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The Health Consequences Of Smoking

CHRONIC OBSTRUCTIVE LUNG DISEASE

a report of the Surgeon General

1984

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

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 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 Services' 16th report on this topic and, like all of the earlier Reports, it identifies cigarette smoking as the chief preventable cause of death and disability in our society.

The enclosed report deals with the relationship between smoking and those disease conditions described as chronic obstructive lung disease, particularly chronic bronchitis and emphysema. These diseases significantly increase patient loads in hospitals and other health care facilities and escalate this Nation's health care costs, including expenditures under the Medicaid and Medicare programs.

This report indicates that chronic obstructive lung diseases can be reduced and, in the case of emphysema, almost eradicated, if individuals stop cigarette smoking. Moreover, stopping smoking also would prevent the enormous suffering and human loss now well-known to be associated with smoking.

This Department has a strong and ongoing commitment to its programmatic and research efforts in the field of disease prevention. In our view, it is essential to apprise individuals of the consequences of smoking. A central part of our efforts is to identify ways to help smokers quit smoking, and to encourage individuals, particularly the youth of this country, not to begin smoking.

Sincerely,

Margaret M. Heckler

Margaret M. Heckler
Secretary

Enclosure

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

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

Dear Mr. President:

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Sincerely,

Margaret M. Heckler

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Secretary

Enclosure

FOREWORD

The 1984 Report on the Health Consequences of Smoking constitutes a state-of-the-art review of the information currently available regarding the occurrence and etiology of chronic obstructive lung diseases.

Traditionally, chronic bronchitis and emphysema have been subsumed under the term chronic obstructive lung diseases (COLD). It is now recognized that COLD comprises three separate, but often interconnected, disease processes: (1) chronic mucus hypersecretion, resulting in chronic cough and phlegm production; (2) airway thickening and narrowing with expiratory airflow obstruction; and (3) emphysema, which is an abnormal dilation of the distal airspaces along with destruction of alveolar walls. The last two conditions can develop into symptomatic ventilatory limitation.

Although there were scientific reports of a link between cigarette smoking and respiratory symptoms as early as 1870, it was not until the comprehensive review in the first Report of the Advisory Committee to the Surgeon General in 1964 that the nature of the observed association was officially recognized by the Public Health Service.

At that time the committee concluded that

> Cigarette smoking is the most important of the causes of chronic bronchitis in the United States and increases the risk of dying from chronic bronchitis and emphysema. A relationship exists between cigarette smoking and emphysema, but it has not been established that the relationship is causal.

On the basis of the evidence reviewed in this volume, we are now able to reach a much stronger conclusion:

> **Cigarette smoking is the major cause of chronic obstructive lung disease in the United States for both men and women. The contribution of cigarette smoking to chronic obstructive lung disease morbidity and mortality far outweighs all other factors.**

The Importance of Chronic Obstructive Lung Disease

Previous Reports on the health consequences of smoking emphasized the impact of cigarette smoking on mortality from smoking-related disease. It is estimated that more than 60,000 Americans died last year owing to chronic obstructive respiratory conditions

Premature deaths = 350,000 Total

(chronic bronchitis, emphysema, and COLD and allied conditions). From available epidemiologic and clinical evidence, it may be reasonably estimated that approximately 80 to 90 percent of these are attributable to smoking. Over 50,000 of the COLD deaths can therefore be considered preventable and premature because these individuals would not have died of COLD if they had not smoked. While smoking-related COLD mortality is less than estimates for smoking-related deaths due to coronary heart disease (170,000) and those due to cancer (130,000), it nonetheless represents a significant number of excess deaths.

COLD morbidity has a greater impact upon society than COLD mortality. Death from COLD usually occurs only after an extended period of disability, and many individuals with disability from COLD will die from other causes before the disease progresses to a degree of severity likely to cause death. The progressive loss of lung function that characterizes COLD can lead to severe shortness of breath, limiting the activity level. In recognizing the morbidity associated with these diseases, it is important to realize that the frequency of activity limitation with COLD exceeds that reported for any other major disease category. In 1979, 52 percent of individuals with emphysema reported that it limited their activity; 27 percent said it resulted in one or more bed days that year; and 73 percent reported at least one visit to a doctor during the preceding year due to emphysema. Forty percent more people with emphysema than with heart conditions reported limitation of activity. More recently, the National Center for Health Statistics has estimated that over 10 million Americans suffer from either chronic bronchitis or emphysema.

The Changing Pattern of Mortality

The 1980 and 1982 Surgeon General's Reports (*The Health Consequences of Smoking for Women* and *The Health Consequences of Smoking: Cancer*) reported a rapidly increasing rate of lung cancer among women compared with the rate for men. As this Report documents, the mortality ratio between men and women for COLD is also narrowing. In just 10 years, while total deaths from COLD increased from 33,000 in 1970 to 53,000 in 1980, the male-to-female ratio narrowed from 4.3:1 in 1970 to 2.3:1 in 1980. This epidemic increase in COLD among women reflects their later uptake of smoking when compared with men.

Findings of the 1984 Report

The mortality ratios for COLD in cigarette smokers compared with nonsmokers are as large as or larger than for lung cancer, the

disease most people usually associate with smoking. In heavy smokers, this risk can be as much as 30 times the risk in nonsmokers. Perhaps even more important, in studies of cross-sections of U.S. populations, cigarette smoking behavior is often the only significant predictor for COLD. Even after 30 years of intensive investigation, only cigarette smoking and α_1-antiprotease deficiency have been established as being able to cause COLD in the absence of other agents.

The decline in lung function with age is steeper in smokers than in nonsmokers, and the rate of decline increases with an increasing number of cigarettes smoked per day. This excess decline in lung function in smokers reflects the progressive lung damage that can eventually lead to symptoms of COLD and ultimately death. Therefore, it is not surprising that the risk of death from COLD increases with an earlier age of smoking initiation, number of cigarettes smoked per day, and deep inhalation of the smoke.

Abnormal lung function can be demonstrated in some cigarette smokers within a few years of smoking initiation. These changes initially reflect inflammation in the small airways of the lung and may reverse with cessation. Beginning in their late twenties, some smokers start to develop abnormal measures of expiratory airflow, an excess decline in lung function that continues as long as they continue to smoke. Some of these smokers will develop enough functional loss to become symptomatic, and some of those who become symptomatic will develop enough functional loss to die of COLD. When the smoker quits, the rate of functional decline slows, but there is little evidence to suggest that the smoker can regain the function that has been lost.

We are also beginning to understand that the impact of cigarette smoke on the lung is not limited to the active smoker. Children of smoking parents have an increased risk of bronchitis and pneumonia early in life, and seem to have a small, but measurable, difference in the growth of lung function.

One of the major advances described in this volume is in the understanding of the mechanisms by which cigarette smoking causes COLD, particularly emphysema. There is now a clear, plausible explanation of how emphysema might result from cigarette smoking. The inflammatory response to cigarette smoke results in an increased number of inflammatory cells being present in the lungs of cigarette smokers. These cells can increase the amount of elastase in the lung, and elastase is capable of degrading elastin, one of the structural elements of the lung. In addition, cigarette smoke is capable of oxidative inactivation of α_1-antiprotease, a protein capable of blocking the action of elastase. The net result is an excess of elastase activity, degradation of elastin in the lung, destruction of alveolar walls, and the development of emphysema.

Research scientists continue to expand our understanding of the process by which cigarettes damage the lung, but the important public health focus must shift to how to prevent children from becoming cigarette smokers and how to help those who now smoke to quit.

Helping Smokers Quit

Smokers can realize a substantial health benefit from quitting smoking, no matter how long they have smoked. As this Report states, sufficient evidence now exists to document lung function improvement in smokers who have quit. Ex-smokers can look forward to improved future health, avoiding long-term and possibly severe disability, or even death, from COLD.

Two chapters in this Report summarize research studies using two vastly different cessation approaches. One focuses on the role of physicians in assisting patient populations to quit smoking; the other looks at communitywide intervention programs. Both can have a significant impact on reducing the number of smokers in our population.

In January of this year, the Food and Drug Administration approved a nicotine chewing gum that physicians can prescribe for their patients as an aid to cessation. Studies have shown encouraging results when the gum is used as part of a complete behavior modification program. It must be cautioned, however, that nicotine chewing gum is not a magic cure. Smokers must be strongly motivated to quit or they are unlikely to meet with long-term success.

Public Attitudes and Knowledge

In 1981, a Federal Trade Commission staff report on cigarette advertising revealed that a sizable portion of the population is not aware of the link between cigarette smoking and chronic bronchitis and emphysema. The report cited a 1980 Roper survey finding that 59 percent of the population, including 63 percent of smokers, did not know that smoking causes *most* cases of emphysema. Over a third of the general population and almost 40 percent of smokers do not know that smoking causes *many* cases.

It is quite clear that physicians and other health professionals must redouble their efforts to persuade more smokers to quit. As in previous years, I call upon all segments of the health care community to provide assistance and encouragement in whatever way possible to reduce the health impact of cigarette smoking on our society, by helping their patients to quit smoking and by encouraging our young people not to take up the habit. It is only through efforts

such as these that we can reduce our country's terrible burden of disability and death due to cigarette smoking.

Edward N. Brandt, Jr., M.D.
Assistant Secretary for Health

PREFACE

This Report *The Health Consequences of Smoking: Chronic Obstructive Lung Disease* completes an examination by the Public Health Service of the three principal disease entities associated with cigarette smoking. In 1982, the Service presented an in-depth review of tobacco's relationship to cancer, and in 1983, a review of its relationship to cardiovascular disease. This 1984 Report evaluates the contribution that tobacco makes to the suffering and premature deaths due to the chronic obstructive lung diseases, including emphysema and chronic bronchitis.

Cigarette smoking is causally related to chronic obstructive lung disease, just as it is to cancer and coronary heart disease; severe emphysema would be rare were it not for cigarette smoking. The evidence presented in this Report supports my judgment and the judgment of five preceding Surgeons General that cigarette smoking is the chief, single, avoidable cause of death in our society and the most important public health issue of our time.

This Report, as were all previous Surgeon General's Reports dealing with cigarette smoking, is the work of many experts both within and outside the Federal establishment. To these authors, editors, and reviewers I again express my great respect and sincere thanks.

C. Everett Koop, M.D.
Surgeon General

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Organization and Development of the 1984 Report

Each year the Office on Smoking and Health (OSH), working in close collaboration with scientists, researchers, and others, compiles the annual Surgeon General's Report *The Health Consequences of Smoking* for submission to the U.S. Congress as part of the Department's responsibility to report new and current information on the topic as required under Public Law 91-222. This Report is the third to examine in detail specific disease entities related to smoking. The 1982 Report was a comprehensive assessment of the relationship between tobacco use and various cancers, and the 1983 Report examined this relationship for cardiovascular diseases. The 1984 volume represents a state-of-the-art comprehensive review of tobacco use and the development of chronic obstructive lung diseases.

The scientific content of this Report is the work of experts in the field of chronic obstructive lung disease research both within the Department of Health and Human Services and from outside the Federal Government. Individual manuscripts were written by experts who are nationally and internationally recognized for their scientific understanding of the etiology of chronic obstructive lung diseases, particularly the relationship with cigarette use.

Manuscripts received from authors were extensively reviewed by numerous outside experts familiar with these specific areas. The entire Report was then submitted to a broad-based panel of 11 distinguished lung disease experts and to experts within the U.S. Public Health Service for their review and comments.

The 1984 Report includes a Foreword by the Assistant Secretary for Health of the Department of Health and Human Services and a Preface by the Surgeon General of the U.S. Public Health Service. The body of the Report consists of 10 chapters, as follows:

- Chapter 1. Introduction, Overview, and Conclusions
- Chapter 2. Effect of Cigarette Smoke Exposure on Measures of Chronic Obstructive Lung Disease Morbidity
- Chapter 3. Mortality From Chronic Obstructive Lung Disease Due to Cigarette Smoking
- Chapter 4. Pathology of Lung Disease Related to Smoking
- Chapter 5. Mechanisms by Which Cigarette Smoke Alters the Structure and Function of the Lung
- Chapter 6. Low Yield Cigarettes and Their Role in Chronic Obstructive Lung Disease
- Chapter 7. Passive Smoking
- Chapter 8. Deposition and Toxicity of Tobacco Smoke in the Lung

- Chapter 9. Role of the Physician in Smoking Cessation
- Chapter 10. Community Studies of Smoking Cessation and Prevention

Historical Perspective

The relationship between cigarette smoking and chronic obstructive lung disease (COLD) was among the first recognized and is now the best understood of the diseases caused by smoking. Sigmund reported as early as 1870 that heavy smokers suffered "affections" of the nose, mouth, and throat more frequently and in a more virulent fashion. In 1897, Mendelssohn reported the incidence of "affections" of the respiratory tract to be 60 percent greater in smokers than in nonsmokers, as well as somewhat greater in those who inhaled compared with smokers who did not inhale.

