compared with those whose exposure began at a younger age.

Differences in age at start of mining and years of followup between the nonsmokers and smokers within a cohort might well influence the relative risks calculated for the two subgroups within any study. However, even if age at start, years of followup, and percentage ultimately developing lung cancer are the same for nonsmoking and smoking subgroups, their relative frequency of induced lung cancer might vary considerably with time, as indicated in Figures 2 and 3.

Interaction of Radiation and Cigarette Smoke (or Its Constituents) in the Generation of Animal Tumors

A number of animal experiments have explored the possible interactions between cigarette smoke or cigarette smoke condensate (CSC) and ionizing radiation. These experiments have used x-ray or alpha or beta radiation. Some have used rat or mouse skin as the test object; others have used the lungs of living animals.

Bock and Moore (1959) found that intense x-ray exposure of a small portion of the mouse body increased the sensitivity of distant areas of the skin to cancer induction by painting with CSC.

An experiment using CSC and beta radiation from ^{90}Sr on mouse skin (400 mice) was reported at two separate time points (Suntzeff et al. 1959; Cowdry et al. 1961). In this experiment both the beta

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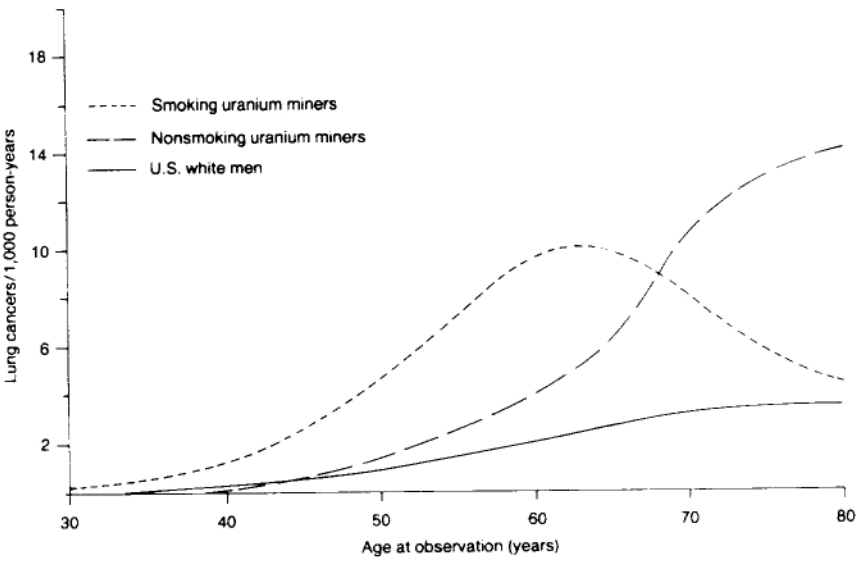


FIGURE 3.—Hypothetical lung cancer distribution among smoking and nonsmoking uranium miners with uniform radon daughter exposure and among U.S. white men

radiation and CSC were applied periodically (both separately and together) so that large total doses of both were used. The first report gave results at 18 months and considered the interaction to be synergistic. Fifty-four percent of the mice with combined agents had skin cancer versus 37 and 5 percent, respectively, when the agents were used singly. However, when the study was completed by following the mice until they died naturally, the sum of the skin cancers among the groups treated with single agents was nearly as large as the number found among the mice treated with both agents. Cancers appeared 6 to 7 months earlier in mice treated with both agents.

A preliminary experiment using CSC and beta particles on rat skin (McGregor 1976) found a threefold increase in skin tumors over that induced by beta radiation alone. The effect was attributed to tumor promotion activity because the CSC applications were started 2 months after beta exposure and because the amount of CSC used did not produce any tumors when used alone. This was followed by further experiments (McGregor and Meyers 1982), using 916 rats. CSC was applied immediately after exposure to 1,600 rad of beta

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particles in one group and 2 months after in another group. When applied immediately, severe ulceration resulted, making tumor yield difficult to interpret. When applied 2 months after radiation, malignant and nonmalignant yields were increased ($p < 0.01$). Again, the levels of CSC used produced no significant increase in cancers by themselves. The experiments were terminated at 14 and 18 months, so the ultimate cancer yields were not determined, but at the end of the experiment there were 2.5 times as many cancers in the beta-plus-CSC group as in the beta-alone group. At 50 weeks, however, the ratio was higher (3.4), indicating that tumors appeared earlier in the group treated with both agents.

Nenot (1977) studied rats that inhaled cigarette smoke plus americium 241, which delivered alpha radiation to the lungs. The smoke increased the yield of lung cancers and made them appear earlier. It was interpreted as a cancer-promoting effect by cigarette smoke, because the smoke alone did not produce cancer at the doses used.

The carcinogenic effects of radon daughters, uranium ore dust, and cigarette smoke in dogs have been reported (Cross et al. 1978, 1982; NCRP 1984b). Dogs were exposed to radon daughters plus uranium ore dust, to radon daughters plus ore dust plus cigarette smoke, to cigarette smoke alone, or to sham cigarettes with room air. Daily cigarette smoking periods both preceded and followed the dust plus radon daughter exposures. There were seven lung cancers among the 20 nonsmoking dogs and none among the controls or the dogs exposed to smoke alone. Although no dogs were exposed to dust alone, other experiments suggest that they would not have developed lung cancer. Exposure to 20 cigarettes per day resulted in pulmonary emphysema and fibrosis. These two conditions, however, were much more severe in the dogs exposed to mixtures that included radon daughters and uranium ore dust. Two nasal carcinomas were found in the dogs exposed to ore dust and radon daughters, and one in the group exposed to these two agents plus smoke. There were none in the other two groups. In these studies, cigarette smoke appeared to be protective.

In an extensive series of experiments in France, cigarette smoke was inhaled by rats, either before or after a series of radon daughter inhalations (Chameaud et al. 1980, 1981, 1982). The cigarette smoke alone did not produce lung cancers at the levels used. When the smoke was given in the weeks preceding radon daughter inhalation, it had no effect; when the exposure to smoke was delayed until after radon daughter exposure was completed, or given during radon daughter exposure, significantly higher numbers of lung cancers were observed. These features were considered to be characteristic of cancer promotion by cigarette smoke, although the terms "cocarcinogenesis" and "synergism" were at times applied by the researchers.

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Interactions of Radiation and Chemical Carcinogens

A number of experiments tested the interaction of radiation and chemical carcinogens. Some of these chemicals are constituents of cigarette smoke or are chemically related to such constituents. Although most carcinogens can also act as cancer-promoting agents, in these experiments the additional tumor promoters in cigarette smoke were absent, making them less pertinent to the topic of radiation and cigarette smoke interaction than the experiments reviewed in the preceding section. With this in mind, they are summarized below. Benzo[a]pyrene (BaP) and polonium 210 (Po-210) were injected intratracheally in hamsters (McGandy et al. 1974; Little and O'Toole 1974; Little et al. 1978). When given simultaneously, tumors appeared earlier, but the effects were additive. When BaP was given 4 to 5 months after radiation, the effects appeared to be synergistic, but because effects were small when BaP was given first and saline injections had nearly the same effect, the BaP action was considered to be mostly tumor promotion. A similar study with intratracheal instillations of BaP and plutonium oxide (PuO_2) was done in rats (Metivier et al. 1984) and was considered to show synergism. Both PuO_2 and Po-210 emit alpha particles.

BaP used with 150 roentgens of whole body x ray on mouse fetuses resulted in more tumors (of all types) than was obtained with x ray alone, but fewer than was obtained with the BaP alone (Urso and Gengozian 1982).

Dimethylbenz[a]anthracene (DMBA) and 0.8 MeV electrons were administrated to rat skin at 28 days of age (Burns and Albert 1984). Multistage analysis of the interaction suggests the existence of two dose-dependent stages for single doses of radiation and multiple doses of DMBA, and also that prolongation of the radiation dose either adds four presumably non-dose-dependent stages or stimulates clonal growth of an early stage cell.

Rats were given 600 WLM, then treated with 5-6 benzoflavone, methylcholanthrene (MCA), or phenobarbital (Queval et al. 1979). MCA is a carcinogen, the other two are not. Phenobarbital had no effect. With both benzoflavone and MCA the number of tumors was doubled. The latent period was greatly shortened with benzoflavone, but only slightly with MCA. Benzoflavone suppresses tumor development when used with BaP.

When rat fetuses were exposed to x ray and the mothers were injected with ethylnitrosourea (ENU) 4 days later, as adults the rats developed fewer neurogenic tumors than with ENU alone. This reduction in tumors was not due to an increased mortality rate of the fetally exposed animals (Kalter et al. 1980).

The administration of 1.25 gray (Gy) whole body x ray followed by injection of ENU was used to induce nervous system tumors (Knowles 1982). The incidence of these tumors was consistently and

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significantly higher in the group given ENU alone than in any of the irradiated groups. The histology of tumors in all groups resembled those induced by ENU.

When mice were irradiated in utero (36 rad x ray) and then given urethane at 21 days of age, the yield of lung tumors was enhanced over urethane alone (Nomura 1984). X ray alone yielded no tumors. The x-ray effect was seen during the first 14 days of gestation, but not during the later fetal or neonatal stages.

Intraperitoneal application of tetradecanoylphorbol acetate (TPA) (a strong tumor-promoting agent) had no influence on the incidence of malignant lymphomas following four doses of 1.7 Gy of x ray (Brandner et al. 1984).

When beta particles from phosphorus 32 were used with TPA and high fat, high protein diets as potential tumor-promoting agents, no evidence of tumor promotion was found on liver cell transformation (Berry et al. 1984).

Comment on Animal Studies

Although the results of the animal studies indicate that the interaction between radiation and cigarette smoke, or its components, ranges from no interaction to protection, promotion, and synergism, there are several features common to many of the experiments. When cigarette smoke or BaP is administered before the radiation, there is little or no interaction with respect to tumors. When administered several months after the radiation, the interaction is greater. In addition, as a general rule, tumors appear earlier in animals when cigarette smoke is used. In some of the experiments, the early appearance of cancers caused investigators to apply the word "synergism" to the interaction, but further followup plus the production of few or no cancers by the smoke or CSC alone, usually led the investigators to conclude that the interaction was mainly one of cancer promotion (Chameaud et al. 1981; McGregor and Meyers 1982). Some of the experiments with cigarette smoke components led to the same conclusion (Little et al. 1978). This conclusion is buttressed by the observation that the cancer-promoting activity of cigarette smoke is greater than its initiating activity (Bock 1968, 1972; Van Duuren et al. 1971; Wynder 1983). Cancer promoters sometimes increase the yield of cancers in animal experiments by simply speeding up the appearance of the tumors. Nonspecific injury sometimes promotes radiation-induced tumors.

Polonium 210 in Cigarette Smoke

Lead 210, which has a 22 year half life, is widely deposited on plant foliage as a result of radon and radon daughter decay in the atmosphere. It decays slowly to Po-210, which emits alpha particles

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that are more dangerous than the beta particles emitted by lead 210. Appreciable amounts of these two radioisotopes are found in tobacco and in tobacco smoke, and may contribute to the cancer potential of cigarette smoke (Radford and Hunt 1964; Kolb et al. 1966; Stahlhofen 1968; Black and Bretthauer 1968). A major fraction of the inhaled Po-210 was shown to be absorbed from the lung directly into the bloodstream (Little and McGandy 1968). Intratracheal instillation of Po-210 into the lungs of hamsters resulted in cancer at levels as low as 15 rad (Little et al. 1978). Calculations of the radiation dose from the Po-210 in cigarettes have been made repeatedly. Doses to small portions of the bronchial epithelium were found in man to be about 1 rad per year (Cohen et al. 1980), 8 rem per year (Steinfeld 1980), and 80 to 100 rad per lifetime (Martell 1983). Average exposures to the bronchial epithelium, however, are much less than these calculated doses, which are administered to very small selected spots. There has been considerable debate as to how much the radiation from Po-210 contributes to the lung cancer that results from smoking, ranging from no effect (Hickey and Clelland 1982) to most of the cancers (Wagner 1982; Ravenholt 1982; Martell 1983; Winters and Di Frenza 1983). The consensus appears to reflect a middle ground—that the radiation in cigarette smoke contributes to its carcinogenicity, but that the chemical agents in smoke also contribute (Radford 1982; Cross 1984).

To the extent that Po-210 in cigarette smoke induces lung cancer, its effect would be expected to be directly additive to the effect of the short half-life radon daughters. To the extent that chemical agents are involved (either as cancer initiators or as promoters), an interaction might be expected to occur. Both the animal data and the human data reviewed indicate at least some interaction, which therefore reflects action by the chemical constituents of cigarette smoke, particularly as promoters.

Hypothesis That Reconciles Discrepancies in Epidemiological Data

A hypothesis that could reconcile the discrepancies in the epidemiologic data has been presented (Archer 1985). Alpha radiation dose from radon daughters may induce a finite number of lung cancers in an irradiated group, with most of these cancers being expressed. In the absence of cigarette smoking, these cancers could have a longer latent period and may or may not be fully expressed among the population, depending on the force of competing causes of death among the older members of the population and the presence or absence of promoting agents. In the presence of continuing exposure to cigarette smoke, these radiation-induced cancers could appear at

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an earlier date following exposure (and at younger ages) than among groups not exposed to cigarette smoke.

The lung cancers that would normally be induced by cigarette smoke would still be present, and added to those induced by radiation in a mining population. Thus, on a lifetime basis, there would appear to be an additive effect (radiation plus smoking), plus perhaps a few extra cancers that would not have been expressed if the latent period had not been shortened by smoking. The earlier appearance of cancers among smokers would give an appearance of synergism in studies conducted within 20 or 30 years after the start of exposure.

This hypothesis is best understood by examining Figure 3. In this hypothetical graph it is assumed that an equal number of smoking and nonsmoking miners of the same age are exposed at age 30 to the same amount of radon daughters. The resultant curves of lung cancer incidence reflect the distribution in time of the appearance of the induced cancers. The shape of the curves might vary somewhat from the curves for people who are first exposed at older ages. It is evident from these curves that investigators who examine lung cancer mortality data at different points in time after the subjects had begun mining could obtain data indicating synergism (at 40 to 60 years of age), or additivity (at 60 to 70 years of age), or protectiveness (at 70 or more years of age). The "synergism" noted in the U.S. uranium miner studies (mean age at death was 55 years for nonsmokers) would thus be explained (Saccomanno et al. 1967), as would the "protection" found in one of the Swedish studies (mean age at death was 70 years for nonsmokers) (Axelson and Sundell 1978). The "additive" effect noted by another Swedish study (mean age at death was 65 years) with deaths collected over a 26-year period (Radford and Renard 1984) would also be explained. The long data-gathering period resulted in a collection of deaths from young as well as aged miners. The short collection period used in another Swedish study (Damber and Larsson 1982) (mean age at death was 69 years), interpreted as "synergism," may have resulted from a biased sampling of deaths because they were from a 5-year period only, or were from the entry into mining at different times or ages by smokers and nonsmokers.

A mortality analysis of radon daughter-exposed miners within 25 years after they started mining would, according to the hypothesis, give an early impression of synergism, just as early observations in two of the animal studies did (Suntzeff et al. 1959; McGandy et al. 1974), even though lifetime studies would indicate otherwise.

According to some experts, even if the final incidence of lung cancer in smoking and nonsmoking irradiated individuals were the same, the net effect could be regarded as synergistic; this is because

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smoking shortens the tumor-free life of those who develop cancer (UN Sci. Comm. 1982).

Interaction of Radiation and Cigarette Smoke on Other Aspects of the Respiratory Tract

Larynx and Nasal Sinuses

The attachment of radon daughters to dust particles that are deposited in the airways (along with unattached ions) of animals and man means that the upper respiratory tract and bronchi receive higher total doses of radiation than any other part of the body. Excess cancers of the larynx have been reported in uranium miners (Tichy and Janisch 1973). Although this cancer site has been associated with cigarette smoking, the possible interaction of the two agents on the larynx has not been evaluated. Cancer of the sinuses has been attributed to the radon and radon daughters that collect in the paranasal sinuses of people with elevated radium body burdens (Rowland et al. 1978; Schlenker and Harris 1979). Cancer of these sinuses has not been attributed to cigarette smoke in U.S. populations. The nasal and pharyngeal and tracheal epithelium in man may be sufficiently thick and covered by enough protective mucus so that the alpha particles from radon daughters rarely penetrate to those cells where permanent injury can result (presumably the basal germinal layer). The thin epithelium of the bronchial subdivisions apparently may not provide similar protection.

Pulmonary Function and Fibrosis

Epidemiologic studies have demonstrated that the pulmonary function of uranium miners is compromised (Archer, Carroll et al. 1964; Archer, Brinton et al. 1964; Trapp et al. 1970; Samet, Young et al. 1984). The loss in pulmonary function is followed in time by greatly elevated mortality rates from or with nonmalignant pulmonary disease (Archer et al. 1976; Archer 1980; Waxweiler et al. 1981). In these analyses several diseases were grouped together—cor pulmonale, silicosis, pulmonary fibrosis, chronic obstructive lung disease, emphysema, and related diagnoses—because diagnostic criteria for them are known to vary greatly between physicians. They usually reflect injury by inhaled toxic agents. Uranium miners were also exposed to a third toxic agent, silica (alpha quartz), in ore dust as well as to radon daughters and cigarette smoke.

Uranium ore dust and tobacco smoke, as well as radiation, undoubtedly contribute to the nonmalignant pulmonary problems of uranium miners. Both human studies and animal studies have indicated that radiation contributes to the lung pathology and functional loss (Archer, Brinton et al. 1964; Cross et al. 1978; Cross, Filipy et al. 1981; Cross, Palmer et al. 1981). Very few of the uranium

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miners disabled by shortness of breath had typical silicotic nodules on x ray and were therefore unable to obtain workmen's compensation for silicosis. Neither the relative roles nor the interactions of these three agents (radon daughters, cigarette smoke, silica) in these conditions is well characterized.

The pathology of radiation pneumonitis after larger acute radiation doses is well known (Gross 1981). Following irradiation at high doses, there is death of some of the epithelial and endothelial cells within 3 to 6 months, resulting in increased capillary permeability and leakage of plasma proteins into the alveolar surface. Within 1 to 3 years, the pneumonitis is followed by a fibrotic reaction, which may represent a healing of the radiation pneumonitis, but has the effect of reducing the functional capacity and compliance of the lung.

After relatively low chronic doses of alpha radiation, as occurs in uranium miners, such changes have not been reported, but some fibrotic change is implied by the aforementioned epidemiologic studies. The high linear energy transfer of alpha radiation leads to the belief that cellular injury and repair after chronic low doses of alpha radiation could slowly lead to fibrotic changes. The injury would be so diffuse, however, that fibrosis would be detectible only after many years. Loss of pulmonary function, fibrosis, and other changes have been observed in the lungs of rats, hamsters, and dogs chronically exposed to radon daughters, cigarette smoke or diesel exhaust, and uranium ore dust (Gaven et al. 1977; Stuart et al. 1977, 1978; Wehner et al. 1979; Cross, Palmer et al. 1981; Cross, Filipy et al. 1981; Cross et al. 1982; NCRP 1984b). Although these experiments were not designed to evaluate the degree of interaction of the different agents, it was clear that the fibrotic and other pathologic changes were much more severe when the animals were exposed to two or three of the agents together than when exposed to a single agent.

The relatively low radon daughter exposures at which pulmonary function effects (possibly due to radiation) have been found in uranium miners (Samet, Young et al. 1984) suggest that there may be no threshold for such effects.

Research Recommendations

1. The possibility that alpha radiation from background radon daughters in homes may contribute to lung cancer in human populations (Axelson 1983; NCRP 1984a, b; Harley 1984; Radford and Renard 1984) and the interaction of both active and involuntary tobacco smoking on this possible effect of radon daughters need further investigation. They may have important implications for the ventilation of homes and for the effects of involuntary smoking.

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2. The influence of tumor-promoting agents on radiation-induced cancers has not been adequately explored. Further animal studies of this interaction are indicated.

Summary and Conclusions

1. There is an interaction between radon daughters and cigarette smoke exposures in the production of lung cancer in both man and animals. The nature of this interaction is not entirely clear because of the conflicting results in both epidemiological and animal studies.
2. The interaction between radon daughters and cigarette smoke exposures may consist of two parts. The first is an additive effect on the number of cancers induced by the two agents. The second is the hastening effect of the tumor promoters in cigarette smoke on the appearance of cancers induced by radiation, so that the induction-latent period is shorter among smokers than nonsmokers and the resultant cancers are distributed in time differently between smokers and nonsmokers, appearing earlier in smokers.

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CHAPTER 12

SMOKING INTERVENTION PROGRAMS IN THE WORKPLACE

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Introduction

Cigarette smoking by employees results in increased expenses for employers. Smokers use the health care system up to 50 percent more than nonsmokers (Fielding 1984); this means higher health insurance costs for companies. Studies have reported higher rates of work-related accidents, disability reimbursement payments, and absenteeism among employees who smoke than among those who do not (Terry 1971). Although it is difficult to assess exact dollar amounts because of the variety of circumstances and assumptions involved (Warner 1983), estimates of excess annual costs to employers per smoking employee generally run from $200 to $500 (Luce and Schweitzer 1978; Kristein 1982). Costs attributable to smoking among employees in the high risk occupations discussed in this Report are likely to be considerably higher than these overall estimates.