Overview

Scientists from a variety of disciplines have investigated the role of cigarette smoking in the development of COLD; today we can trace the progressive decline in lung function in smokers with increasing smoke exposure, describe the concurrent pathologic changes, demonstrate that both COLD prevalence and COLD death are limited largely to smokers, and describe in detail a plausible mechanism by which cigarette smoking can lead to the development of emphysema. Some gaps in the understanding of the details of this process may still exist, but the experimental and epidemiologic evidence leaves no room for reasonable doubt on the fundamental issue: cigarette smoking is the major cause of COLD in the United States.

The earliest recognized response to cigarette smoke is an increase in airway resistance that occurs with the inhalation of smoke by the smoker. This increase in resistance is a response to the irritants in the smoke, as is coughing, which is more frequent in smokers than in nonsmokers, even among adolescents. By the time smokers become young adults, a substantial proportion of them will have developed pathologic changes in their small airways. These abnormalities are demonstrable using a variety of physiologic tests, and are a result of pathologic changes or inflammation in the airways less than 2 mm in diameter. Part of this small airways response, but perhaps a later manifestation of it, is the development of smooth muscle hypertrophy, goblet cell hyperplasia, and mild peribronchiolar fibrosis. The prevalence of abnormalities on tests of small airways function increases as these young smokers grow older, and is greater in heavy smokers than in light smokers. While it is clear that changes in the small airways represent an early response to cigarette smoking and that they are a significant finding in the pathophysiology of COLD, it is not clear that abnormal function of the small airways, per se, is

useful as a marker for identifying who will progress to develop symptomatic COLD. It may identify a large group of smokers who manifest an irritant response to smoke in the small airways, of whom only a subset actually develop symptomatic airflow obstruction.

Measurable differences in tests of expiratory airflow exist between smokers and nonsmokers after age 25. Smokers as a group have a more rapid decline in FEV_1 with age than that observed in nonsmokers, and the decline is even greater among heavy smokers. However, this increased rate of decline in lung function is not distributed evenly, even among smokers with similar smoking histories. Some smokers have a far more rapid decline than the average smoker, and clearly those individuals who have developed symptomatic chronic airflow obstruction have had a larger total decline in lung function than the average smoker. This has led to the suggestion that individuals with a particularly rapid decline in FEV_1 early in life may represent a group especially susceptible to the later development of symptomatic COLD. The nature of this susceptibility remains unclear, but differences in depth or pattern of inhalation, variations in the cellular and biochemical response of the lung to smoke, differences in immune or repair mechanisms, and childhood infections or exposure to environmental tobacco smoke as a child have been suggested as potential factors.

The accumulation of lung damage, marked by the excess decline in FEV_1 and other measures of expiratory airflow, can lead to shortness of breath and other symptoms that characterize clinically significant COLD. These symptoms can result in disability due to ventilatory limitation and may vary from patient to patient in severity and duration. Many patients with clinically disabling COLD die with the disease rather than because of it. Death from COLD usually results only after extensive lung damage and commonly occurs because of failure of the severely damaged lungs to maintain adequate gas exchange.

The cessation of cigarette smoking has a substantial salutary impact on the incidence and progression of COLD. Cigarette smokers who quit prior to developing abnormal lung function are unlikely to go on to develop ventilatory limitation; when the abnormalities are demonstrable only on tests of small airways function, cessation often results in a reversal of these changes and a return to normal function. The presence of significant fixed reduction in measures of expiratory airflow usually reflects the presence of substantial lung damage. Cessation of smoking at this stage of COLD results in a slowing in the rate of decline in lung function with age, in comparison with that in continuing smokers. After a period of cessation, this rate of decline in function may approximate the rate found in nonsmokers, but there is little evidence to suggest that

those who quit are able to regain their prior excess functional loss. Therefore, those who quit continue to have reduced lung function when compared with those who have never smoked, but their lung function begins to decline less rapidly with age when compared to the lung function of those who continue to smoke.

The importance of cigarette smoking as a causative factor in COLD is emphasized by cross-sectional studies of populations in the United States where often the only major predictor for developing or dying of COLD is smoking behavior. In the absence of cigarette smoking, clinically significant COLD is rare.

As the smoker enters the sixth decade of life, pathologically definable pulmonary emphysema begins to become evident. In older age groups, mild to moderate emphysema is present in most smokers and is rare in nonsmokers. Once again, however, only a small percentage of smokers develop severe emphysema; this minority includes a disproportionate number of heavy smokers.

A mechanism for smoking-induced emphysematous lung injury has been proposed and continues to evolve as our understanding of cellular and biochemical responses of the lung increases. Emphysema can be produced by the presence of excessive amounts of elastase (an enzyme capable of degrading the structural elements of lung tissue) or by the absence of α_1-antiprotease (a protein that inhibits the action of elastase). As part of the inflammatory response to cigarette smoke, an increased number of inflammatory cells are present in the lungs of smokers; these cells may result in an increased amount of elastase being present in the lung. In addition, cigarette smoke can oxidize the α_1-antiprotease in the lung, further contributing to the imbalance between levels of elastase and levels of α_1-antiprotease. The net result can be excess elastase activity, leading to degradation of elastin in the lung, destruction of alveolar walls, and development of emphysema.

The text of this Report discusses in detail the relationship of cigarette smoking to COLD morbidity and mortality, the pathology of smoking-induced COLD, some of the mechanisms by which smoking results in COLD, the impact on the lung of low tar and nicotine cigarettes and of involuntary smoke exposure, the deposition and toxicology of tobacco smoke, and the role of the physician and of community intervention programs in smoking cessation.

The overall conclusion of this Report is clear: **Cigarette smoking is the major cause of chronic obstructive lung disease in the United States for both men and women. The contribution of cigarette smoking to chronic obstructive lung disease morbidity and mortality far outweighs all other factors.**

Conclusions of the 1984 Report

COLD Morbidity

1. Cigarette smoking is the major cause of COLD morbidity in the United States; 80 to 90 percent of COLD in the United States is attributable to cigarette smoking.
2. In population-based studies in the United States, cigarette smoking behavior is often the only significant predictor for the development of COLD. Other factors improve the predictive equation only slightly, even in those populations where they have been found to exert a statistically significant effect.
3. In spite of over 30 years of intensive investigation, only cigarette smoking and α_1-antiprotease deficiency (a rare genetic defect) are established causes of clinically significant COLD in the absence of other agents.
4. Within a few years after beginning to smoke, smokers experience a higher prevalence of abnormal function in the small airways than nonsmokers. The prevalence of abnormal small airways function increases with age and the duration of the smoking habit, and is greater in heavy smokers than in light smokers. These abnormalities in function reflect inflammatory changes in the small airways and often reverse with the cessation of smoking.
5. Both male and female smokers develop abnormalities in the small airways, but the data are not sufficient to define possible sex-related differences in this response. It seems likely, however, that the contribution of sex differences is small when age and smoking exposure are taken into account.
6. There is, as yet, inadequate information to allow a firm conclusion to be drawn about the predictive value of the tests of small airways function in identifying the susceptible smoker who will progress to clinical airflow obstruction.
7. Smokers of both sexes have a higher prevalence of cough and phlegm production than nonsmokers. This prevalence increases with an increasing number of cigarettes smoked per day and decreases with the cessation of smoking.
8. Differences between smokers and nonsmokers in measures of expiratory airflow are demonstrable by young adulthood and increase with number of cigarettes smoked per day.
9. The rate of decline in measures of expiratory airflow with increasing age is steeper for smokers than for nonsmokers; it is also steeper for heavy smokers than for light smokers. After the cessation of smoking, the rate of decline of lung function with increasing age appears to slow to approximately that seen in nonsmokers of the same age. Only a minority of smokers will develop clinically significant COLD, and this group will have

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demonstrated a more extensive decline in lung function than the average smoker. The data are not yet available to determine whether a rapid decline in lung function early in life defines the subgroup of smokers who are susceptible to developing COLD.

10. Clinically significant degrees of emphysema occur almost exclusively in cigarette smokers or individuals with genetic homozygous α_1-antiprotease deficiency. The severity of emphysema among smokers increases with the number of cigarettes smoked per day and the duration of the smoking habit.

COLD Mortality

1. Data from both prospective and retrospective studies consistently demonstrate a uniform increase in mortality from COLD for cigarette smokers compared with nonsmokers. Cigarette smoking is the major cause of COLD mortality for both men and women in the United States.
2. The death rate from COLD is greater for men than for women, most likely reflecting the differences in lifetime smoking patterns, such as a smaller percentage of women smoking in past decades, and their smoking fewer cigarettes, inhaling less deeply, and beginning to smoke later in life.
3. Differences in lifetime smoking behavior are less marked for younger age cohorts of smokers. The ratio of male to female mortality from COLD is decreasing because of a more rapid rise in mortality from COLD among women.
4. The dose of tobacco exposure as measured by number of cigarettes or duration of habit strongly affects the risk for death from COLD in both men and women. Similarly, people who inhale deeply experience an even higher risk for mortality from COLD than those who do not inhale.
5. Cessation of smoking leads eventually to a decreased risk of mortality from COLD compared with that of continuing smokers. The residual excess risk of death for the ex-smoker is directly proportional to the overall lifetime exposure to cigarette smoke and to the total number of years since one quit smoking. However, the risk of COLD mortality among former smokers does not decline to equal that of the never smoker even after 20 years of cessation.
6. Several prospective epidemiologic studies examined the relationship between pipe and cigar smoking and mortality from COLD. Pipe smokers and cigar smokers also experience higher mortality from COLD compared with nonsmokers; however, the risk is less than that for cigarette smokers.
7. There are substantial worldwide differences in mortality from COLD. Some of these differences are due to variations in

terminology and in death certification in various countries. Emigrant studies suggest that ethnic background is not the major determinant for mortality risk due to COLD.

Pathology of Cigarette-Induced Disease

1. Smoking induces changes in multiple areas of the lung, and the effects in the different areas may be independent of each other. In the bronchi (the large airways), smoking results in a modest increase in size of the tracheobronchial glands, associated with an increase in secretion of mucus, and in an increased number of goblet cells.
2. In the small airways (conducting airways 2 or 3 mm or less in diameter consisting of the smallest bronchi and bronchioles) a number of lesions are apparent. The initial response to smoking is probably inflammation, with associated ulceration and squamous metaplasia. Fibrosis, increased muscle mass, narrowing of the airways, and an increase in the number of goblet cells follow.
3. Inflammation appears to be the major determinant of small airways dysfunction and may be reversible after cessation of smoking.
4. The most obvious difference between smokers and nonsmokers is respiratory bronchiolitis. This lesion may be an important cause of abnormalities in tests of small airways function, and may be involved in the pathogenesis of centrilobular emphysema. The severity of emphysema is clearly associated with smoking, and severe emphysema is confined largely to smokers.

Mechanisms of COLD

1. Increased numbers of inflammatory cells are found in the lungs of cigarette smokers. These cells include macrophages and, probably, neutrophils, both of which can release elastase in the lung.
2. Human neutrophil elastase produces emphysema when instilled into animal lungs.
3. Alpha$_1$-antiprotease inhibits the action of elastase, and a very small number of people with a homozygous deficiency of α_1-antiprotease are at increased risk of developing emphysema. The α_1-antiprotease activity has been shown to be reduced in the bronchoalveolar fluids obtained from cigarette smokers and from rats exposed to cigarette smoke.
4. The protease–antiprotease hypothesis suggests that emphysema results when there is excess elastase activity as the result of increased concentrations of inflammatory cells in the lung

and of decreased levels of α_1-antiprotease secondary to oxidation by cigarette smoke.

5. Cigarette smokers have been shown to have a more rapid fall in antibody levels following immunization for influenza than nonsmokers. Whole cigarette smoke has been shown to depress the number of antibody-forming cells in the spleens of experimental animals.
6. Cigarette smoke produces structural and functional abnormalities in the airway mucociliary system.
7. Short-term exposure to cigarette smoke causes ciliostasis in vitro, but has inconsistent effects on mucociliary function in man. Long-term exposure to cigarette smoke consistently causes an impairment of mucociliary clearance. This impairment is associated with epithelial lesions, mucus hypersecretion, and ciliary dysfunction.
8. Chronic bronchitis in smokers and ex-smokers is characterized by an impairment of mucociliary clearance.
9. Both the particulate phase and the gas phase of cigarette smoke are ciliotoxic.

Low Tar and Nicotine Cigarettes

1. The recommendation for those who cannot quit to switch to smoking cigarette brands with low tar and nicotine yields, as determined by a smoking-machine, is based on the assumption that this switch will result in a reduction in the exposure of the lung to these toxic substances. The design of the cigarette has markedly changed in recent years, and this may have resulted in machine-measured tar and nicotine yields that do not reflect the real dose to the smoker.
2. Smoking-machines that take into account compensatory changes in smoking behavior are needed. The assays could provide both an average and a range of tar and nicotine yields produced by different individual patterns of smoking.
3. Although a reduction in cigarette tar content appears to reduce the risk of cough and mucus hypersecretion, the risk of shortness of breath and airflow obstruction may not be reduced. Evidence is unavailable on the relative risks of developing COLD consequent to smoking cigarettes with the very low tar and nicotine yields of current and recently marketed brands.
4. Smokers who switch from higher to lower yield cigarettes show compensatory changes in smoking behavior: the number of puffs per cigarette is variably increased and puff volume is almost universally increased, although the number of cigarettes smoked per day and inhalation volume are generally

unchanged. Full compensation of dose for cigarettes with lower yields is generally not achieved.