These data, as well as consideration for the welfare of their employees, have led a number of businesses to establish workplace antismoking programs. Because of the magnitude of the health effects of smoking and the benefits of cessation, smoking cessation programs are likely to yield a higher return on investment than worksite health promotion programs targeting other risk factors such as obesity and lack of exercise (Fielding 1984). Surveys reveal that 11 to 15 percent of American businesses provide smoking reduction programs and many more are considering such programs (Dartnell Inst. 1977; NICSH 1980). In response to the recommendations of a panel of experts concerning priorities for health promotion activities, the Health Insurance Association of America has established a smoking reduction program that is available to its members (Fielding 1984). From one-third to one-half of the large organizations have designated no-smoking areas (Dartnell Inst. 1977; NICSH 1980).

A great variety of worksite smoking-modification approaches have been devised, including monetary incentives and contests for not smoking, distribution of self-help materials, physician messages and health education lectures on the adverse effects of smoking, and stop-smoking clinics (Chesney and Feuerstein 1979; Danaher 1980; Klesges and Glasgow 1985; Orleans and Shipley 1982). Stop-smoking sessions have been led by coworkers, volunteers from health organizations, commercial cessation consultants, and health professionals. Ongoing multiple risk factor intervention programs, either for the entire workforce or for individuals at especially high risk of developing cardiovascular disease, have been offered. The purpose of this chapter is to critically review the literature on such programs. First, however, it is helpful to consider both the potential advantages and the possible disadvantages of worksite smoking modification programs versus the more traditional, clinic-based programs.

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The potential advantages of worksite-based smoking modification programs can be considered from the perspective of employees, employers, and public health researchers. For employees, the primary potential advantages appear to be increased convenience (particularly if the program is held during work hours), reduced expenditure if the company pays all or part of the program fee, and the opportunity to participate with friends and coworkers rather than a group of strangers. For the employer, potential benefits include increased worker productivity, better employee morale, and better employee and public relations from health promotion efforts. The potential monetary savings from reduced absenteeism and medical costs are also appealing.

For public health researchers, worksite programs offer the advantages of a much larger number (and possibly different types) of smokers involved in efforts to quit than would otherwise be the case, greater ease in obtaining long-term followup data, and the opportunity to provide sustained or ongoing programs rather than one-time offerings. In worksite programs, treatment is conducted in the environment in which participants spend a large portion of their day, which should facilitate generalization of treatment effects and potentially lead to the establishment of nonsmoking norms. Possibly the greatest potential resource available in worksite programs from all three perspectives is the additional incentive and motivational components that can be brought to bear through both monetary and social support manipulations.

It is important to realize, however, that these potential benefits do not occur automatically (Klesges and Glasgow 1985), and that they may be offset by possible disadvantages of worksite smoking modification programs. From an employee perspective, participation may interfere with work activities or be outwardly condoned, but not supported, by a supervisor. Meetings may be held at inconvenient times or in inconvenient locations. If promotional activities are not handled appropriately, workers may feel coerced to participate. From an employer's perspective, there are the direct costs of the program, such as advertising, counselor time, and materials, as well as indirect costs, such as time off work for employees to participate. Sponsoring an antismoking program can also create employee relations problems. Nonsmoking employees may resent the time off work available to smokers and may demand that their own participation in health promotion programs be subsidized. The critical issue here may be company norms, whether time off is consistent with previous company practice regarding other programs for employee benefit. In organizations in which workers are exposed to hazardous substances such as asbestos, unions may view smoking cessation programs as attempts by management to absolve them-

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selves of responsibility for occupationally related disabilities (Ellis 1980).

There are also problems from the perspective of public health researchers in conducting programs in the workplace. Most of these potential disadvantages result from a reduced degree of control over variables that can influence outcome. For example, company program planners (organizational steering committee) might decide to conduct additional stop-smoking activities (e.g., changes in company smoking policies, added incentives for not smoking, participation in other health promotion activities, a contest with a rival business) that are not part of the study design. Finally, some participants may take part solely as a way of getting out of work rather than from a desire to change their smoking behavior.

Criteria for Evaluating Worksite Programs

The criteria for evaluating program effects are considered under three general headings: changes in participants' smoking behavior, effects on smoking and health-related variables for all employees in the organization, and "secondary" effects of a program on nonhealth variables of concern to employers. Most reports on worksite-based programs assess only one or two of these areas.

Changes in Participants' Smoking Behavior

The same considerations that apply to the measurement of adult smoking behavior in clinic settings apply also to worksite smoking modification programs. Specification of reported smoking data is particularly important. Following a program, there is often a bimodal distribution of smoking rate, with a number of individuals successfully quitting and many nonquitters smoking at close to their baseline rate. Presentation of reductions in the "average" number of cigarettes smoked can therefore be misleading. It is important to separate data about subjects who are abstinent from data about those who are still smoking, albeit at a reduced rate, when reporting either reductions in smoking behavior or biochemical indices of smoking exposure.

It is critical, of course, to have information about the long-term (6 to 12 months minimum) effects of smoking modification programs (Lichtenstein and Brown 1982; McFall 1978). Interest in research in the "dynamics of cessation and relapse" is much more recent (US DHHS 1983, p. 246; Ockene et al. 1982). It is helpful to know, for example, whether a 30 percent long-term abstinence rate resulted from the same 30 percent of participants remaining abstinent throughout the followup period or from 10 percent new quitters, 10 percent previous relapsers, and 10 percent who remained abstinent throughout the assessment periods.

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Objective verification of changes in smoking behavior has become the standard for defining smoking behavior. Recent reviews have been conducted of several biochemical measures of smoking status, including carbon monoxide, saliva thiocyanate, and cotinine (Frederiksen and Martin 1979; Leupker et al. 1981; Benowitz 1983; Bliss and O'Connell 1984). Simply having an informant, usually a spouse or coworker, "confirm" a participant's smoking status may not be sufficient corroboration. Such people are not in a position to continuously observe a participant's smoking behavior throughout the day and may be persuaded to falsify their report on the participant's smoking behavior.

Worksitewide Program Effects

The impact of a worksite program may include effects on workers other than those enrolled in the program and effects other than smoking cessation. The localized nature of a worksite program and the repetitive interactions of workers in the program with those who did not participate may produce changes in the attitudes and behaviors of the active workforce that promote smoking cessation and improve employee morale and productivity. For these reasons, one criterion for evaluating worksite programs should be the fraction of the workforce whose smoking behavior is altered in addition to the fraction of the participants who quit. All of these effects are important in evaluating the reported success rate of a program because a very high cessation rate for a program may have little overall impact if only small numbers of employees are willing to participate (Kanzler et al. 1976). Whenever possible, program costs should be reported in addition to data on the effects on smoking patterns of nonparticipating smokers. In the same vein, ongoing worksite programs conducted over a number of years should attempt to document the effects of a smoking modification program on variables such as absenteeism, medical care expenses, and health services utilization.

General Effects

Variables such as employee morale and productivity, commitment to the organization, turnover, and employee–employer relations are important potential secondary effects of a worksite program. Because these issues do not directly concern the topic of smoking and health and have been infrequently assessed, they are not considered in this review. It should be noted, however, that Brownell (1985) makes a convincing case that if the field of worksite health promotion is to prosper, concerted attention needs to be directed toward demonstrating the effects of worksite programs on these organization management issues. He argues that managers may be more interested in such results than in changes in health status.

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General Review of Worksite Programs

A large number of worksite smoking control programs have been conducted. Unfortunately, only a small percentage of these programs have been evaluated. The characteristics and results of experimental investigations of occupational smoking control programs that have presented more than anecdotal data are outlined in Tables 1 through 3. Many of these studies have consisted of pretest–posttest or post-test-only evaluations without control conditions and have not reported objective measures to validate self-reports of smoking status. The sample size, type of worksite setting, and reported results of such uncontrolled studies are listed in Table 1. Because of the absence of comparison conditions, the lack of verification of smoking status, and the general sparsity of information about program procedures and treatment effectiveness in these reports, there are a host of alternative explanations of their results. Therefore, they are only briefly summarized.

Uncontrolled Studies

Although programs have been conducted in a variety of worksite settings (Table 1), the majority have been either conducted in companies of small to moderate size with white-collar employees or offered only to supervisory personnel. The number of participants is generally small. Self-reported abstinence rates for these uncontrolled studies ranged from 25 to 90 percent (median, 60 percent) at posttreatment and from 6.5 to 91 percent (median, 33 percent) at 6-month or 1-year followup. These figures, while encouraging, must be interpreted with caution because it is often unclear whether the reported rates have excluded subjects who dropped out of treatment or followup, and because, in several studies, subjects received sizable monetary rewards based upon reports of abstinence that were not corroborated by objective measures of smoking.

Not known is the impact of the programs listed in Table 1 on overall rates of smoking in the worksites in which they were conducted (see Bishop and Fisher 1984). The majority of investigations do not report rates of participation in their programs, but the studies that have reported (other than in very small companies as noted below) have been discouraging. For example, Kanzler and colleagues (1976) found that despite an intensive promotional campaign, only 4 percent of smokers in their workplace began the cessation program. Grove and colleagues (1979) found that of 409 smokers in their worksite, only 101 attended the first meeting, and only 33 (8 percent of the smokers in the workforce) completed treatment. Of these 33 subjects, only 9 were abstinent at 6-month followup. Stachnik and Stoffelmayr (1981), noting these generally low participation rates, stated: "The question of how one can

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TABLE 1.—Uncontrolled studies without objective measures of smoking status

Study	Number of subjects, type of worksite	Cessation rate (percent)	
		Posttreatment	Followup (No. months)
Andrews (1983)	965 hospital employees	Not reported	26 (20)
Bauer (1978)	81 Bell Laboratories employees	90	30 (6)
Bishop and Fisher (1984)	10–46 employees in each of six companies	25–60	6.5–33 (12)
Dawley et al. (1984)	15 VA hospital employees and 2 patients	88	50 (6)
Ellis (1980)	Asbestos company employees	Not reported	30 (48)
Grove et al. (1979)	33 Blue Cross employees	33	27 (6)
Heckler (1980)	16 Thomas Lipton, Inc. employees	Not reported	50 (1)
Kanzler et al. (1976)	9 psychiatric institute employees and 21 community members	67	40 (12)
Miller (1981)	33 engine manufacturing company employees	Not reported	55 (12)
Rosen and Lichtenstein (1977)	12 ambulance company employees	58	33 (12) (at work)
Shepard (1980)	26 electronics mfg. company employees	Not reported	35 (48) (at work)
Sorman (1979)	55 Riviera Motors employees	Not reported	31 (12)
Stachnik and Stoffelmayr (1983)	Employees in three companies: bank, manufacturer, and health services	Not reported	80–91 (6)

increase participation in smoking cessation programs should receive the same attention that the more standard question of which cessation technique is most effective has received in the past" (p. 49). The exceptions to these low participation rates are seen in studies in the companies with fewer than 100 employees that have employed incentive procedures (e.g., Rosen and Lichtenstein 1977; Sorman 1979; Shepard 1980; Stachnik and Stoffelmayr 1983).

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Controlled Studies

Studies that have included control or comparison conditions are presented in Tables 2 and 3[2]. To emphasize the importance of worksite and participant characteristics, these characteristics as well as data on the public health issues of recruitment strategies employed and on the participation and attrition rates experienced are listed in Table 2. The type of intervention and experimental design employed, short- and long-term cessation rates, and type of biochemical validation of smoking status obtained, if any, are described in Table 3. In this section, a general discussion of the status of the worksite smoking modification literature with emphasis on the characteristics of the most successful programs is followed by a more detailed review and discussion of several important subtopics within the occupational smoking modification field—the role of social support, physician assistance, incentive approaches, employees at particularly high risk for the development of cardiovascular or respiratory disease, multiple risk factor reduction programs, and organizational characteristics that affect program success.

The varied programs conducted have ranged in intensity from a brief physician message (e.g., Li et al. 1984) to ongoing programs involving multiple components over a 4- to 5-year period (e.g., Rose et al. 1980). Recent programs have offered participants a variety of behavior change options. In particular, 7 of the 14 studies outlined in Tables 2 and 3 allowed subjects to select as goals either smoking reduction or abstinence.

The most encouraging finding is that the long-term success rates of the programs reviewed are relatively high. Although initial cessation rates do not appear to differ from those typically produced by community-based smoking clinics, the longer term followup data are more positive if viewed as a percentage of posttreatment cessation outcome. Abstinence rates at 6 to 24 months after a program are approximately 60 to 65 percent of those observed at posttest, in contrast to the 20 to 30 percent figures classically cited for clinic programs (Hunt and Bespalec 1974; McFall 1978). In fact, the *lowest* maintenance rate in the studies summarized in Tables 1 and 3 was 26 percent of the posttest rate, and some studies report followup results equal to or better than posttest (e.g., Malott et al. 1984; Meyer and Henderson 1974; Schlegel et al. 1983). On the other hand, much higher long-term abstinence rates, 50 percent or better of all subjects, have recently been reported from a number of treatment programs (US DHHS 1982), and results from the 22-center Multiple

[2] Stitzer and colleagues at Baltimore City Hospitals have conducted a series of studies with hospital employees to investigate the effects of making monetary incentives contingent upon reductions in carbon monoxide levels (Rand et al. 1984; Stitzer and Bigelow 1982, 1983, in press). These studies have been excluded from the tables because the participants were not asked to produce long-term changes in their smoking behavior, but have simply been paid to participate in laboratory research. Only the Rand group study (1984) has attempted to produce complete cessation; it is included in Tables 2 and 3.

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TABLE 2.—Worksite, subject, and procedural characteristics of controlled outcome studies

Study	Size and type of worksite	Participation rate (percent)	Characteristics of participants	Attrition rate (percent)	Recruitment strategies
Abrams et al. (1985)	800-employee medical manufacturing company and 1,600-employee insurance carrier	Not reported (estimated 6)	54 clerical and blue-collar employees	42	Paycheck stuffers, posters, newsletter articles
Glasgow et al. (1984)	600-employee telephone company	Not reported (estimated 18)	25 female, 11 male employees	Not reported	Employee organization sponsorship, newsletter notices, posters
Glasgow et al. (in press)	VA hospital, health care services company, and savings and loan	Not reported	20 female, 9 male employees	7	Brochures, posters, newsletter notices, memos
Klesges et al. (1985)	Four banks and one savings and loan, 115–180 workers each	88 with competition; 53 without ($p < 0.05$)	82 female, 25 male employees	9	Brochures, announcements by bank presidents, time off work for participation; prize to bank with highest participation
Kornitzer, Dramaix et al. (1980)	30 Belgian factories	84 agreed to screening	19,390 male employees, aged 40–59 years; high risk: upper 20 percent of risk distribution	Not reported	Not reported
Li et al. (1984)	Naval shipyard	87	871 male shipyard workers	17	Participation asked at required screening

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TABLE 2.—Continued

Study	Size and type of worksite	Participation rate (percent)	Characteristics of participants	Attrition rate (percent)	Recruitment strategies
Malott et al. (1984)	Medical clinic and telephone company	Not reported (estimated 7)	20 female, 4 male employees, primarily clerical and nurses	0	Newsletter notices, brochures distributed by supervisors, recruitment in lunchrooms
Meyer and Henderson (1974)	Varian Corporation; 240 employees, volunteers for risk factor screening (13 percent of workforce)	Not reported	36 employees identified at screening as high risk for cardiovascular disease	0	Invitation to health screening
Nepps (1984)	Johnson & Johnson Corporation	Not reported	36 white-collar employees: 20 women, 16 men	67	Posters, desk drops, company newsletter
Rand et al. (1984)	Large city hospital	Not applicable	18 female employees	Not reported	Advertisements, word of mouth
Rose et al. (1980)	24 large British industrial groups	86 agreed to screening	18,210 male employees, 40–59 years old; high risk: upper 12–15 percent of distribution	6–12	Invitation to health screening exam
Schlegel et al. (1983)	28 Canadian military bases	Not reported	243 armed forces personnel (65 percent male)	Not reported	Posters, news releases
Scott et al. (1983)	Large VA hospital	100	26 nurses (22 women, 4 men)	0 of those continued at VA	Individually approached

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TABLE 3.—Design and outcome of controlled worksite smoking modification studies

Study	Program intensity and components	Experimental design	Cessation rate (percent)		Biochemical verification
			Post-treatment	Followup (No. months)	
Abrams et al. (1985)	Basic four-session nicotine-fading cessation program; four-session maintenance treatment	Basic program plus health education (n=18); stress management (n=18); or social support (n=18)	38[1] 33[1] 6[2]	33[1] (3) 27[1] 6[2]	CO
Glasgow et al. (1984)	Seven weekly small group meetings on brand changing and number reduction; goal choices, abstinence or controlled smoking	Gradual reduction (n=12); abrupt reduction (n=13); gradual plus feedback (n=11)	Not reported	33[1] (6) 0[2] 0[2]	CO
Glasgow et al. (in press)	(See Glasgow et al. 1984) Social support with two meetings, installments of manual, and phone calls	Basic treatment program (n=13) vs. basic treatment plus significant other social support (n=16)	54 36	25 (6) 23	CO SCN
Klesges et al. (1985)	(See Glasgow et al. 1984) Competition, with monetary prizes, weekly feedback charts	Quasi-experimental; basic treatment (n=16) vs. basic treatment plus competition (n=91)	31 22	14 (6) 18	CO SCN

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TABLE 3.—Continued

Study	Program intensity and components	Experimental design	Cessation rate (percent)		Biochemical verification
			Post-treatment	Followup (No. months)	
Kornitzer, Dramaix et al. (1980)	Multiple risk factor program, written advice and antismoking posters; high risk subjects, semiannual physician counseling and stop-smoking booklet	Treatment (n=7,398) vs. screening only (n=8,824)	Not reported	High risk 19[1] (24) 12[2] Random sample 12.5 12.6	No
Li et al. (1984)	One-session physician advice and stop-smoking pamphlet	3- to 5-minute behavioral counseling (n=215) vs. warning to quit (n=361)	Not reported	8.4[1] (3, 11) 3.6[2]	CO
Malott et al. (1984)	(See Glasgow et al. 1984) Coworker support: partner support manual, buddy system, individualized support behaviors	Basic treatment program (n=12) vs. basic treatment plus coworker social support (n=12)	17 17	27 (6) 17	CO
Meyer and Henderson (1974)	Multiple risk factor program, 9 to 12 meetings; 2- to 3.5-hour behavior modification group meetings with spouses	Behavior modification (n=12) vs. individual counseling (n=10) vs. physician advice alone (n=14)	40 25 0	20 (3) 25 33	No
Nepps (1984)	Nine written self-help modules; minimal therapist contact	Quasi-experimental: minimal contact (n=36) compared with earlier group cessation program	22	14 (6)	CO

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TABLE 3.—Continued

Study	Program intensity and components	Experimental design	Cessation rate (percent)		Biochemical verification
			Post-treatment	Followup (No. months)	
Rand et al. (1984)	Monetary incentives for low daily CO levels; 1 week of reducing CO levels and 2 weeks of abstinence	Within-subjects design (n=18): baseline—cutdown—abstinence goals	61	28 (3 wks)	CO
Rose et al. (1980)	Multiple risk factor program: posters and stop-smoking booklets; high risk subjects, four company physician consultations	Treatment (n=9,734) vs. screening only (n=8,476)		High risk 12[1] (5 yrs) 0[2] Others 7[1] 0[2]	No
Schlegel et al. (1983)	6-month program; 160-page workbook; abstinence or reduced smoking goal choice; base personnel were therapists	Full treatment (17 sessions) vs. minimal contact (4 sessions) vs. self-help; crossed with nicotine gum/no nicotine gum	45–68[3] 28–31[3] 6–14[3]	25–38[3] (12) 17–29[3] 7–10[3]	No
Scott et al. (1983)	Brief daily sessions with brand fading, treatment manual, and CO feedback, 3 months; abstinence or reduced smoking goal choice	Treatment (n=16) vs. no treatment (n=10)	56[1] 0[2]	25 (9) 0	CO

NOTE: The sample sizes reflect the number of subjects receiving each treatment condition, which in some instances differs from the total number of subjects initiated into the study (see Table 2). Except for the Kleeges and colleagues (1985) and the Li and colleagues (1984) studies, in experiments using between-subjects designs there was random assignment to treatment conditions.

NOTE: CO = carbon monoxide; SCN = saliva thiocyanate.

[1,2] At each assessment point, conditions that were significantly different ($p < 0.05$) are identified by different superscripts.

[3] Results of this factorial study are complex and difficult to summarize with a notation system; see text for clarification (numbers for treatment conditions not reported).

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Risk Factor Intervention Trial (MRFIT) study showed that long-term abstinence rates actually rose from 1-year to 6-year followup under both intervention and control conditions (US DHHS 1983). These results again indicate the need to separate point prevalence of nonsmoking rates from continuous abstinence rates. Unfortunately, data are seldom presented in terms of survival curves (e.g., Curry et al., in press) or in a manner that permits assessment of the consistency in smoking status over time.