5. Nicotine has long been regarded as the primary reinforcer of cigarette smoking, but tar content may also be important in determining smoking behavior.
6. Depth and duration of inhalation are among the most important factors in determining the relative concentration of smoke constituents that reach the lung. Considerable interindividual variation exists between smokers with respect to the volume and duration of inhalation. This variation is likely to be an important factor in determining the varying susceptibility of smokers to the development of lung disease.
7. Production of low tar and nicotine cigarettes has progressed beyond simple reduction in tobacco content. Additives such as artificial tobacco substitutes and flavoring extracts have been used. The identity, chemical composition, and adverse biological potential of these additives are unknown at present.

Passive Smoking

1. Cigarette smoke can make a significant, measurable contribution to the level of indoor air pollution at levels of smoking and ventilation that are common in the indoor environment.
2. Nonsmokers who report exposure to environmental tobacco smoke have higher levels of urinary cotinine, a metabolite of nicotine, than those who do not report such exposure.
3. Cigarette smoke in the air can produce an increase in both subjective and objective measures of eye irritation. Further, some studies suggest that high levels of involuntary smoke exposure might produce small changes in pulmonary function in normal subjects.
4. The children of smoking parents have an increased prevalence of reported respiratory symptoms, and have an increased frequency of bronchitis and pneumonia early in life.
5. The children of smoking parents appear to have measurable but small differences in tests of pulmonary function when compared with children of nonsmoking parents. The significance of this finding to the future development of lung disease is unknown.
6. Two studies have reported differences in measures of lung function in older populations between subjects chronically exposed to involuntary smoking and those who were not. This difference was not found in a younger and possibly less exposed population.
7. The limited existing data yield conflicting results concerning the relationship between passive smoke exposure and pulmonary function changes in patients with asthma.

Deposition and Toxicity of Tobacco Smoke in the Lung

1. The mass median aerodynamic diameter of the particles in cigarette smoke has been measured to average approximately 0.46 μm, and particulate concentrations have been shown to range from 0.3×10^9 to 3.3×10^9 per milliliter.
2. The particulate concentration of the smoke increases as the cigarette is more completely smoked.
3. Particles in the size range of cigarette smoke will deposit both in the airways and in alveoli; models predict that 30 to 40 percent of the particles within the size range present in cigarette smoke will deposit in alveolar regions and 5 to 10 percent will deposit in the tracheobronchial region.
4. Acute exposure to cigarette smoke results in an increase in airway resistance in both animals and humans.
5. Exposure to cigarette smoke results in an increase in pulmonary epithelial permeability in both humans and animals.
6. Cigarette smoke has been shown to impair elastin synthesis in vitro and elastin repair in vivo in experimental animals (elastin is a vital structural element of pulmonary tissue).

Role of the Physician in Smoking Cessation

1. At least 70 percent of North Americans see a physician once a year. Thus, an estimated 38 million of the 54 million adults in the United States who smoke cigarettes could be reached annually with a smoking cessation message by their physician.
2. Current smoking prevalence among physicians in the United States is estimated at 10 percent.
3. While the majority of persons who smoke feel that physician advice to quit or cut down would be influential, there is a disparity between physicians' and patients' estimates of cessation counseling, with physician advice being reported by only approximately 25 percent of current smokers.
4. Studies of routine (minimal) advice to quit smoking delivered by general practitioners have shown sustained quit rates of approximately 5 percent. Followup discussions enhance the effects of physician advice.
5. A median of 20 percent of pregnant women who smoke quit spontaneously during pregnancy. That proportion can be doubled by an intervention consisting of health education, behavioral strategies, and multiple contacts.
6. Large controlled trials of cardiovascular risk reduction have demonstrated that counseling on individual specific risk factors, including smoking cessation techniques, can be effective.
7. Studies of pulmonary and cardiac patients indicate that severity of illness is positively related to increased compliance

in smoking cessation. Survivors of a myocardial infarction have smoking cessation rates averaging 50 percent.

8. Nicotine chewing gum has been developed as a pharmacological aid to smoking cessation, primarily to alleviate withdrawal symptoms. Cessation studies conducted in offices of physicians who prescribe the gum have produced mixed results, however, with outcome depending on motivation and intensity of adjunctive support or followup.
9. Physician-assisted intervention quit rates vary according to the type of intervention, provider performance, and patient group. In general, quit rates in recent research appear to be lower than in older studies.

Community Studies of Smoking Cessation and Prevention

1. Community studies of smoking cessation and prevention are becoming an established paradigm for public health action research. Such studies emphasize large-scale delivery systems, such as the mass media, and include community organization programs seeking to stimulate interpersonal communication in ways that are feasible on a large-scale basis.
2. Although there are methodological limitations to nearly all communitywide studies, the results yield fairly consistent positive results, indicating that large-scale programs to reduce smoking can be effective in whole populations. Person-to-person communication appears to be a necessary part of a successful community program to reduce smoking.
3. Further research is needed, with both improved methodology and more emphasis on low socioeconomic status groups that have not yet shown population trends toward reduced smoking.
4. Several promising directions for research are clear, but the most important future trends will be toward the establishment of smoking reduction programs within existing health services, the combination of chronic disease prevention with mental health promotion via mass media and community intervention, and the development of social policy to establish integrated strategies for smoking cessation and prevention.

CHAPTER 2. EFFECT OF CIGARETTE SMOKE EXPOSURE ON MEASURES OF CHRONIC OBSTRUCTIVE LUNG DISEASE MORBIDITY

CONTENTS

INTRODUCTION

This chapter describes the sequential development of smoking-induced chronic lung disease, traced from the early structural changes limited to the small airways to the severe and widespread changes involving the small airways, large airways, and lung parenchyma. Chronic obstructive lung disease (COLD) develops relatively slowly, and the progression of lung injury and alterations in function can be followed using an individual smoker's symptoms and performance on a variety of pulmonary function tests. Early in the duration of the smoking behavior, a person may be asymptomatic, but often there are abnormalities demonstrable in the small airways that probably represent an inflammatory response to the constituents of cigarette smoke. Later, usually after 20 or more years of smoking, a constellation of symptoms and functional changes may develop, particularly in heavy smokers and in those who will later develop clinically significant COLD. The clinical picture of cigarette-induced chronic lung injury includes three separate, but often interconnected, disease processes. They are (1) chronic mucus hypersecretion (cough and phlegm), (2) airway narrowing with expiratory airflow obstruction, and (3) abnormal dilation of the distal airspaces with destruction of alveolar walls (emphysema). Patients with severe COLD commonly have some degree of all three processes, but individual patients vary significantly in the relative contribution of the processes to their overall disease state.

Some alteration in lung structure or function is demonstrable in the majority of long-term smokers, but only a minority of smokers will develop clinically limiting COLD. In fact, only 10 to 15 percent of smokers will develop moderate or severe airflow obstruction (Bates 1973; Fletcher et al. 1976).

This chapter details the relationship between cigarette smoking and morbidity from COLD. The relationship of cigarette smoking to changes in the small airways is described first, followed by discussion of the role of smoking to chronic mucus hypersecretion, chronic airflow obstruction, and emphysema.

EARLY CHANGES IN RESPONSE TO CIGARETTE SMOKING

The tests of small airways function were developed in the late 1960s and early 1970s, and grew out of a series of studies calling attention to the functional importance of disease in the small airways. Macklem and Mead (1967) predicted that there could be considerable peripheral airway obstruction that might influence the distribution of ventilation but would have little effect on lung mechanisms; subsequently, Anthonisen et al. (1968) and Ingram and Schilder (1967) demonstrated the existence of early functional changes in smokers. These investigators showed that in a group of patients with clinically mild chronic bronchitis and normal lung function measured by spirometric tests, all had abnormalities of regional gas exchange, as determined by Xenon[133]. They attributed this finding to peripheral airway disease and suggested that the functionally important lesion in chronic bronchitis may be in the small airways. Brown and coworkers (1969), using excised lobes of dog and pig lung, demonstrated that considerable obstruction may be present in the airways smaller than 2 mm with little or no effect on overall pulmonary resistance. Hogg and coworkers (1968), using a retrograde catheter technique, measured central and peripheral airway resistance in excised normal and emphysematous human lungs and found that the peripheral airway resistance (accounting for only 25 percent of total airway resistance in the normal lungs (Macklem and Mead 1967)) was greatly increased in the lungs with emphysema. In an early structure–function correlation study, these investigators correlated the physiologic findings with histologic and bronchographic evidence of mucus plugging and narrowing and obliteration of small airways. Woolcock and coworkers (1969) reported that a group of bronchitic subjects with normal responses to routine lung function tests (lung volumes, flow rates, and diffusing capacity) demonstrated a decrease in the dynamic-to-static compliance ratio with increasing breathing frequency. These studies provided clear evidence that there can be measurable obstruction in airways 2 mm in diameter or smaller with little or perhaps no detectable influence on total airway resistance, and, therefore, on lung function measured by conventional tests such as lung volumes, spirometry, and diffusing capacity.

With the concept of small airways disease firmly established, a number of new tests considered capable of detecting the abnormality were introduced, along with reinterpretation of existing tests. The new measures included frequency dependence of compliance, the single breath N_2 test for the measurement of closing volumes (closing volume as a percent of vital capacity [CV/VC%] and closing capacity as a percent of total lung capacity [CC/TLC%]), the slope of the alveolar plateau, maximal expiratory flow volume (MEFV) curves using gases of different densities, and moment analysis of the forced

expiration. The measurements obtained from the MEFV curve, breathing gases of different densities, are (a) the difference in maximal flow at 50 and 75 percent of the forced vital capacity breathing air and breathing a helium-oxygen (HeO_2) mixture ($\Delta\dot{V}_{max50\%}$ and $\Delta\dot{V}_{75\%}$), and (b) a measurement of the lung volume at which the air and HeO_2 curves cross, the volume of isoflow (Viso$\dot{V}$). Tests already in common use included the volume–time curve (the spirogram) and the MEFV curve breathing air. The measurements obtained from standard tests that were thought to be sensitive to mild airflow obstruction are (a) from the spirogram, the forced expiratory flow between 75 and 85 percent of the forced vital capacity ($FEF_{75-85\%}$); and (b) from the MEFV curve: maximal flow at 50 and 75 percent of the forced vital capacity, $\dot{V}_{max\ 50\%}$ and $\dot{V}_{max\ 75\%}$.

The important question of structure–function correlation in tests of small airways function has received much attention over the past 5 years, and has been addressed via a series of attempts to correlate physiologic tests with the actual structural changes observed in lobes or lungs obtained at thoracotomy or post mortem.

Fulmer and coworkers (1977) correlated measurements of dynamic compliance with measurements of small airway diameter obtained from lung biopsies in patients with idiopathic pulmonary fibrosis. These investigators demonstrated a highly significant correlation between dynamic compliance and an overall estimate of small airways diameter.

Cosio and coworkers (1978) and Berend et al. (1979) did pulmonary function tests before lung resection and correlated the function tests with morphologic abnormalities that divided the subjects into four groups based on increasing degree of pathologic change. They found that an index of overall histologic small airways disease could be related to CC/TLC, Viso$\dot{V}$, and the slope of the alveolar plateau of the single breath N_2 test (Figure 1); inflammation, fibrosis, and squamous metaplasia were the most important lesions. The important conclusions that can be drawn from this study are that abnormalities of both spirometry and the special tests of small airways function are associated with structural changes in the peripheral airways, and that inflammation is the most important cause of obstruction to flow in small airways dysfunction.

Berend and coworkers (1979) noted a significant relationship between narrowing of the peripheral airways and CV/VC and $FEF_{25-75\%}$. In contrast to the study of Cosio et al. (1978), the slope of the alveolar plateau did not correlate with peripheral airway narrowing, and the volume of isoflow was essentially useless because of its high variability. They found that the FEV_1 was also related to peripheral airway narrowing.

Berend (1982) has recently provided new information by reanalysis and expansion of his earlier study. In measurements of small and

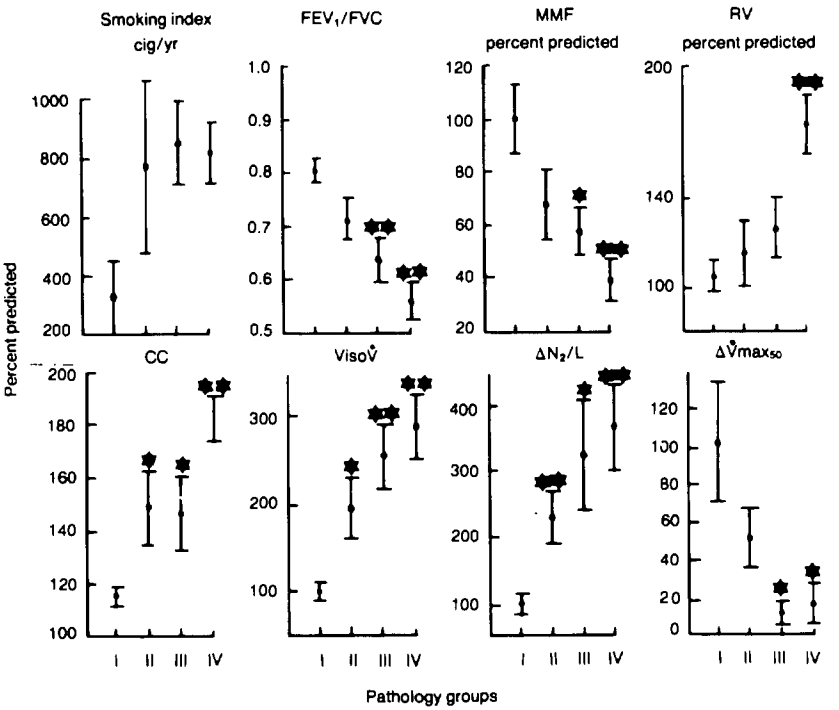

FIGURE 1.—Comparison of increasing small airways disease (Groups I to IV) to smoking index and various pulmonary function tests, by mean ± S.E.

*P < 0.05.
**P < 0.01.
SOURCE: Cosio et al. (1978).

TABLE 1.—Correlation coefficients (r) between morphologic variables and tests of pulmonary function

	FEV_1	MMFR	$\dot{V}_{50}$	R_L	Slope phase III	CV/VC	T_L CO
Bronchiolar diameter	0.28	0.37	0.48[1]	−0.36	−0.06	−0.03	0.20
Total path score	−0.39	−0.42[1]	−0.48[1]	0.03	0.22	0.30	—
Inflammation score	−0.55[2]	−0.46[1]	−0.41	0.17	0.61[2]	0.50[1]	—
Reid index	−0.50[1]	−0.41	−0.34	0.31	0.06	0.07	−0.37
Emphysema	−0.33	−0.45[1]	−0.43	0.28	0.45	0.19	−0.72[3]

[1] P < 0.05.
[2] P < 0.01.
[3] P < 0.001.

large airway lesions, he found that inflammation correlates best with the slope of the alveolar plateau, FEV_1, CV/VC, and the $FEF_{25-75\%}$ (Table 1).

Petty and coworkers (1981) studied a younger group of subjects (average age, 32) who came to autopsy. They found that inflamma-

tion and increased muscle in the small airways correlate with CC/TLC and that the slope of the alveolar plateau correlates with inflammation, increased muscle in the small airways, and increased intraluminal cells and mucus.

Berend and Thurlbeck (1982) obtained volume–pressure and MEFV curves with air and HeO_2 in 25 excised human lungs obtained at autopsy from nonhospitalized patients (age 57, ± 13 years) who died suddenly from nonrespiratory causes. The emphysema grade was measured, and the total pathological score was determined from four variables: inflammation, smooth muscle hyperplasia, fibrosis, and pigmentation. Correlations were then made between the measurements obtained from the MEFV curves with air and HeO_2 and the morphology. A significant correlation was obtained between maximal flow ($\dot{V}_{max}$) and the inflammation score, fibrosis score, and emphysema grade. Small airways dimensions correlated poorly with $\dot{V}_{max\ 75\%}$ and $\dot{V}_{max\ 50\%}$, and Viso$\dot{V}$ showed no significant correlation with any small airways measurement or score.

Cosio and coworkers (1980) have also studied lungs obtained at autopsy, but did not attempt to provide structure–function correlation. They examined the lungs of smokers and nonsmokers and showed that structural changes in the small airways are more severe in smokers than in nonsmokers, with the main lesions being inflammation, goblet cell metaplasia, and hypertrophied muscle. In smokers, all the airways less than 2 mm were about equally involved. This study used slightly older subjects than an earlier study by the same investigators. In the earlier study, goblet cell metaplasia, increased smooth muscle, and airway narrowing were not observed, suggesting that perhaps these lesions are a later stage in the evolution of the response to injury in the small airways.

In another study of lungs obtained at autopsy, Salmon and coworkers (1982) correlated morphologic measurements of the central and peripheral airways and the alveolar surface-to-volume ratio with the slope of the alveolar plateau measured in the lung post mortem. They found a significant inverse correlation between the slope of the alveolar plateau and the peripheral airway diameter, but no significant relationship between the slope of the alveolar plateau and the alveolar-to-surface volume ratio, once age had been controlled. They concluded from these findings that the slope of the alveolar plateau does indeed assess the properties of the peripheral airways.

Mink and Wood (1980) performed physiologic studies on the lungs of six men (average age, 66 years) who died of atherosclerotic heart disease. Morphometrics were performed on one lung of each of two of the subjects. The physiologic studies involved ventilating a lung through a main-stem bronchus in a volume displacement plethysmograph with two catheters placed to record pressure: one in the lower

lobe to measure lateral bronchial pressure and the other within the plethysmograph to record pleural surface pressure. MEFV curves were obtained in lungs ventilated with either air or a HeO_2 mixture. They found that an abnormal response to breathing HeO_2 is not necessarily indicative of either airway or parenchymal disease, and concluded that the ability of the HeO_2 breathing to discriminate between normal and obstructed peripheral airways is affected by large between-subject variation in normal maximal flow, which is probably due to normal variation in the caliber of the central airways. They therefore questioned the use of MEFV curves breathing air and HeO_2 as a means of distinguishing between peripheral and central airflow obstruction or as a means of identifying mild airflow obstruction due to structural changes in the small airways. A similar conclusion was reached by MacNee and coworkers (1983).

These structure–function correlation studies have provided fairly convincing evidence that at least some of the tests purported to measure small airways function can indeed identify structural changes in the small airways. These changes appear initially to involve macrophage accumulation around respiratory bronchioles, with subsequent development of epithelial abnormalities in the terminal bronchioles. With cumulative injury over a long period, chronic inflammation leads to fibrosis and perhaps to an increase in the amount of smooth muscle. These are strictly airway lesions. The alveolar wall destruction of emphysema is not as clearly related to the tests of small airways function (Petty et al. 1981).

Acute Response to Cigarette Smoke

Before the tests of small airways function were introduced in the late sixties and early seventies, it was established that smoking a cigarette results in an immediate increase in airway resistance and a decrease in expiratory flow (Attinger et al. 1958; Chiang and Wang 1970; Clarke et al. 1970; Nadel and Comroe 1961; Robertson et al. 1969; Simonsson 1962; Zamel et al. 1963; Sterling 1967). It was thought that this response is mediated by the vagus nerve, and may be suppressed by isoproterenol and atropine (Nadel and Comroe 1961; Sterling 1967; Zamel et al. 1963).

Using the MEFV curve and closing volume, Da Silva and Hamosh (1973) showed a decrease in the maximum expiratory flow at 50 percent of the vital capacity, with the MEFV curve assuming a concave shape in 21 subjects immediately following cigarette smoking. Sobol et al. (1977) found the greatest change following smoking in airway resistance and specific conductance, with significant but lesser changes in the 1-second forced expiratory volume (FEV_1), the forced expiratory flow over the middle half of the forced vital capacity ($FEF_{25-75\%}$), and the ratio of FEV_1 to the forced vital capacity (FVC), FEV_1/FVC. Neither study found a change in closing volume.

From this limited information, it can be reasonably concluded that the large airways, rather than the small airways, respond acutely to the inhalation of cigarette smoke.

Chronic Response to Cigarette Smoke

In the late 1800s, Mendelssohn (1897) reported that smoking had a deleterious effect on the respiratory system. The early studies were hampered by the lack of sensitive physiologic tests of lung function, and relied heavily on differences between smokers and nonsmokers in the prevalence of respiratory symptoms. Confirmation of the structural basis of excessive respiratory symptoms seen in the smokers came from the classic paper by Reid in 1954, in which she described the pathology of chronic bronchitis (Reid 1954). Ventilatory limitation usually occurs late in the course of COLD. In contrast, the inflammatory response of the small airways is demonstrable relatively early in life in cigarette smokers.

Smoking and Tests of Small Airways Function in Population Studies

A large number of studies using tests of small airways function have been conducted over the past 15 years in groups and populations of various sizes, ages, and other characteristics. In some of these studies, the investigators have developed their own normal test ranges from a group of asymptomatic nonsmokers, but the normal ranges obtained by others (Buist and Ross 1973a, b; McCarthy et al. 1972; Collins et al. 1973) have been more commonly used.

In one of the earliest reported studies using the single breath N_2 test, Buist and coworkers (Buist and Ross 1973b; Buist et al. 1973) examined 1,073 persons attending a screening center, of whom 524 were current cigarette smokers. Among the smokers, an abnormal CV/VC was found in 35 percent, an abnormal CC/TLC in 44 percent, and an abnormal slope of the alveolar plateau in 47 percent. When the three measurements obtained from the single breath N_2 test were taken in conjunction, 64 percent of the smokers and 61 percent of the ex-smokers had an abnormal test result. In contrast, only 11 percent of the smokers had an abnormal FEV_1 and 21 percent had an abnormal $FEF_{25-75\%}$. This study suggested that the prevalence of measurable small airways dysfunction among cigarette smokers exceeds 50 percent. It must be kept in mind, however, that this study was carried out in a screening center and was therefore presumably biased toward a high disease prevalence.

A collaborative study was conducted in three North American cities (Montreal and Winnipeg, Canada, and Portland, Oregon)(Buist et al. 1979a) to avoid the pitfall of using a biased volunteer population. Random population samples were used in two of the

cities and a random sample of a working population in the third. Only people aged 25 to 54 were studied. Among the nonsmokers in each of the three cities, the age-related regressions for the single breath N_2 variables (CV/VC, CC/TLC, and the slope of the alveolar plateau) and for FEV_1/FVC had very similar slopes. As a result, a combined set of reference values was derived and used for comparison with the smokers and ex-smokers. No single test consistently showed the greatest prevalence of abnormality among the three cities. The slope of the alveolar plateau was abnormal most often in the women who smoked, and the CC/TLC was abnormal most often in the men who smoked. However, the prevalence of abnormalities was considerably lower than that reported in the screening center population study described above. Among the smokers for the three cities combined, CV/VC was abnormal in 17 percent of the men and in 26 percent of the women, CC/TLC was abnormal in 32 percent of the men and in 29 percent of the women, and the slope of the alveolar plateau was abnormal in 13 percent of the men and in 37 percent of the women. In comparison, the FEV_1/FVC ratio was abnormal in 7 percent of the men who smoked and in 25 percent of the women who smoked.

In another large-scale study, Knudson and Lebowitz (1977) used the single breath N_2 test in a random, stratified, cluster sample of 1,900 white, non-Mexican-American residents of Tucson, Arizona. These investigators established their own reference values from the asymptomatic nonsmokers, and then compared their smokers to the reference values. Figure 2 reveals the prevalence of an abnormal test result in three groups: normals, asymptomatic smokers, and symptomatic subjects (a group comprised largely of smokers). For the $\dot{V}_{max\ 75\%}$ and slope of phase III as well as for combined parameters of the MEFV curve and single breath N_2 test, asymptomatic smokers had approximately twice the prevalence of abnormal test results compared with the normal nonsmoking population. When the analysis was limited to the population aged 25 to 54, the results were even more striking. Of the asymptomatic smokers, 21.5 percent had an abnormal $\dot{V}_{max\ 75\%}$, and 33.9 percent had some abnormality on either the single breath N_2 test or the MEFV curve.

Manfreda and coworkers (1978) studied population samples stratified by sex, age, and smoking habits from a rural community (Portage la Prairie) and an urban community (Charleswood) in Manitoba. They tested 246 persons in Portage la Prairie and 256 subjects in Charleswood. Reference values for asymptomatic nonsmokers were established for the single breath N_2 test variables and for FEV_1/FVC and RV/TLC. In both communities, the slope of the alveolar plateau was abnormal (more than 2 SD from the mean) more often in smokers than in nonsmokers in both sexes (Figure 3).

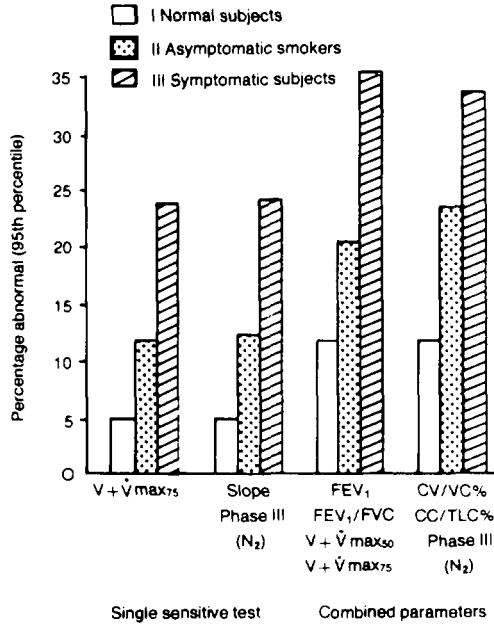

FIGURE 2.—The relative sensitivity in three adult groups of a single sensitive test and of combined measurements for maximal expiratory flow volume (MEFV) versus closing volume (CV)

NOTE: I = normal; II = asymptomatic smokers; III = symptomatic subjects.
SOURCE: Knudson and Lebowitz (1977).