These high followup rates suggest that the worksite may offer more than a convenient location for cessation interventions, and that interactions or changes in attitudes or behaviors in the worksite may be important determinants of the successful maintenance of abstinence. Although there are several potential explanations for these relatively good maintenance data, the most obvious is the ongoing contact that coworkers have with each other during the followup period. Consistent with this hypothesis, the clinic-based smoking cessation program in the MRFIT study, which produced one of the most impressive maintenance rates of any study (Hughes et al. 1981; Ockene et al. 1982), involved ongoing contact over several years. Even if coworkers are not highly supportive of each other, they may come to provide no-smoking cues for other participants.

It is important to note that people involved in many of the worksite studies described here are both self-selected and self-motivated, as there are few usual care or no-treatment conditions. Some of the high maintenance rates may be reflective of new quitters who would stop in any program, or even without one.

This comparison of clinic-based programs and worksite programs assumes that participants in each setting are similar. Although the demographic and smoking history characteristics of subjects in these reports do not appear to differ systematically from other studies in the cessation literature, there may still be marked differences between the groups. For example, since worksite programs generally attract a higher percentage of smokers than do community-based clinics, some of these subjects may be more recalcitrant smokers (Bishop and Fisher 1984). The convenience of the worksite setting may also attract more smokers. On the other hand, it may be that only individuals who have repeatedly failed to quit on their own will expend the time, effort, and money often involved in participating in community clinics (Schachter 1982). To date, the primary determinant of participant characteristics in the controlled outcome studies (Table 2) seems to be the type of worksite in which a program is conducted. Research is needed on the hypotheses concerning possible differences between participants in worksite programs and smokers attending community clinics.

Several differences between studies reporting high success rates and those with less favorable results are clear. One of the more

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striking differences to emerge is that the results of the better controlled studies summarized in Table 3 (median posttest cessation rate, 28 to 31 percent) are generally lower than those of the uncontrolled studies outlined in Table 1 (median posttest cessation rate, 60 percent). The most obvious explanation for this finding is that most of the controlled studies included objective biochemical indices of treatment outcome and subjects in these studies may have more accurately reported their smoking status.

The intensity of smoking modification programming also appears to be related to treatment outcome. Programs involving only a brief session or two or relying primarily on self-help materials generally produced the lowest cessation rates—from 4 to 14 percent long-term abstinence (e.g., Li et al. 1984; Nepps 1984). In contrast, the best cessation rate reported came from an intensive multicomponent program involving 20 group meetings over a 7-month period (Stachnik and Stoffelmayr 1983). The only worksite study to directly compare different levels of program intensity found that a greater number of sessions was associated with higher cessation rates (Schlegel et al. 1983).

Another fairly consistent finding is that programs conducted in larger worksites generally seem to produce poorer outcomes. Of the abstinence-based programs, studies taking place in worksites with 100 or fewer employees (e.g., Miller 1981; Shepard 1980; Stachnik and Stoffelmayr 1983) seem to attain the highest abstinence rates, and the larger scale controlled trials (e.g., Kornitzer, Dramaix et al. 1980; Li et al. 1984; Rose et al. 1980) to result in much lower abstinence rates. Bishop and Fisher (1984), who have conducted programs in a variety of different sized worksites, concluded that larger worksites also typically produce lower participation rates than do smaller companies. However, a greater number of employees may still be served.

Programs addressing multiple risk factors (e.g., Rose et al. 1980) in worksite settings generally yielded poorer cessation rates (and tended to be conducted in larger worksites) than did smoking-modification-only programs. Multiple risk factor programs may achieve greater overall reductions in morbidity and mortality because of their effects on other risk factors, however. Finally, programs providing incentives for smoking abstinence (e.g., Shepard 1980; Stachnik and Stoffelmayr 1983) were among those with the more impressive outcomes, although not objectively verified. These findings are discussed in more detail in the section on incentives.

Remaining Issues

Few worksite studies have investigated participant characteristics associated with treatment outcome. The most consistent finding to emerge is that smokers of lower numbers of cigarettes have greater

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success at quitting than do heavier smokers (e.g., Kornitzer, Dramaix et al. 1980; Li et al. 1984; Rand et al. 1984). This finding is consistent with results of clinic-based programs (e.g., Ockene et al. 1982) and suggests that special attention needs to be devoted to ways to successfully treat heavy smokers.

Relatively little is known about the long-term effects of the non-abstinence-based smoking reduction programs under review (Tables 2 and 3). Allowing subjects to choose the treatment goal of abstinence or of reduced smoking may attract more participants, provide initial success experiences that can be built upon in later cessation efforts, and benefit those subjects not able to achieve or maintain abstinence. On the other hand, such programs may dissuade subjects from pursuing a goal of complete cessation and allow participants to rationalize that smoking is not hurting them because they have made changes in smoking rate, topography, or cigarette brand. It is beyond the scope of this chapter to review the complex literature on potential compensation effects resulting from changes in smoking behavior (see McMorrow and Fox 1983; Moss and Prue 1982). It should be noted, however, that subjects selecting smoking reduction goals have generally shown reliable, although not always large, reductions in carbon monoxide levels (e.g., Glasgow et al. 1984).

There has been improvement in the research methodology employed in worksite smoking modification studies. The majority of studies conducted in the recent past have included both comparison conditions and biochemical measures of smoking exposure. There are still, however, a number of methodological deficiencies in current worksite studies. Comparison conditions do not usually include no-intervention or usual care groups; differences among interventions are most commonly studied, and randomization is not always used. Little is known about participation rates (only one-third of the studies listed in Table 2 provide information on the percentage of smokers participating). Data are seldom presented on effects of a program on *all* smokers in an organization, and no data have been published on characteristics of employees who participate in worksite programs versus those who do not. Finally, there are so few data on the health benefits or cost effectiveness of specific programs that this information was not included in Table 3. Only the large-scale multiple risk factor reduction trials (Kornitzer, De Backer et al. 1980; Rose et al. 1980) have presented such data.

Special Issues Relevant to Worksite Programs

Social Support

One of the most frequently cited reasons for conducting smoking modification programs in occupational settings is the potential for

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invoking peer and environmental support for nonsmoking (Chesney and Feuerstein 1979; Stachnik and Stoffelmayr 1981). It has been argued that peer support has important, long-lasting effects on the outcome of stop-smoking efforts (Janis 1983), and there have been several calls for increased study of the role of social support in smoking modification (Klesges and Glasgow 1985; Lichtenstein 1982; Stachnik and Stoffelmayr 1981). There are also correlational findings that suggest the importance of social support to successful smoking cessation (e.g., Coppotelli and Orleans, in press; Mermelstein et al. 1983).

Given this background, it is surprising that a large-scale correlational study of occupational settings by Caplan and colleagues (1975) found that the degree of perceived support from coworkers was *inversely* related to smoking status. Among workers with low levels of job stress, ex-smokers reported lower levels of support than current smokers. There was no relationship between social support and smoking status for people with high levels of job stress. However, Caplan and colleagues' measure of social support was not specific to smoking cessation, and may have been more an index of the employee's responsibility for supervising or otherwise interacting with other worksite personnel. More recent studies by Malott and colleagues (1984) and by Glasgow and colleagues (in press) have found a complex relationship between social support and outcome of worksite smoking modification programs. Using a measure that produced a score for both supportive and nonsupportive (negative) social interactions, these two studies found that the presence of smoking-related negative social interactions was inversely related to treatment success. The presence of positive social support, which is more frequently the target of social support interventions, was not related to outcome.

Social support procedures such as use of a buddy system and inclusion of nonsmoking coworkers or family members in treatment sessions have been part of a variety of worksite programs (e.g., Bauer 1978; Sorman 1979; Stachnik and Stoffelmayr 1983). Unfortunately, it is impossible to evaluate the contribution of social support in these studies because of the multitude of other intervention strategies also employed. In a review of studies on the effects of worksite incentive programs for smoking cessation, Shepard and Pearlman (in press) concluded that incentive programs that included spouses produced better outcomes than those that did not.

The few worksite smoking studies that have attempted to experimentally manipulate the level of social support have produced discouraging results. Abrams and colleagues (1985) compared a social support/social skills training program including a buddy system with health education and cognitive-behavioral stress management procedures as ways to improve the long-term effectiveness

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of a nicotine-fading cessation program. By the end of the program, subjects in the social support/skills condition had relapsed significantly *more* than subjects in the other conditions, and these differences persisted at followup. In addition, consumer satisfaction ratings revealed that subjects liked the social support/skills program less well than other options. Abrams and colleagues concluded on the basis of these findings that factors such as social support, theoretically assumed to enhance treatment, may actually reduce the effectiveness of a treatment program in some instances.

Malott and colleagues (1984) evaluated the effects of adding a coworker support component to a multicomponent treatment program offering subjects the options of abstinence or controlled smoking. They found that the addition of coworker support did not improve treatment outcome on any dependent variable and that subjects found the condition with social support to be less credible than the basic treatment program. A replication and extension of the Malott group's (1984) study by Glasgow and colleagues (in press) involved family or significant-other social support and included a partner-support manual, two group meetings for supportive others, individualization of support procedures, and semiweekly phone calls to partners. The results of this study were consistent with those of Malott and colleagues (1984): no incremental effects of the social support program were obtained from any dependent variable.

Thus, in research conducted to date, the inclusion of existing social support procedures has not been found to enhance outcome in worksite smoking modification programs. This is not to say that social support is not important to treatment success, but that the issue is more complex than was initially believed. It may prove difficult to alter existing levels of social support, and novel ways of enhancing coworker and family support for smoking modification need to be developed.

Physician Advice

Because as many as 70 percent of adults in our country visit their physician at least once in a given year (US DHEW 1979), there has been growing interest in finding ways in which physicians can convince patients to give up smoking (Ewart et al. 1983; Russell et al. 1979).

Some of the best data come from recent European clinical trials (Rose et al. 1980, 1982; Kornitzer, Dramaix et al. 1980). The Belgian Heart Disease Prevention project (Kornitzer, Dramaix et al. 1980) found that significantly more individuals at high risk for developing heart disease stopped smoking in an intervention condition emphasizing semiannual physician messages than in a screening-only control condition (see Table 3). When comparing a representative sample of all intervention subjects (many of whom did not receive

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the physician messages) with a similar sample of control subjects, however, almost identical and fairly low cessation rates were observed in both conditions.

The most intensive worksite physician-intervention program was evaluated in a similar study conducted by Rose and colleagues (1980). In this study, the 12 to 15 percent of subjects in the intervention condition who were at greatest risk for cardiovascular disease were provided four physician consultations, each approximately 15 minutes in length. Results were similar to the Belgian study in that a greater percentage of the high risk subjects stopped smoking in the intervention group than in the control condition (see Table 3). But considering all participants (many of whom did not receive the intensive physician messages), there were no significant differences between conditions.