Detels and coworkers (1979) studied population samples in two California communities, one being exposed to photochemical/oxidant pollutants (3,465 subjects). They used the single breath N_2 test, but measured the change in N_2 concentration between 750 and 1,250 cm^3 of expired air ($\Delta N_{2(750-1250)}$) rather than the more traditional way of looking at the slope of the alveolar plateau. They found that the mean values for $\Delta N_{2(750-1250)}$ and CV/VC were consistently higher for smokers than for nonsmokers.

Tockman and coworkers (1976) studied two groups of subjects selected from the Baltimore metropolitan area and not known to have disease. One group consisted of neighborhood control subjects participating in an epidemiologic study of obstructive pulmonary disease, and the other consisted of teachers in the Baltimore public schools who volunteered for a study of health and disease. Of the 133 subjects studied, 78 were smokers and 55 were nonsmokers. The investigators analyzed their data in a slightly different way from the approach used in the studies described above, in that they looked for differences between the age-related regression equations for the various tests in smokers and nonsmokers. They found significant differences between the adjusted mean smoker and nonsmoker

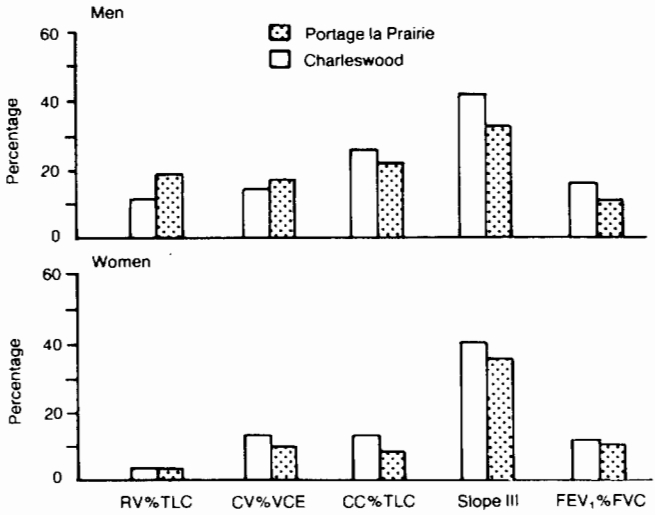

FIGURE 3.—Prevalence of lung function abnormalities among smokers in an urban and a rural community

SOURCE: Manfreda et al. (1978).

values, but no differences associated with age for CC/TLC, the slope of the alveolar plateau, RV/TLC, the steady state diffusing capacity, and the number of respiratory symptoms. Differences between smoker and nonsmoker mean values *and* an increasing difference between smokers and nonsmokers with increasing age were found for the FEV_1, $FEF_{25-75\%}$, $\dot{V}_{max\ 50}$, and moment analysis. The researchers suggest that the first group of tests may measure an all-or-none response that occurs relatively soon after the onset of smoking and is not affected by duration of smoking, and that the second group of tests may measure the effect of continued smoking, thus reflecting the increasing abnormality associated with longer exposure. This theory should be tested as part of an evaluation of the predictive value of small airways function.

Nemery and coworkers (1981) used the single breath N_2 test and MEFV curves to study a group of 272 European blue-collar workers, aged 45 to 55, from a steel plant near Brussels, Belgium. They first obtained reference values from their asymptomatic nonsmokers and defined their limit of normality as the 95th percentile for each of the tests. CC/TLC and the slope of the alveolar plateau had the highest prevalence of abnormality among the smokers (47 and 44 percent,

respectively), followed by CV/VC% (34 percent), $\dot{V}_{max\ 75\%}$ (33 percent), and $\dot{V}_{max\ 50\%}$ (30 percent). When the indices derived from the single breath N_2 test were combined, 60 percent of their smokers had an abnormality in one or more of the measurements obtained from the test, whereas 52 percent had an abnormality in one or more measurements obtained from the forced expiratory maneuver. They pointed out that combining the measurements obtained from a test increases its sensitivity but decreases its specificity.

In addition to the studies described above, which involved fairly large population groups, numerous studies have been carried out in smaller groups (McCarthy et al. 1972; Stanescu et al 1973; Gelb and Zamel 1973; Cochrane et al. 1974; Abboud and Morton 1975; Marcq and Minette 1976). These studies have also found the measurements obtained from the single breath N_2 test and MEFV curve to be abnormal more often among smokers than among nonsmokers.

There have been very few published studies using MEFV curves with air and HeO_2 in reasonably large population groups. This is probably because the test is more difficult to perform than the single breath N_2 test or the forced expiration maneuver, and because of the wide range of within-individual and between-individual variability associated with these tests. Lam and coworkers (1981) obtained spirometry and MEFV curves with air and HeO_2 in 423 subjects participating in epidemiologic health surveys in British Columbia. The subjects consisted of four groups: nonsmokers and smokers not exposed to air pollutants at work, and nonsmoking and smoking grain elevator workers. Reference values were established from the 78 healthy, asymptomatic nonsmokers who were not exposed to any air pollutant at work. They found that in the subjects not exposed to air pollutants at work, $\dot{V}_{max\ 50}$ was the best test for discriminating the effects of cigarette smoking, but $\Delta\dot{V}_{max\ 50}$ and Viso$\dot{V}$ were not significantly different between the smokers and the nonsmokers. Interestingly, the FEV_1 was the best discriminator of the effect of grain dust, and there was poor concordance among the FEV_1, $\dot{V}_{max\ 50}$ and $\Delta\dot{V}_{max\ 50}$, and Viso$\dot{V}$. They concluded that a comparison of MEFV curves breathing air and HeO_2 is less helpful than the standard MEFV curves in distinguishing the effects of smoking and the effects of exposure to an air pollutant.

A careful evaluation of moment analysis in a reasonably large population group of adults has not been published. The limited information in the literature comes from studies of small groups of children (Neuberger et al. 1976; Liang et al. 1979; MacFie et al. 1979) and adults (Permutt and Menkes 1979; MacFie et al. 1979). These preliminary studies look promising, but a more extensive evaluation of the technique in carefully chosen population groups must be carried out before conclusions are reached on the value of this approach. Moment analysis is particularly sensitive to changes in

the terminal part of the forced expiratory spirogram, which is particularly sensitive to an artifact in the MEFV curve when volume is measured by a spirometer at the mouth rather than by plethysmography. This artifact relates to the fact that there are volume changes due to gas compression that are measured by plethysmography but not by a spirometer at the mouth. The appropriate method to measure volume in moment analysis is by plethysmography, but very few such measurements have been made, most measurements having been made by spirometry. The magnitude of the resulting error has not been assessed.

In summary, the prevalence of abnormalities observed in any group of smokers depends on the age and characteristics of the group (how they were selected), on the reference values used (external reference values or reference values obtained from the population under study), and the cutoff used to define abnormality. However, this prevalence is uniformly higher in smoking than in nonsmoking populations. In a randomly selected sample of the general population below age 55, at least a third (and usually more) of the smokers can be classified as having small airways dysfunction.

Dose–Response Relationship Between Amount Smoked and Small Airways Dysfunction

In general, population-based studies involving adults of all ages with a reasonable range of cigarette consumption consistently show a fairly strong dose–response relationship between the number of cigarettes smoked and the degree of impairment.

Burrows and coworkers (1977a), studying a randomly stratified cluster sample of Tucson, Arizona, households comprised of 2,360 white, non-Mexican-American adults over age 14, found a highly significant quantitative relationship between pack-years of smoking and functional impairment, as measured by $\dot{V}_{max\ 75\%}$, FEV_1 percent predicted, and FEV_1/FVC percent. The shift in the mean FEV_1 percent predicted and the distribution of the FEV_1 percent predicted with increasing cigarette consumption is illustrated in Figure 4.

Buist and coworkers found a positive correlation between total cigarette consumption and the frequency of abnormalities in tests of small airways function in 524 smokers attending an emphysema screening center. However, tests of significance were not reported in the description of the relationship between pack-years and CV/VC and CC/TLC (Buist et al. 1973). Tests of significance were reported in the description of the relationship between the slope of the alveolar plateau and cigarette consumption (Buist and Ross 1973b); no clear relationship between daily cigarette consumption and an abnormal slope of the alveolar plateau was found. Among women who smoked more than 20 cigarettes a day, however, the prevalence of an abnormal slope of the alveolar plateau was significantly increased;

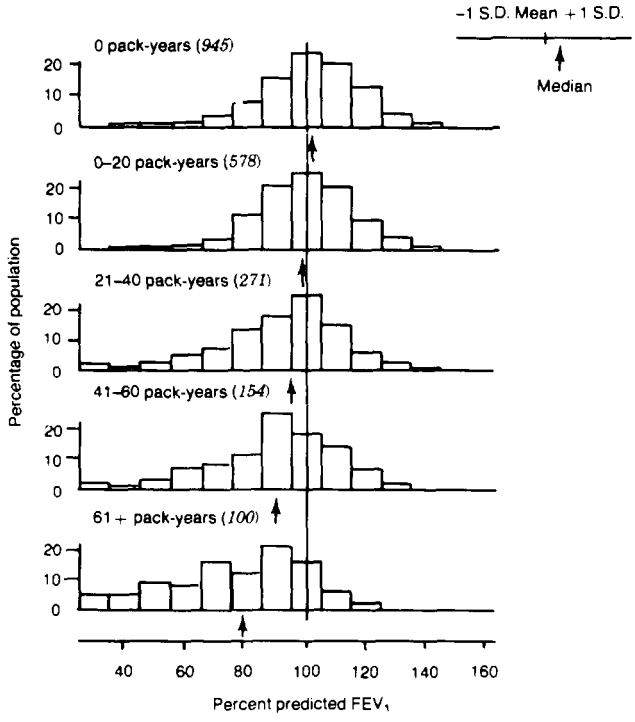

FIGURE 4.—Percentage distribution of predicted forced expiratory volume in 1-second (FEV_1) values in subjects with varying pack-years of smoking

* Subjects with "respiratory trouble" before age 16 are excluded.

NOTE: Means, medians, and ±1 standard deviation of the data for each group are shown in the abscissae.

SOURCE: Burrows et al. (1977a).

among men, a significant increase was found only for those who smoked more than 40 cigarettes a day.

Somewhat similar conclusions were reached by Tockman and coworkers (1976) in their study of healthy Baltimore residents. These investigators found that the CC/TLC, the slope of the alveolar plateau, RV/TLC, the steady state diffusing capacity, and respiratory symptoms were significantly different between smokers and nonsmokers, but there were no significant age-related differences for these variables. In contrast, tests of forced expiration (FEV_1/FVC, $\dot{V}_{max\ 50}$, and moment analysis) showed both differences between smokers and nonsmokers *and* increasing smoker versus nonsmoker differences with increasing age. These investigators interpreted their findings as suggesting that the tests of small airways function measure an all-or-none response that occurs at the onset of smoking but is not affected by duration of smoking. They proposed that the

measurements obtained from a forced expiration maneuver probably measure the effects of continued smoking and reflect increasing abnormality associated with longer duration of smoking.

In their study of population samples in Manitoba, Manfreda and coworkers (1978) found a significant relationship between the current number of cigarettes smoked per day and the slope of the alveolar plateau and CC/TLC in both sexes and RV/TLC in women. These investigators found that an index of lifetime exposure to smoke had no effect after accounting for the effect of current smoking. Among all the lung function measurements, smoking status accounted for the largest proportion of variance due to the three smoking variables (smoker versus nonsmoker, number of cigarettes smoked per day, and lifetime amount smoked). They interpreted this finding as suggesting that responses on these lung function tests are related more to whether one does or does not smoke than to the amounts smoked.

Buist and coworkers, in the three-city collaborative study described earlier (Buist et al. 1979a), considered the effect of smoking in two ways, first by means of multiple regression analysis using age and cigarette-years data from both smokers and nonsmokers. Using the pooled data from the three cities, they found that cigarette consumption had a significant effect on the CC/TLC, CV/VC, the slope of the alveolar plateau, and FEV_1/FVC (only in women). In this analysis, the effect of aging was considerably greater than the effect of smoking. The second approach involved data only from smokers, and a linear regression of the percentage of the predicted value for each variable on cigarette-years was obtained. A significant regression occurred in only one-third of the city/sex groups, and in each case the regression coefficients were very small. They concluded that a dose effect was not apparent when smokers only were considered, using both cigarettes per day and years smoked as indicators of cigarette consumption. They interpreted these findings similarly to Manfreda and coworkers (1978): it could be smoking itself and not the quantity of cigarettes smoked that is the crucial factor in the development of early functional impairment. The researchers suggest that absence of a clear-cut dose–response relationship in this study may also have resulted from the limited age range (25 to 54 years) and the relatively few heavy smokers in the study. They also speculate that the single breath N_2 test variables, especially the slope of the alveolar plateau, may be so "sensitive" that they reflect an on–off effect of smoking rather than cumulative damage.

Dosman and coworkers (1976) looked for a dose–response relationship in 49 smokers, aged 28 to 67, of whom 60 percent were attending a smoking cessation clinic. They found a significant relationship between a smoking index (cigarettes per day $\times$ years smoked) and $V_{iso}\dot{V}$ and $\dot{V}_{max\ 50}$. They did not find a significant relationship

between symptoms and frequency dependence of compliance, CC/TLC, the slope of the alveolar plateau, or $\dot{V}_{max\ 50}$ (Figure 5).

Beck and coworkers (1981, 1982), in a cross-sectional study of three communities (Lebanon and Ansonia, Connecticut, and Winnsboro, South Carolina) sought a dose–response relationship in 1,209 smokers. Dividing the sample into light smokers (1 to 20 cigarettes/day) and heavy smokers (>20 cigarettes/day), they found a trend of increasing dysfunction across smoking categories that was evident as early as age group 15 to 24 for both men and women. A difference between men and women occurred in terms of the relationship between residual lung function (observed–predicted FEV_1) and pack-years of smoking. In male smokers, the combination of number of cigarettes smoked per day and duration of smoking was the best indicator of loss in lung function, as measured by residual lung function (FEV_1, $\dot{V}_{max\ 50\%}$, and $\dot{V}_{75\%}$). For women smokers, pack-years best explained lung function loss as measured by residual lung function. These investigators thus found a very definite dose–response relationship between the amount smoked and lung function loss. They do point out, however, that smoking variables and age accounted only for up to 15 percent of the variation in residual lung function.

In summary, the data suggest a dose–response relationship between number of cigarettes smoked per day and the prevalence of abnormal results on tests of small airways function. That is, heavy smokers are more likely to have abnormal small airways function than light smokers. However, there is only a weak relationship between the degree of abnormality in small airways function and the number of cigarettes smoked per day or pack-years of smoking. In contrast, tests obtained from the forced expiration maneuver have a stronger dose–response relationship. This is consistent with the theory that cigarette smoking induces an inflammatory response in the small airways and that this response is more likely to happen in heavy smokers, as measured by sensitive measures of small airways function such as the single breath nitrogen test. The extent of chronic airway disease that reflects the dose and duration of the smoking habit is better measured by changes in the forced expiratory maneuver.

How Soon Do Changes in Small Airway Function Occur?

The first study to look at the prevalence of abnormalities on tests of small airways function by age in a large group of smokers was reported by Buist and coworkers (1973a). These investigators found that abnormalities of small airways function could be detected before age 30 by means of the single breath N_2 test, with CV/VC discriminating best between smokers and nonsmokers in the age decade of the twenties (Figure 6).

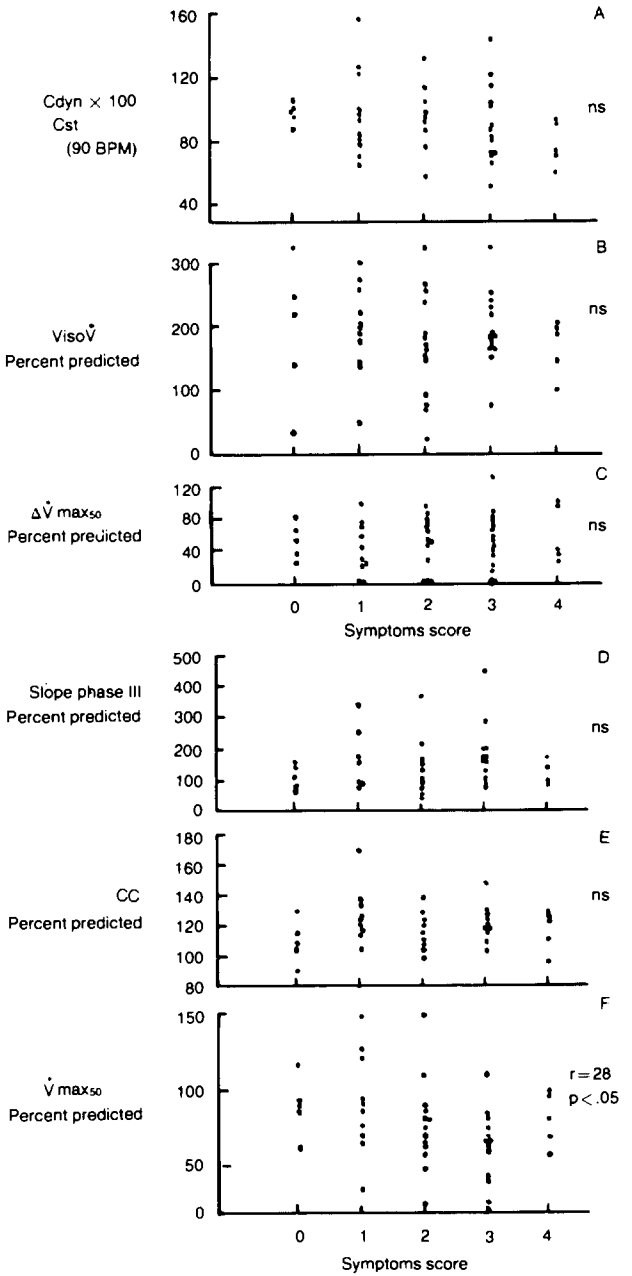

FIGURE 5.—A composite of six tests plotted against symptoms score

SOURCE: Doeman et al. (1976).

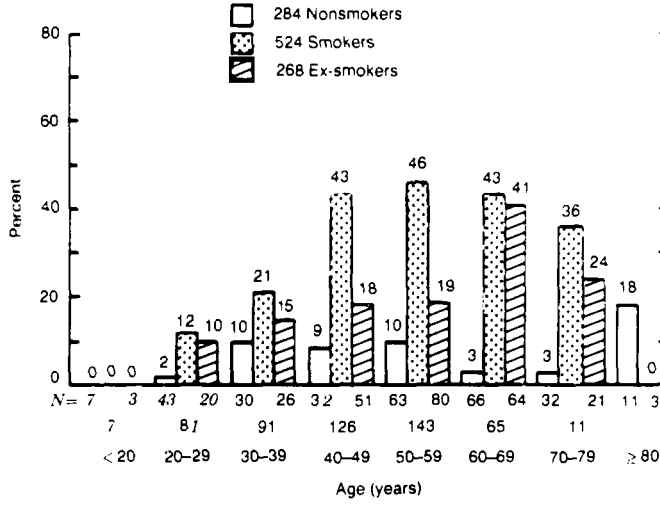

FIGURE 6.—Prevalence of abnormal closing volume/vital capacity ratios in nonsmokers, smokers, and ex-smokers, by age decade

SOURCE: Buist et al. (1973).

In their cross-sectional survey of residents in three separate communities in Connecticut and South Carolina, Beck and coworkers (1981, 1982) found that the age of onset of abnormalities in lung function may occur as early as age 15 to 24. Their approach used residual lung function (observed–predicted value) for FEV_1, $\dot{V}_{max\ 50\%}$, and $\dot{V}_{max\ 75\%}$, with a negative residual indicating an observed value below prediction. Negative residuals for all three measurements began to occur in women in the age group 15 to 24 (Figure 7). Significant differences among smoking categories—nonsmokers, ex-smokers, light smokers (1 to 20 cigarettes/day), and heavy smokers (>20 cigarettes/day)—were seen for $\dot{V}_{max\ 50\%}$ and $\dot{V}_{max\ 75\%}$ in women aged 15 to 24 and for FEV_1 in age group 25 to 34 (Figure 8). In male smokers, negative residuals began to occur for all three measurements in the age 25 to 34 group. Significant differences among the smoking categories were seen for FEV_1 in the 35 to 44 age group and for $\dot{V}_{max\ 50\%}$ and $\dot{V}_{max\ 75\%}$ in the 45 to 54 age group.

Seely and coworkers (1971) found lower values for $\dot{V}_{max\ 50\%}$ and $\dot{V}_{max\ 75\%}$ in a group of high school students with 1 to 5 years of smoking experience. These differences were significant in boys who smoked more than 15 cigarettes per day and in girls who smoked more than 10 cigarettes per day. Significant differences between the smokers and nonsmokers were not found for FEV_1.

Dosman and coworkers (1981) studied 1,202 adults, aged 25 to 59, living in Humboldt, Saskatchewan. Among smokers in the 25 to 29

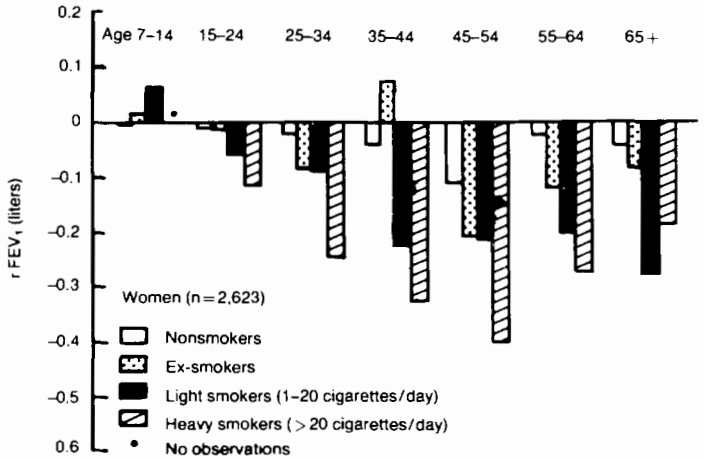

FIGURE 7.—Mean residual FEV_1 in women, by smoking status and age

SOURCE: Beck et al. (1981).

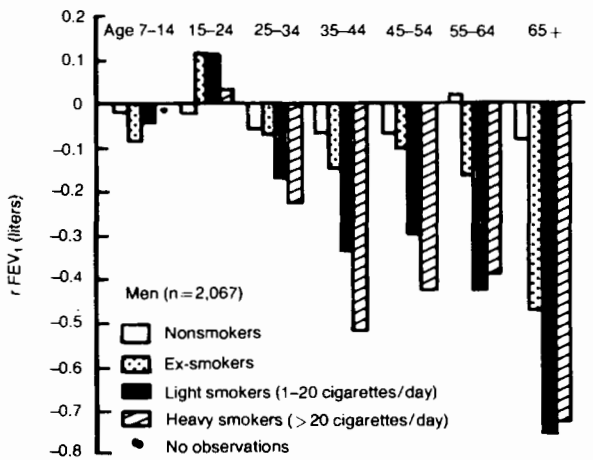

FIGURE 8.—Mean residual FEV_1 in men, by smoking status and age

SOURCE: Beck et al. (1981).

age group, 14.9 percent of the women and 18.5 percent of the men had an abnormal test value for the slope of the alveolar plateau, for CV/VC, or for both. Comparable rates of abnormality for FEV_1/FVC

were 2.1 percent in women and 5.6 percent in men. For both the slope of the alveolar plateau and CV/VC, the prevalence of abnormal test value increased steadily with increasing age, so that 63.6 percent of the female smokers aged 55 to 59 and 46.2 percent of the male smokers aged 55 to 59 had abnormal values. Comparable rates for an abnormal FEV_1/FVC were 4.5 and 19.2 percent in the women and men, respectively.

Walter and coworkers (1979) studied 102 Indian male medical students in their late teens and early twenties. Of the 102 subjects, 60 were nonsmokers, 23 were light smokers (lifetime total of $<10{,}000$ cigarettes), and 19 were heavy smokers (lifetime total of $>10{,}000$ cigarettes). The researchers compared mean pulmonary function values obtained from the spirograms across the smoking categories. There was a consistent trend for all the lung function variables examined ($FEF_{20-30\%}$, $FEF_{35-55\%}$, $FEF_{70-80\%}$, $FEF_{80-90\%}$, $FEF_{25-75\%}$, and FEV_1/FVC), with the highest mean values being seen in the nonsmokers, intermediate values in the light smokers, and the lowest values in the heavy smokers. There were no significant differences among the three groups in height and weight. No information was given in this report about the type of cigarettes smoked.

The consistency of results from the studies attempting to define the age of onset of measurable abnormalities in tests of small airways function is striking. Even though statistical significance was not always found, the trend is clear and provides strong evidence that measurable abnormalities of small airways function do occur in some smokers within a few years of smoking onset.

Male–Female Differences in the Responses of the Small Airways to Cigarette Smoking

When looking at variations between the sexes in response to cigarette smoking, one must take into account possible differences in the manner in which cigarettes are smoked, in the amount smoked, and in environmental exposures that may interact with smoking. Most investigators have found little or no difference based on sex for the relationship between the various tests of small airways function and age in nonsmokers. Thus, a difference between the sexes in response to smoking, if it exists, probably represents a true biological difference in the effect of smoking on lung function or variations in exposure dose resulting from method of smoking or amount smoked.