A series of four physician visits was also utilized in a carefully controlled study by Rose and Hamilton (1978) of British civil servants at high risk of cardiorespiratory disease. Although not actually conducted in occupational settings (and therefore not included in Tables 2 and 3), subjects for the study were recruited through their worksite. This study produced the highest cessation rates of any physician-advice study (self-reported abstinence rates of 51 and 36 percent at 1 and 3 years, respectively). Over a third of these subjects were still smoking pipes and cigars, however, and a relatively high percentage of "normal care" subjects also stopped smoking (10 and 14 percent at 1 and 3 years, respectively). Although there were differences in favor of the intervention condition in rate of decline in airway obstruction and rates of phlegm production, there were no differences between conditions in absenteeism over a 1-year period or in overall mortality over a 7- to 10-year period.

As these studies indicate, there are both advantages and disadvantages in using physician stop-smoking messages in worksite settings. One distinct advantage is that if stop-smoking advice is incorporated into regularly scheduled physician visits, a relatively large number of workers can be advised and treated quickly and cost effectively (Lichtenstein and Danaher 1978). Another advantage of the physician model is that it is relatively unobtrusive in comparison with management-sponsored programs (Danaher 1980). Physician advice can also be used to augment other interventions rather than to replace them, by assisting workers in deciding to seek help and by promoting participation in intervention programs, therefore facilitating better use of these programs.

Although self-reported cessation rates resulting from physician advice are low in an absolute sense, research is underway to attempt to increase the impact of stop-smoking messages. Li and colleagues (1984), in a study conducted in a navy shipyard clinic, found that implementation of a 3- to 5-minute session of behavioral counseling

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by staff physicians significantly increased cessation rates over those resulting from a simple warning to quit smoking (see Table 3). In addition, the compliance of health care providers with treatment protocols also affects outcome. For example, Li and colleagues (1984) reported great difficulty in getting clinic physicians to consistently deliver a brief 3- to 5-minute message to patients, yet Ewart and colleagues (1983) found that providing physicians with regular performance feedback appears to improve the quality and quantity of stop-smoking messages. Future research should identify procedures to improve both the implementation and the outcome of physician stop-smoking advice. Perhaps a stop-smoking message in conjunction with other interventions may increase success rates.

Basic research on the effects of threatening communications such as those describing health risks of smoking indicates that such messages have their greatest impact if individuals know not only what to do (e.g., stop smoking) but how to do it, and believe themselves capable of acting (Leventhal 1970). The recent approval of nicotine chewing gum by the U.S. Food and Drug Administration and the availability of high quality self-help stop-smoking manuals (e.g., Davis et al. 1984) now present an opportunity for physicians to deliver a health warning accompanied by concrete recommendations for what to do and how to do it. Recent data suggest that nicotine chewing gum may assist heavier or more addicted smokers in quitting (Fagerstrom 1978, 1984; Raw et al. 1980), and gum prescriptions can be written at the same time that a stop-smoking message is given. Only one study reviewed in this chapter has investigated the use of nicotine gum (Schlegel et al. 1983). That study, which did not involve physician advice, found that the gum enhanced treatment outcome in self-help conditions, but in the context of an intensive 17-session treatment program, subjects receiving the gum actually had lower cessation rates than subjects not receiving gum. Particularly in companies that employ their own medical staff or in which employees are at risk because of occupational hazards, programs combining physician stop-smoking advice with other intervention options should be evaluated.

Incentives

Recently there has been increased interest in the motivational factors associated with smoking behaviors (Shepard and Pearlman, in press; Brownell 1985). This section focuses on two recent approaches to increasing motivation: personal incentives and competition among participants.

Rosen and Lichtenstein (1977) published the first report on the effects of an employee incentive program for stopping smoking. Of the employees of a small ambulance company who smoked, 75 elected to participate in a program that involved a $5 per month

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bonus for not smoking at work—for all employees regardless of their initial smoking status. At the end of the year, the owner also matched the total amount of bonuses received during the program. No other intervention techniques were used, and no stop-smoking meetings were held. This study underscores the potential power of incentives to modify smoking behavior: at posttest, 58 percent of the pretest smokers reported no longer smoking at work.

Sorman (1979) reported on a program that combined personal incentives, a stop-smoking program, social support, low-calorie food alternatives, and an exercise program. Of 202 employees, 55 enrolled in the program in which each employee who quit smoking for 1 year received a $200 reward. Thirty-one percent of the participants reported having successfully stopped smoking for the entire year. Shepard (1980) presented results from an ongoing incentive program involving weekly $7 paycheck bonuses to employees not smoking at work. After approximately 4 years, only 20 percent of the employees reported smoking in the worksite compared with 67 percent at pretest.

Stitzer and Bigelow (1982, 1983, in press) have conducted a variety of studies that cogently demonstrate that contingent reinforcement for reductions in carbon monoxide (CO) levels of expired breath samples can produce reliable short-term reductions in CO levels in hired cigarette smokers. A recent study (Rand et al. 1984) investigated contingent reinforcement for smoking *abstinence* in 18 hospital employees. After 1 week of baseline smoking and a week-long "cutdown test," subjects could earn $12 a day for 2 weeks if they totally abstained from smoking and if their daily CO readings were consistent with abstinence (<11 ppm). Sixty-one percent of the participants were abstinent throughout the 2-week contingency period, and 28 percent remained abstinent throughout a 3-week followup.

Finally, Stachnik and Stoffelmayr (1983) evaluated a comprehensive 7-month-long worksite program involving sizable financial incentives as well as health information, social support, and public commitment to nonsmoking in the context of 20 gradually paced group meetings. The program was conducted in three different worksites, with from 47 to 70 percent of smokers enrolling in the program and an astounding 80 to 91 percent of participants reporting abstinence 6 months after participation in the program. These results are obviously very impressive, but it is not possible to evaluate the contribution of incentives versus the other procedures employed.

Shepard and Pearlman (in press) recently reviewed 15 (mostly unpublished) programs that used incentives to produce changes in smoking behavior in the worksite. Some programs provide incentives for not smoking at the worksite, and others have a goal of total

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abstinence. Although incentive programs seem to be gaining in popularity and self-reported cessation rates appear high, there are a number of problems with evaluations of incentive-based smoking programs. Most studies are uncontrolled, and with notable exceptions (e.g., Rand et al. 1984), measures of smoking status during nonwork hours and biochemical verification of smoking status are lacking. Clearly, incentive programs deserve further investigation, because they appear to be effective, relatively inexpensive, and easy to implement in a variety of different settings.

Another approach to providing incentives for improvements in health-related behaviors is to arrange competitions among different worksites or teams within a given worksite. For example, Brownell and colleagues (in press) report high participation rates, low attrition rates, and impressive outcome data in a recent worksite obesity competition. Given these promising results, Klesges and colleagues (1985) conducted a worksite smoking competition among four banks. Prizes to benefit both smokers and nonsmokers were awarded to the bank with (1) the highest participation rate, (2) the largest reductions in carbon monoxide levels at posttest, and (3) the greatest abstinence rate at the 6-month followup. All participants in this study received a gradually paced smoking control program previously used in worksite settings (Glasgow et al. 1984). Finally, a "Smoking Barometer" placed in the lobby or lounge of each worksite provided employees with weekly feedback on how their bank was doing compared with the other three.

Participation rates in the program were exceptionally high. Overall, 88 percent of all bank employees who were smokers entered the program, compared with a 53 percent participation rate at a comparable savings and loan organization that received the identical program without competition, a significant between-groups difference. There were, however, no differences between conditions in cessation rates among participants in the program. This may have been because subjects in the competition condition were more nicotine dependent, as assessed by the Fagerstrom (1978) Tolerance scale, than subjects in the noncompetition condition ($p < 0.02$). Because of the higher participation rate, however, the competition condition produced a higher long-term cessation rate (15 percent) throughout the worksite than the comparison condition (7 percent).

One of the major advantages of incentive and competition programs is that they do not require large amounts of therapist or participant time. If the success rates of the uncontrolled studies (Table 1) can be replicated in controlled studies, incentive programs may prove to be the most cost-effective approach to worksite smoking modification. On the other hand, at least some people may require additional guidance and support (Danaher 1980). One convenient, low-cost method of providing skills training in the

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context of incentive programs is through provision of self-help stop-smoking materials (Glasgow and Rosen 1978; Windsor and Bartlett 1984). Although a number of worksite studies have employed written self-help materials as part of multicomponent interventions (Li et al. 1984; Kornitzer, Dramaix et al. 1980; Nepps 1984; Rose et al. 1980), self-help manuals have not been used in incentive programs for smoking cessation and studies to investigate their unique contribution to treatment outcome have not been conducted.

Overall, the results of incentive- and competition-based programs are very promising. However, almost all of these studies have been conducted in small worksites, and systematic replications of these findings in controlled investigations in larger companies are needed. Future research should also investigate the types of personal incentives (e.g., paycheck bonuses versus lotteries for quitters) and competitions (e.g., within a worksite versus between worksites) that work best in different organizations. Finally, nonsmokers should be carefully considered in incentive programs—in their role as supporters of quitters and as nonsmokers, with bonuses for all nonsmokers, old and new—and worksite resources should be provided for all employees.

High Risk Populations

With the exception of the few large-scale clinical trials listed in Table 2 (e.g., Kornitzer, Dramaix et al. 1980, Li et al. 1984; Rose et al. 1980; Schlegel et al. 1983), the majority of participants in worksite smoking programs have been young, from middle or upper socioeconomic levels, and in occupations that do not place them at increased health risk. Although smoking cessation efforts should continue with such populations, an argument can be made for focusing efforts on individuals at particularly high risk for cancer, cardiovascular disease, or respiratory disease—the major causes of excess morbidity and mortality due to cigarette smoking. Given limited resources, it should be more cost effective to direct interventions primarily toward those most likely to develop disease. Three overlapping approaches have been used to reach the following types of high risk smokers in the worksite: blue-collar male workers, workers at risk because of occupational hazards, and individuals predisposed to disease for reasons in addition to smoking (e.g., obesity, hypertension, abnormal lipid levels).

Few worksite programs have been offered by companies employing primarily male blue-collar workers, even though such groups have higher than average smoking rates. Although there is little or no documentation of the reasons for this inconsistency, it may be due to mistaken beliefs among health professionals that such individuals would be less likely to participate in or follow through with a smoking modification program. Ellis (1980) found that blue-collar

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workers may be at least as interested in quitting as others in the general population. Resistance on the part of some labor unions may constitute another reason for fewer programs conducted in blue-collar worksites.