Unfortunately, the information available in the literature about sex-related differences in small airways response to cigarette smoking is scanty and conflicting. Manfreda and coworkers (1978) found a higher prevalence of abnormality in tests of small airways function among male smokers than among female smokers in their study of two communities in Manitoba. The opposite finding has been

reported by Buist and coworkers (Buist and Ross 1973a, b; Buist et al. 1973, 1979a) in their studies of a screening center population and of population samples and groups in Montreal, Winnipeg, and Portland. It is quite possible that selection bias in the screening center study limits the ability to extrapolate this study to the general population. The three-cities study, however, did not suffer from that flaw, and showed clear differences (women higher than men) in the prevalence of abnormalities of CV/VC and the slope of the alveolar plateau. The prevalence of abnormality of CC/TLC, on the other hand, was slightly higher in male smokers than in female smokers (32 and 29 percent, respectively). A surprising finding was that the prevalence of FEV_1/FVC abnormality was considerably higher among women who smoked than among men who smoked (25 and 7 percent, respectively).

At this point, a generalization is not yet possible on sex-related differences in the response of the small airways to cigarette smoking. However, it seems likely that the contribution of sex difference is relatively small once age and dose are taken into account.

Effect of Smoking Cessation on Small Airway Function

The correlation between abnormalities in tests of small airway function and the pathologic changes of inflammation of the small airways suggests that cessation of smoking may lead to a return toward normal in these tests. A number of authors have examined changes in tests of small airways function in cigarette smokers who have quit.

Ingram and O'Cain (1971) examined six smokers with an abnormal frequency dependence of compliance who quit smoking. After 1 to 8 weeks of cessation, values in all six returned to the normal range.

Bode et al. (1975) examined 10 subjects aged 29 to 61 with normal FEV_1 values while they were active smokers and again 6 to 14 months after they had stopped smoking. Static volume pressure curves, slope of phase III, and forced expiratory flow rates on air were unchanged by cessation. However, the maximum expiratory flow rates with helium at 50 and 25 percent of the vital capacity increased, and the volume of isoflow and closing volume decreased.

McCarthy et al. (1976) followed 131 smokers aged 17 to 66 who volunteered to attend a smoking cessation clinic. Cessation resulted in a significant reduction in the closing capacity (CC/TLC%) and the slope of phase III within 25 to 48 weeks in the 15 persons who were able to abstain from cigarettes completely.

Buist et al. (1976) followed a group of 25 cigarette smokers who attended a smoking cessation clinic and found that cessation resulted in significant improvements in the closing volume (CV/VC%), closing capacity (CC/TLC%), and the slope of the alveolar plateau (phase III) at 6 and 12 months following cessation.

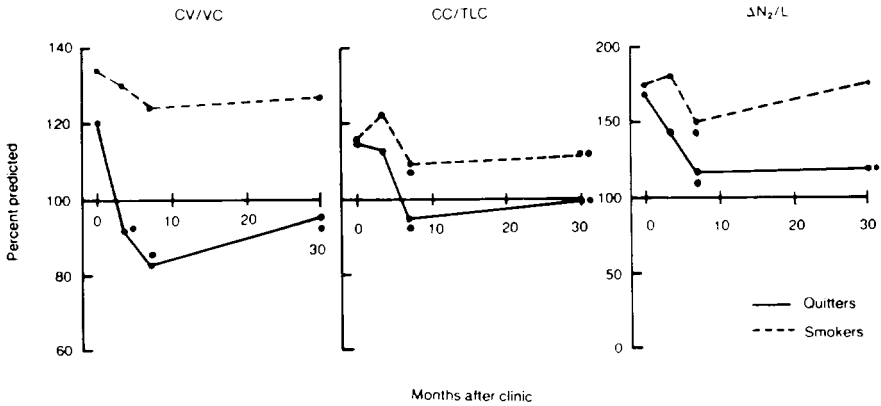

FIGURE 9.—Mean values for the ratio of closing volume to vital capacity (CV/VC), of closing capacity to total lung capacity (CC/TLC), and slope of phase III of the single breath N_2 test ($\Delta N_2/L$), expressed as a percentage of predicted value (12, 13) in 15 quitters and 42 smokers, during 30 months after two smoking cessation clinics

* A significant difference from the initial value at $p < 0.05$.

NOTE: Data from 3-month followup of the 1973 clinic and 4-month followup of the 1975 clinic have been combined, as have 6-month and 8-month data for the 1973 clinic.

SOURCE: Buist et al. (1979a).

This study was expanded using a second group of subjects (Buist et al. 1979b) and a 30-month followup. Once again, the three parameters of the single breath N_2 test showed improvement in smokers who quit; this improvement continued for 6 to 8 months, and then leveled off (Figure 9). In addition, the values for the single breath N_2 test in those who quit returned to the levels predicted for nonsmokers, suggesting that the changes in the small airways can be substantially reversed with cessation.

Bake et al. (1977) also showed an improvement in the slope of phase III following cessation in a small group who were followed for 5 months.

In summary, abnormalities in the small airways are substantially reversible in smokers who have not developed significant chronic airflow obstruction. This suggests that the inflammatory response in the small airways, which may be the earliest change induced by smoking, is also a change that reverses with the cessation of chronic exposure to the irritants in cigarette smoke.

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Relationship Between Small Airways Disease and Chronic Airflow Obstruction

There is no question that the information obtained over the past 15 years from studies of small airways function has helped to describe more accurately the natural history of chronic airflow obstruction. The practical question of the place of tests of small airways function in clinical practice has not yet been resolved, and will not be fully answered until longitudinal studies using the tests have been completed. The important issue to be addressed is whether the tests of small airways function can be be used to identify the smoker who will progress to develop irreversible airflow obstruction. This question can be answered satisfactorily only by following a fairly large group of smokers prospectively over a period of time long enough for some of the smokers to develop an abnormal FEV_1. If the tests of small airways function can be used alone, or in conjunction with other qualitative or quantitative data about risk factors, they will clearly be useful to the practicing physician. If they are too sensitive or have a poor predictive value, their use will be more limited.

Buist and coworkers (1984) determined the positive and negative predictive value of tests of small airways function in their study of two cohorts followed prospectively over a 7- to 11-year period. They found that the positive and negative predictive values of the tests of small airways function varied greatly between the cohorts, largely because of the different ages and prevalences of an abnormal FEV_1 between the cohorts. They concluded that significant associations existed between the single breath N_2 test variables and spirometric variables in smokers, but the weakness of these associations and the high misclassification rates suggest that small airways disease does not necessarily lead to clinical airflow obstruction.

Over a period of 8 years, Marazzini and coworkers (Marazzini et al. 1977, 1981) followed a group of 69 asymptomatic workers in an iron foundry (49 smokers, 20 nonsmokers) living in the same area. They found that 39 percent of the smokers and 15 percent of the nonsmokers, initially diagnosed as having peripheral airways disease, developed central airways obstruction (defined as 1 or more of the vital capacity (VC), FEV_1 or FEV_1/VC being more than 15 percent different from normal) within the 8-year followup.

An indirect way to assess the predictive value of the tests of small airways function was proposed by Tattersall and coworkers (1978). These investigators proposed that any valid test of chronic airflow obstruction must yield results that are systematically worse in middle-aged smokers than in middle-aged nonsmokers, and that such a test should also correlate with the FEV_1 in middle-aged smokers. Using these criteria in a cross-sectional study of a sample of working

men in West London, they concluded that the most informative and repeatable tests were $\dot{V}_{max\ 75\%}$ and the slope of the alveolar plateau.

Nemery and coworkers (1981) addressed the question of the significance of tests of small airways function in their study of 2,072 blue-collar workers, aged 45 to 55, from a steel plant near Brussels. They found that smokers with an abnormal CC/TLC or slope of the alveolar plateau and a normal FEV_1/FVC had a significantly lower $FEV_1/(height)^3$ than subjects with normal CC/TLC and slope of the alveolar plateau. They interpret their data as suggesting that smokers with small airways dysfunction experience a more rapid decline in FEV_1 than smokers without small airways dysfunction, leading to a higher susceptibility to long-term smoking effects in the former group.

The opposite conclusion was reached by Fletcher (1976), who examined the relationship between CV/VC, the slope of the alveolar plateau, and FEV_1 in 200 male smokers aged 40 to 55. In this group, he found a relatively poor correlation between FEV_1 and the single breath N_2 variables.

There is thus, as yet, inadequate information to allow a firm conclusion to be drawn about the predictive value of the tests of small airways function in identifying the susceptible smoker who is going to progress toward clinical airflow obstruction. The tests of small airways function are probably abnormal for many years before the FEV_1 becomes abnormal in those smokers who go on to develop airflow obstruction. However, many smokers with abnormal tests of small airways function may never develop clinically significant airflow obstruction. Therefore, functional changes in the small airways may not always be related to the widespread alveolar destruction seen in smokers or to the development of clinical airflow obstruction. It may be that varying degrees of inflammation and fibrosis occur in virtually all smokers, and that there is something very different about the smokers who develop extensive airway or emphysematous changes.

Summary

A number of tests have been developed that can identify small airways dysfunction in individuals with normal lung volumes and standard measures of forced expiratory airflow. These tests correlate well with the presence of pathologic changes in the airways 2 mm or less in diameter, particularly with peribronchiolar inflammation. Cigarette smokers have a significantly higher frequency of abnormal tests of small airways function. Heavy smokers have a greater prevalence of small airways dysfunction than light smokers, but there is only a weak dose–response relationship between numbers of cigarettes smoked per day or duration of smoking and the extent of small airways dysfunction. This suggests that the response of the

small airways may be an "all or nothing" inflammatory response to cigarette smoke irritants rather than a progressive response representing a cumulative injury.

Cessation of cigarette smoking results in significant improvement in small airways function, which in those smokers without evidence of chronic airflow obstruction, may return to normal.

The relationship between changes in the small airways and the development of chronic airflow obstruction remains unclear. It seems likely that those smokers who will go on to develop ventilatory limitation will have abnormal small airways function before the FEV_1 becomes abnormal, but many smokers with small airways dysfunction may never progress to significant airflow obstruction. Therefore, the usefulness of tests of small airways function for identifying those who will develop ventilatory limitation remains to be established.

CHRONIC MUCUS HYPERSECRETION

Introduction

The association of cigarette smoking and chronic cough was recognized by the general public in the term "smokers cough" well before the demonstration of this association in epidemiologic studies. Cough is the symptom most frequently experienced by smokers, and it is often accompanied by excess mucus secretion resulting in phlegm production or a "productive" cough. Chronic bronchitis was defined by the Ciba Foundation Guest Symposium report (1959) as "the condition of subjects with chronic or recurrent excess mucus secretion into the bronchial tree." The position was taken that any production of sputum was abnormal, and chronic was defined as "occurring on most days for at least 3 months of the year for at least 2 successive years." Also, the sputum production could not be on the basis of specific diseases such as tuberculosis, bronchiectasis, or lung cancer.

Measurement of Cough and Phlegm in Epidemiologic Studies

The increasing use of standardized questionnaires in interviews to ascertain the presence of cough, phlegm, or other symptoms of respiratory disease has improved the quality of measurements of prevalence and incidence of these symptoms and the validity of comparisons within and between studies. Similar attention has been given to developing questions about smoking habits, including questions about the type and number of cigarettes used at the time of interview and in the past. The first British Medical Research Council (BMRC) questionnaire published in 1960 (Medical Research Council 1960) had been tested, revised, modified, and extended, and many studies have resulted from its widespread use. However, difficulties in using this questionnaire in epidemiological studies of populations in the United States and the desire to collect additional information led to modification in individual studies and to a loss of comparability between studies. This motivated the American Thoracic Society and the Division of Lung Diseases of the National Heart, Lung, and Blood Institute to establish the Epidemiology Standardization Project. Extensive methodological studies were done, standardized questionnaires were developed, and techniques for measuring pulmonary function and evaluating chest radiographs were proposed (Ferris 1978). Samet (1978) has reviewed the history of the development of respiratory symptom questionnaires. Although many investigators now use the methods advocated by the BMRC or the Epidemiology Standardization Project, several of the studies reviewed in this chapter of the Report are based on other, nonstandard questionnaires. A comparison between studies of different popula-

tions, or the same population studied at different times, must be made cautiously and only after careful consideration of technical and methodological issues. Low rates of participation and use of unrepresentative samples may cause biased estimates of the frequency and distribution of symptoms. Attitudes toward smoking have changed, and comparisons of questionnaire responses and objective measurements of smoking habits indicate that at least in some situations, less reliance can now be placed on answers to questions about smoking habits (MRFIT Research Group 1982). Estimates of prevalence and incidence of respiratory symptoms are imprecise, and too much importance should not be attached to relatively small differences in rates of reporting cough and phlegm. Each author's criteria for detecting the presence of cough or phlegm should be considered, especially when combinations of symptoms or diagnostic labels such as chronic bronchitis or mucus hypersecretion are used. Notwithstanding methodological differences, however, consistent patterns or trends found in many studies indicate that the associations between smoking and chronic mucus hypersecretion are real and that the findings are widely applicable.