Initial worksite smoking research with blue-collar workers has been conducted both at military bases and in Veterans' Administration (VA) hospitals. Schlegel and colleagues (1983) offered programs at 28 different military bases across Canada. Although their outcome results were comparable with other studies, they did report relatively low followthrough (compliance) rates with homework assignments. Also, they must have failed to recruit a high percentage of smokers, because an average of fewer than 10 smokers per base participated. Perhaps a different intervention approach is needed for blue-collar populations—one that does not require employees to devote much time and effort, and one that tailors materials and tasks to be appropriate socioculturally. Dawley and colleagues (1980, 1984) conducted research with employees and patients in VA hospitals and have advocated increased smoking modification efforts within the VA system. They point out that it is ironic that for many years the Nation's largest health care provider sold cigarettes at cutrate prices, owing to tax-exempt status.

Little systematic research with smokers in jobs that place them at risk because of occupational hazards has been reported. For example, asbestos workers are at high risk for respiratory disease, and asbestos workers who smoke increase their risk synergistically (US PHS 1977; see the chapter on asbestos in this Report). Ellis (1980) informally reported on the results of a program for former employees of an asbestos company that involved incorporating antismoking advice into regularly scheduled appointments with company physicians, pairing written self-help materials with feedback on physical status, and offering individual smoking cessation counseling. Over a 4-year period, this relatively low cost intervention was associated with a 30 percent reduction in the proportion of employees who reported being smokers. A related publication by Ellis (1979) provides suggestions for recruiting and treating asbestos workers.

The most extensive no-smoking program involving high risk occupations has been been conducted by the Johns-Manville asbestos company. In addition to a smoking ban throughout the worksite and a company policy of no longer hiring new employees who smoke (Cooper 1978), Johns-Manville launched an intensive antismoking campaign at 14 company sites. This program involved an educational campaign coordinated with SmokEnders cessation clinics and the institution of the companywide smoking ban. Although systematic, published reports of this program could not be located, Orleans and Shipley (1982) reported participation rates of 15 to 20 percent in the cessation clinics and an approximately 75 percent posttreatment

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quit rate among participants (apparently without biochemical validation). In the only controlled study to date of worksite intervention in high risk occupations, Li and colleagues (1984) recently studied the effects of physician stop-smoking advice on asbestos-exposed naval shipyard workers. They found, somewhat surprisingly, that subjects who had abnormal pulmonary function tests did not have higher cessation rates (4 percent prolonged abstinence) than workers with normal pulmonary function tests (6 percent prolonged abstinence) who received the same intervention.

The third approach to reaching high risk participants has been to conduct comprehensive health screenings to identify *individuals* at risk for the development of chronic disease. Rose and colleagues (1980) assigned people at high risk of developing heart disease who worked in 24 large industrial companies to intervention or screening-only control conditions. High risk people in the intervention condition were more successful at quitting smoking (12 percent cessation at 5 years) than similar subjects in the control condition (0 percent cessation rate). Similar results were reported by Kornitzer and Dramaix and colleagues (1980) in a parallel large-scale trial conducted in Belgium (see Table 3).

In summary, some promising initial studies have been conducted with high risk individuals. But such studies are few in number and much more intensive study of ways to best reach high risk individuals is needed.

Multiple Risk Factor Reduction Programs

A number of organizations have offered smoking cessation programs as part of employee wellness or lifestyle-modification programs. Such programs typically focus on achieving modifications in several risk factors in addition to cigarette smoking, such as obesity, elevated cholesterol levels, hypertension, and a sedentary lifestyle. Some programs also include components on stress management and modifying Type A behavior. Almost all programs include an initial health screening to identify risk factors, but subsequently there is a considerable divergence in approaches. Some programs focus solely on high risk participants (e.g., Meyer and Henderson 1974; Ware and Block 1982); others invite all employees to participate regardless of risk status (e.g., Naditch 1984). There is also considerable variation in how smoking programs are implemented, with some programs holding separate meetings for smokers and others including information on smoking modification as part of their general wellness program.

The concept of providing smoking modification services as part of a more general lifestyle program is appealing. Stopping smoking can be seen as one aspect of adopting a more healthy lifestyle, and other program components such as increased levels of exercise may

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reinforce smoking abstinence (Morgan 1981). Many smokers, particularly women, are concerned about potential weight gain as a result of smoking cessation, and such programs can address these concerns (Ellis 1980).

There are also potential disadvantages of multiple risk factor reduction programs. They may be difficult to implement because staff expertise is required in multiple areas and because some risk factors, such as smoking, may not be relevant for all participants. In addition, multiple risk factor reduction programs must present a large amount of complex information, usually in a limited time, and consequently the amount of attention devoted to a given risk factor such as smoking must often be less than is the case in single modality programs.

Two main types of multiple risk factor reduction programs have involved smoking cessation. The first is large-scale clinical trials for the prevention of coronary heart disease. The Belgian and British WHO studies reported by Kornitzer and Dramaix and colleagues (1980) and by Rose and colleagues (1980) were conducted solely in industrial settings and were discussed in detail in the 1983 Report of the Surgeon General (US DHHS 1983). These studies are well designed and have collected multiple dependent variables, including indices of overall health risk or morbidity and mortality statistics.

The other main type of multiple risk factor reduction program that has been developed is worksite wellness programs conducted by large companies for their employees. Examples include the STAY-WELL program of the Control Data Corporation (Naditch 1984), the Live for Life program of Johnson and Johnson (Nathan 1984), and programs offered by IBM, the Campbell Soup Company, and the Ford Motor Company (Parkinson et al. 1982; Ware and Block 1982). Unfortunately, the outcomes of almost all industry-sponsored programs reported to date are difficult to interpret owing to varying methods of reporting results, difficulties in following subjects, and lack of objective measures of smoking status. Reports of company wellness programs with more than anecdotal data on smoking modification results (e.g., Grove et al. 1979; Sorman 1979) are summarized in Table 1.

Cessation rates in multiple risk factor reduction programs in worksites have ranged from 7 to 33 percent at followup. Many of these rates are lower than those typically reported in other worksite smoking studies and are not consistently better than comparison conditions in controlled studies (Kornitzer, De Backer et al. 1980; Meyer and Henderson 1974). Interpretation of these data is problematic because of the lack of direct comparisons with smoking-cessation-only interventions, because subjects with multiple risk factors may be more recalcitrant than other subjects, and because

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TABLE 4.—Organizational characteristics potentially affecting outcome of worksite smoking programs

(1)	Size of worksite	(7)	Union/management relations
(2)	Current worksite smoking policies	(8)	Percent of smokers in the worksite
(3)	Degree of management support for program	(9)	Growth oriented vs. consolidating climate of organization
(4)	History of health promotion efforts in the worksite	(10)	Rank and sociometric standing of primary contact person
(5)	Sex ratio of employees		
(6)	Job stability/turnover	(11)	Socioeconomic level of employees

the risk factor reduction programs reported in this section tend to be ongoing programs rather than one-shot smoking clinics.

Organizational Characteristics and Other Factors

Conducting outcome research in worksite settings involves a number of unique factors that may mediate or interact with program success. The organizational characteristics that may mediate program success are outlined in Table 4. Although this list is certainly not exhaustive, investigators should consider these factors when conducting worksite smoking programs. An example of the potential effects of organizational characteristics is the variability in outcome reported by Glasgow and Klesges and their colleagues (Glasgow et al. 1984, in press; Klesges et al. 1985). The basic treatment programs utilized in these studies were almost identical and were implemented by many of the same therapists. Yet, the 6-month abstinence rates in the different organizations ranged from 14 to 33 percent.

Few of these variables have been addressed in worksite smoking studies. Bishop and Fisher (1984) have conducted similar multilevel smoking cessation programs in a number of different organizations, ranging in size from 200 to 6,000 employees. They reported substantially lower participation rates in large companies, a finding that is consistent with results of studies of worksite weight loss programs (Brownell et al., in press). Also, the studies outlined in Tables 1 through 3 suggest that the highest cessation rates are obtained in smaller worksites. Taken together, these trends suggest that different interventions and different ways to assure participation need to be developed for large corporations. The problem may be one of

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implementation, not design. Company policy regarding vesting responsibility in division leadership may be a critical variable.

In terms of the second variable in Table 4, worksite smoking policies, it is important to emphasize that smoking cessation groups are but one way to influence rates of worksite cigarette smoking (Bennett and Levy 1980). Although there have certainly been more reports on cessation programs than on other approaches to occupational smoking control, evaluations of alternative procedures are beginning to appear. In particular, Dawley and colleagues (Dawley and Baldwin 1983; Dawley and Burton, in press; Dawley et al. 1980) and Jason and colleagues (Jason and Liotta 1982; Jason and Clay 1978; Jason and Savio 1978) have studied the effects of no-smoking signs and requests not to smoke. These studies indicate that the posting of nonsmoking signs and the establishment of nonsmoking areas temporarily reduce smoking rates, but that active enforcement of such policies is necessary to produce substantial or lasting decrements in smoking behavior (Dawley et al. 1980; Jason and Liotta 1982; Jason and Savio 1978). One caveat to be kept in mind in evaluating the effects of worksite smoking restrictions is that workers may "compensate" by smoking more during breaks and after work (Meade and Wald 1977). Evaluations of the effectiveness of smoking restrictions should therefore assess smoking rates during both work and nonwork hours and include objective measures of smoking exposure.

Dawley and colleagues subdivided smoking modification efforts into three categories: smoking control (limiting or restricting smoking to designated areas); smoking discouragement (educational efforts to encourage people to stop smoking); and smoking cessation (more formal treatment programs). They also suggested that "worksite smoking cessation programs operate most effectively when offered in conjunction with worksite smoking control and discouragement efforts" (Dawley et al. 1984, p. 329), a highly testable hypothesis that has yet to be experimentally investigated.

The potential to use modifications of the work environment to aid in smoking cessation, including restricting smoking, removing cigarette machines, and altering work rules or situations that promote smoking, make the worksite more than simply a location for cessation interventions. The elimination of environmental supports for smoking, alteration of the smoker's self-image, changing the perception of the smoker among peers, and revising the social norms about smoking in the worksite may all provide a powerful motivation for the smoker to quit and support the successful maintenance of cessation. These changes in the workplace environment and attitudes may be more important than the components of the behavioral intervention used to get workers to quit, and experimental verification of the impact of these changes would provide a useful

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guide for the structuring of future comprehensive worksite interventions. Because it would probably be unlikely that researchers would gain access to experimental manipulation of some of the more controversial aspects of guidelines (hiring policies and penalities for smoking), opportunities that may arise to study such changes in noncontrolled research would be worth pursuing.

Few data have been collected on the other variables listed in Table 4. Research on worksite smoking programs should at least provide descriptive information to determine how these variables affect program success. The fit between organizational and program characteristics has been neglected in past occupational smoking control research. It is hoped that future research will be able to identify the types of programs that are most effective in each different worksite setting.

Implementation of Worksite Smoking Programs

This section focuses on two major classes of implementation issues: recruitment procedures and characteristics of intervention programs.

Promotion and Recruitment

The initial contact with a worksite can prove critical to the success of a project. It is generally recommended that the initial meeting be with the chief executive of the organization (Klesges and Glasgow 1985). Although this officer typically does not coordinate the program, support from top-level management appears to be important in program recruitment and implementation (Grove et al. 1979). Another method of enhancing participation and organizational involvement is the formation of a steering committee (Bishop and Fisher 1984; Stachnik and Stoffelmayr 1981) composed of key representatives from both labor and management. Employees should perceive that the program is voluntary and that they have input into its implementation. Steering committees of this kind may be particularly important in large worksites with unionized employees. Management support appears to be quite important to the success of the committee (Bishop and Fisher 1984).

Upon securing permission to offer a program, it is helpful to conduct a brief worksite needs assessment (e.g., Heckler 1980; Kanzler et al. 1976; Klesges and Glasgow 1985). The survey can be used to determine (1) the number and characteristics of smokers in the worksite, (2) the number of smokers potentially interested in participating, and (3) preferences concerning the types of programs that might be offered (e.g., self-help versus group meetings; abstinence versus reduced smoking) and the most convenient times for meetings to be scheduled.

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During the recruitment phase, information about the program should come from a variety of sources, such as posters, memos, and brochures. Advertising experts recommend providing multiple exposures to a "product" (in this case, a smoking program) to promote attitude change and to convince participants to take action regarding the product (Sawyer 1981). Promotional materials should include information about the cost of a program, stress that participation is voluntary and individual results are confidential, and counter possible misconceptions (e.g., "I have to quit at the first session"; "I'll lose my job if I don't participate"). It is helpful if at least one memo or announcement comes from top management. At this stage, human resources or personnel directors can be extremely useful in suggesting the best ways to promote the program in their particular setting. Involving the local media may also increase the credibility of the program as well as provide no-cost advertising for both the program and the worksite.

Prior to the actual implementation of a smoking program, some programs prepare worksites for health-behavior change (Andrews 1983; Bennett and Levy 1980; Ellis 1979; Grove et al. 1979; Heckler 1980). These preparatory procedures have ranged from prescreening health exams (Ellis 1979) to the initiation of smoking restrictions (Andrews 1983; Bennett and Levy 1980). Warnings of the impending restrictions with indications of the "target restriction date" allow workers to prepare for changes, such as by joining available programs. Although empirically untested, these recruitment procedures may help to convince employees to join smoking programs.

Program Characteristics

The advantages of occupational smoking control programs discussed earlier do not *automatically* or *necessarily* occur. Programs must be made convenient. Higher participation rates are usually found in programs that offer time off work (e.g., Klesges et al. 1985; Scott et al. 1983). Time off work for participation can be a double-edged sword, however. It may increase the number of smokers who participate primarily to be excused from their work stations, and it may also create demands among nonsmoking employees for time off work to attend other health-related classes. Generally, the benefits of conducting programs during work hours outweigh the potential costs, and if management is not willing to grant time off work, it may at least be possible to negotiate time sharing between employee and employer (e.g., 1/2 hour of work time, 1/2 hour during lunch hour or after work). Investigators should also be aware of the difficulties involved in scheduling group meetings in worksites where employees work rotating shifts, such as hospitals.

In addition to being convenient, programs should be attractive to participants. For example, allowing smokers to choose the type of

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program (such as nicotine fading versus aversive smoking), the modality of intervention (self-help manual versus group meetings), the treatment goals (abstinence versus reduced smoking), and the type of group leader (health professional versus peer facilitator) may be helpful in attracting and retaining participants. Different components of a comprehensive program, such as physician advice, no-smoking policies, stop-smoking contests, or group meetings, may mutually reinforce each other. While these suggestions await empirical verification, providing smokers with a number of choices should serve to increase participation rates.

Finally, feedback on progress may serve to increase the magnitude of behavior change. For example, participants can be provided with frequent feedback on carbon monoxide levels as they reduce their smoking (e.g., Rand et al. 1984; Scott et al. 1983). Charts displaying the weekly progress of different groups can be posted in employee lunchrooms or lounges. Periodic progress reports to department supervisors might also be helpful. To avoid stigmatizing particular individuals, public feedback should be provided on progress by the group rather than by individuals.

There are a number of problems in conducting worksite smoking modification groups that should be avoided, or at least anticipated. Group composition is one such sensitive issue. For example, mixing high-ranking executives with production workers can almost eliminate group discussion. However, this may depend on the company's tradition of interaction among workers of different levels, on the skills of the group leaders, and so on. Scheduling difficulties can arise in settings were employees rotate shifts or travel frequently, or where meeting rooms are scarce or distant from work stations. One also needs to be sensitive to negativism or complaining, which can become contagious; the group's focus must be kept positive. A positive perspective is particularly important when conducting competition or incentive interventions in which certain individuals or groups must "lose." A more optimistic perspective that can be used to encourage participants is that eveyone can win something by changing their smoking, so there are no losers.

Finally, Marlatt and Gordon's (1985) concept of stopping smoking as a "journey" can be quite helpful. On their journey, people may experience temporary setbacks or detours (relapses), but this should not prevent them from reaching their destination (abstinence). The presence of an ongoing program that makes it easy to try different options or to recycle a procedure can serve to reinforce this concept and to improve long-term results.

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Recommendations for Future Research

A number of suggestions for the implementation of worksite smoking modification programs have been outlined. Given the limited nature of the data available, few of these guidelines are experimentally derived. Research is needed to empirically support or refute these recommendations. This section discusses needs for future research in the field of worksite smoking modification. Recommendations are made on both research methodology and substantive issues for further investigation.

Methodological Issues

Greater use should be made of creative experimental and quasi-experimental designs, as discussed by Cook and Campbell (1979). In particular, it should be possible to sequentially introduce an intervention or intervention components in different worksites using time-series or multiple baseline designs or to investigate the incremental effects of adding different strategies, such as physician messages, incentives, and social support procedures, to a basic treatment program.

Greater consistency across studies in the criteria used to define smoking status would substantially aid in the interpretation of results. Berglund and colleagues (1974) and Shipley and colleagues (1982) have provided guidelines for reporting outcomes of smoking cessation studies that should be more widely adopted. For calculating abstinence rates, a standard common denominator representing the number of subjects entering a program should be used across all points in time and any dropouts should be considered conservatively as smokers. In studies in which it is deemed important to evaluate reductions in smoking behavior (e.g., percent reduction in number of cigarettes smoked or nicotine content) in addition to the proportion of abstinent subjects, analyses should be conducted on nonabstinent subjects only. This procedure avoids confounding the results due to cessation with results due to changes in smoking rate or topography. Worksite programs should report cessation success as the fraction of the smokers in the workforce as well as the fraction who agreed to participate in the program.

Objective verification of smoking status is particularly important in programs involving financial incentives, competition between rival organizations, social pressure and support to quit, or controlled smoking instead of abstinence. Each of the biochemical measures of smoking exposure has its own advantages and limitations (Benowitz 1983; Pechacek et al. 1984).

Another methodological problem faced by occupational smoking modification programs concerns the consistency between units of assignment and units of analysis (Biglan and Ary 1985). Typically,

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whole companies are assigned to treatment or control conditions, but results are analyzed using individual subjects as the unit. This creates interpretive problems because of the potential dependency among results of smokers within a given worksite (or treatment group). Although there are no easy answers to this dilemma, investigators should consider (1) conducting treatment in a sufficiently large number of companies that the worksite can be used as the unit of analysis; (2) utilizing hierarchical or nesting designs to separate the effects of worksite from intervention condition (Myers 1972); or (3) when feasible, assigning individuals within worksites to different treatment conditions.

Future research should pay greater attention to possible interactions between worksite and treatment variables. For example, interorganizational competition procedures may be highly effective in worksites where employees feel highly committed to the company, but ineffective in settings low in organizational commitment. Organizational and social network factors may also interact with, mediate, or enhance program impact.

More data also need to be collected on the "generalization" effects of worksite smoking modification programs. Employers may be more interested in program effects on employee morale, job satisfaction, and absenteeism than on health outcomes such as smoking status. Similarly, more information should be reported on the costs and health benefits of occupational smoking reduction programs. Progress in this area would be facilitated by a systematic review of and recommendation for procedures to be employed in determining the cost effectiveness and cost benefit of worksite smoking programs.

Substantive Areas

Three primary objectives need to be achieved by future research in worksite smoking modification. First, more research should be conducted on ways to increase participation and followthrough rates in worksite programs. For example, using various incentive procedures (e.g., paycheck bonuses versus team competition versus lotteries) might be expected to enhance participation. Further investigations are needed on the impact on participation rates of interventions such as quitting contests, self-help materials, or hotlines that do not require a large investment of time and effort by participants. The majority of worksite smoking studies to date have focused on group cessation programs, but surveys consistently indicate that most smokers are not interested in participating in such programs (US DHHS 1982; Schneider et al. 1984). For the reasons discussed earlier, renewed emphasis on physician stop-smoking messages is also indicated.

The second main content issue is how to enhance the outcome rates of worksite smoking modification programs. One approach to

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this problem is to evaluate the utility of comprehensive intervention programs and environmental changes (no-smoking policies, cigarette machine removal, prominent no-smoking posters) with cessation groups. Other approaches are assessing the impact of multiple risk factor programs versus single modality programs and of ongoing, continuous intervention programs in place for a year or more versus one-time-only program offerings.

The final category of recommendations for future research involves investigating subject and therapist factors that affect treatment outcome (Klesges and Glasgow 1985; Orleans and Shipley 1982). Additional study is needed of the enrollment patterns and success rates of men versus women, white-collar workers versus blue-collar workers, and heavy smokers versus light smokers. Also, little is known about the characteristics of successful program leaders (e.g., ex-smoker coworkers versus professional group leaders).

Summary and Conclusions

1. Smoking modification and maintenance of nonsmoking status among initial quitters has the promise of being more successful in worksite programs than in clinic-based programs. Higher cessation rates in worksite programs are achieved with more intensive programs.
2. Incentives for nonsmoking appear to be associated with higher participation and better success rates. Further research is needed to specify the optimal types of incentive procedures.
3. Success of a worksite smoking program depends upon three primary factors: the characteristics of the intervention program, the characteristics of the organization in which the program is offered, and the interaction between these factors.
4. Research is needed on recruitment strategies and participation rates in worksite smoking programs and on the impact of interventions on the entire workforce of a company.
5. More investigations are needed on worksite characteristics associated with the success of occupational programs and on comprehensive programs including components such as quit-smoking contests, no-smoking policies, physician messages, and self-help materials in addition to smoking cessation clinics.
6. The implementation of broadly based health promotion efforts in the workplace should be encouraged, with smoking interventions representing a major component of the larger effort to improve health through a worksite focus.

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