Prevalence of Cough and Phlegm

Unpublished data from the National Center for Health Statistics estimate that there were almost 8 million persons with chronic bronchitis in the United States in 1981 (3.4 million men, 4.5 million women). This is probably an underestimate of the true frequency of cough and phlegm in the population, since people who had these symptoms were not counted as chronic bronchitics unless they responded affirmatively to the question about bronchitis. On the other hand, some cases of acute bronchitis may have been included incorrectly and inflated the estimate. The apparently higher prevalence rates of chronic bronchitis in women than in men in the National Health Interview Surveys in 1970 and 1979 (3.4 and 3.7 percent for women in 1970 and 1979, respectively, and 3.1 and 3.2 percent for men in 1970 and 1979) are probably due to ascertainment being less complete for men (USDHEW 1980b). Prevalence rates of chronic bronchitis ranged from 4.2 percent at ages under 17 years to 2.7 percent at 17 to 44 years, 3.6 percent at 45 to 64, and 4.5 percent at ages over 65 years. The high rate in the youngest group is presumably because of the inclusion of cases of acute bronchitis.

Standard questions about chronic cough were asked in the National Health and Nutrition Examination Surveys (NHANES) of representative samples of the U.S. population. Some supplementary questions were asked about phlegm and other respiratory symptoms, and these data are presented in the appendix to this chapter. Prevalence rates of diagnosed chronic cough in 18- to 74-year-old participants in NHANES 1 (1971–1975) were 3 percent for men and 2

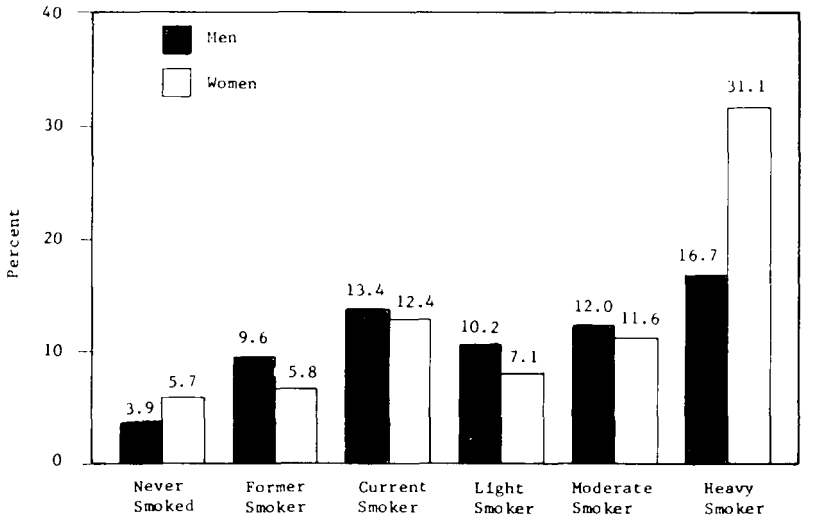

FIGURE 10.—Percentage of recurring persistent cough attacks by sex and smoking status for adults 25–74, United States, 1971–1975

NOTE: Light smoker: 1–14 cigarettes per day
Moderate smoker: 15–24 cigarettes per day
Heavy smoker: ≥ 25 cigarettes per day

SOURCE: National Center for Health Statistics. Unpublished data from the first National Health Nutrition and Examination Survey (NHANES 1).

percent for women; they increased with age from 1 percent at 18 to 24 years to 6 percent at 65 to 74 years for men, and from 1 percent at 18 to 24 years to 3 percent at 65 to 74 years for women (National Center for Health Statistics, unpublished data).

The prevalence of self-reported recurring persistent cough by smoking status for men and women of different ages is presented in the appendix and in Figure 10 based on NHANES 1. For the entire NHANES population, the prevalence of the persistent cough increased threefold in male smokers and twofold in female smokers compared with nonsmokers (Figure 10), and the prevalence of cough increased with increasing cigarette consumption in both men and women.

Relationship of Cough and Phlegm to Smoking

Relationships between smoking and cough or phlegm are strong and consistent; they have been amply documented and are judged to be causal (USPHS 1964, 1971; USDHEW 1979; USDHHS 1980a, 1981). Associations between smoking and cough or sputum are apparent in the recent studies listed in Tables 2 and 3 and are illustrated in Figures 11 and 12. Although cough, phlegm, and

chronic bronchitis occur in nonsmokers, prevalence rates are consistently higher in cigarette smokers.

The excess prevalence of cough and phlegm in cigarette smokers increases with the amount smoked (see below). The frequency of reporting cough and phlegm is at least twice as high for smokers as for nonsmokers except in some groups with minimal exposure. Differences in prevalence rates between smokers and nonsmokers tend to be greater at older ages among men, whereas differences in rates between smoking and nonsmoking women tend to be as great or greater at younger ages (Tables 2 and 3). Rates are not given for pipe or cigar smokers in most of these studies, presumably because the numbers of such smokers were too small for reliable rates; male pipe smokers and cigar smokers in Tecumseh reported cough and phlegm more frequently than nonsmokers or ex-smokers, but less frequently than cigarette smokers (Higgins et al. 1977).

Individual studies have evaluated other factors as well as smoking, but smoking has been judged the most important determinant of symptom prevalence (Fletcher et al. 1976; Ferris et al. 1976; Kiernan et al. 1976; Bouhuys 1977; Higgins et al. 1977). Consideration of evidence from many different studies has led to the conclusion that cigarette smoking is the overwhelmingly most important cause of cough, sputum, chronic bronchitis, and mucus hypersecretion (Speizer and Tager 1979; USDHHS 1980b).

Effects of Smoking Cessation

Cross-sectional information on ex-smokers suggests that stopping smoking is followed by a reduction in cough and phlegm because symptoms are less prevalent than in current smokers, but these symptoms are generally more prevalent in ex-smokers than in lifelong nonsmokers (Huhti et al. 1978; Gulsvik 1979; Park 1981; Schenker et al. 1982). However, the differences between ex-smokers and nonsmokers were either very small or absent in the studies reported by Higgins et al. (1977) and Manfreda et al. (1978).

The longitudinal studies cited in Table 3 strengthen the evidence from cross-sectional studies that cigarette smoking causes cough and phlegm. Prevalence rates were higher at followup examinations in persons who started to smoke after being nonsmokers at a previous examination (Kiernan et al. 1976; Leeder et al. 1977). Rates of reporting cough or phlegm decreased in smokers who stopped smoking in two British studies (Kiernan et al. 1976; Leeder et al. 1977) and in populations in the United States (Ferris et al. 1976; Friedman et al. 1980; Beck et al. 1982). Many people who stop smoking report a rapid reduction in cough and phlegm. Although remission of symptoms occurs in some persistent smokers, remission rates are generally higher and incidence rates lower in those who quit than in those who continue to smoke.

TABLE 2.—Prevalence (percent) of cough, phlegm, and other symptoms for nonsmokers (NS), smokers (SM), and ex-smokers (EX), cross-sectional studies

Author, year, country	Population	Cough	Phlegm	Other	Comments
Tager and Speizer, 1976, U.S.	507 residents, aged 15-65+, East Boston	Chronic bronchitis Men NS 7.0 SM (pack-years) 1-5 8.7 5-10 25.0 10-20 28.6 >20 47.5 Women NS 4.6 SM (pack-years) 1-5 14.3 5-10 9.1 10-20 20.8 >20 30.0			Chronic bronchitis (cough and phlegm ≥3 mos/yr for 2 years); no age trend for either sex after adjusting for smoking; prevalence greater for men than women at each age; significant increase in chronic bronchitis with increased lifetime cigarette consumption for current smokers, but not ex-smokers

TABLE 2.—Continued

Author, year, country	Population	Cough		Phlegm		Other		Comments
Dean et al., 1978 United Kingdom	6,277 men and 6,459 women, aged 37–67, England, Scotland, and Wales	Morning cough			Men	Bronchitis syndrome		Bronchitis syndrome (cough and phlegm 3 mos/yr, shortness of breath); significant increase of all symptoms with age; prevalence of cough, phlegm, and wheeze increased with number of cigarettes smoked; filter vs. nonfilter cigarette effects small, nonsignificant for most symptoms
		NS	12.5	NS	11.4	NS	3.5	
		SM (filter)		SM (filter)		SM (filter)		
		1–7	19.6		14.4		5.1	
		8–12	32.8		20.8		8.6	
		13–17	36.3		25.4		9.4	
		18–22	44.0		26.9		8.5	
		23–27	50.6		34.2		1.0	
		28–32	56.8		34.5		8.7	
		33+	52.1		28.4		13.8	
					Women			
		NS	9.8	NS	7.5	NS	2.5	
		SM (filter)		SM (filter)		SM (filter)		
		1–7	16.9		13.8		3.8	
		8–12	25.8		16.6		4.2	
		13–17	29.6		16.6		5.1	
		18–22	45.1		25.8		10.6	
		23+	56.6		34.3		12.0	

TABLE 2.—Continued

Author, year, country	Population	Cough	Phlegm	Other	Comments
Higgins et al., 1977, U.S.	4,699 men and women, aged 20–74, Tecumseh			Chronic bronchitis Men NS 5.1 EX 2.6 SM <20/day 13.4 ≥ 20/day 29.9 Pipe/cigar 8.4 Women NS 3.5 EX 4.7 SM <20/day 4.8 ≥ 20/day 15.3	Chronic bronchitis (cough and phlegm ≥ 3 mo/yr); chronic bronchitis increased with age for male smokers; no age trend apparent for male or female nonsmokers; dose–response relationship between chronic bronchitis and cigarette smoking (age adjusted)

TABLE 2.—Continued

Author, year, country	Population	Cough	Phlegm	Other	Comments
Lebowitz and Burrows, 1977, U.S.	2,857 men and women, aged 14–96, Tucson	Chronic cough and/or phlegm			Male prevalence consistently greater than female only in older age groups; frequency of symptoms increased with age; impossible to distinquish effects of aging and increased duration of smoking
		Men			
		NS	10.3		
		SM (pack years)			
		<6	29.0		
		6–20	35.8		
		21–40	47.9		
		41+	61.1		
		Women			
		NS	12.1		
		SM (pack-years)			
		<6	21.0		
		6–20	33.1		
		21–40	40.5		
		41+	60.4		

TABLE 2.—Continued

Author, year, country	Population	Cough	Phlegm	Other	Comments
Bland et al., 1978, Great Britain	6,320 first-year secondary school children, Derbyshire	Morning cough Boys NS 3.1 SM once 2.9 Occas. 4.0 1 per wk. 19.2 Girls NS 1.8 SM once 4.5 Occas. 6.0 1 per wk. 13.5 Cough at other times Boys NS 20 SM once 27 Occas. 34 1 per wk. 47 Girls NS 19 SM once 30 Occas. 35 1 per wk. 47		Breathlessness Boys NS 12 SM once 14 Occas. 22 1 per wk. 35 Girls NS 17 SM once 22 Occas. 29 1 per wk. 40	No questions on phlegm; child's smoking habits more important than parents' smoking habits; parents' smoking habits independently related to most symptom frequencies for boys and girls

TABLE 2.—Continued

Author, year, country	Population	Cough	Phlegm	Other	Comments
Huhti et al., 1978, Finland	1,162 men, aged 25–65, Hankasalmi	All day in winter	All day in winter	Chronic bronchitis	For total group, significant increase with age of cough, phlegm, and severe breathlessness; for nonsmokers, signficant increase with age for phlegm and breathlessness only
		Age NS	NS	Age NS	
		25–39 2	5	25–39 9	
		40–49 2	2	40–49 2	
		50–59 5	8	50–59 15	
		60–69 4	7	60–69 19	
		Age EX	EX	EX	
		25–39 —	11	25–39 11	
		40–49 —	10	40–49 14	
		50–59 4	8	50–59 11	
		60–69 12	18	60–69 28	
		Age SM	SM	SM 1–14 g/day	
		25–39 9	14	25–39 29	
		40–49 19	29	40–49 39	
		50–59 19	24	50–59 31	
		60–69 30	27	60–69 39	
				SM 15–24 g/day	
				25–39 13	
				40–49 45	
				50–59 46	
				60–69 46	
				SM ≥25 g/day	
				25–39 50	
				40–49 63	
				50–59 57	
				60–69 53	

TABLE 2.—Continued

Author, year, country	Population	Cough			Phlegm			Other			Comments
Manfreda et al., 1978 Canada	273 men and 229 women, aged 24–55, two communities in Manitoba	Most days ≥3 mo/yr			Most days ≥3 mo/yr			Wheeze apart from colds			No consistent difference in symptom prevalence for two communities; higher prevalence of cough, phlegm, and wheeze among smokers than nonsmokers or ex-smokers; *CH=Charleswood **PLP=Portage la Prairie
			CH*	PLP**	Men	CH	PLP		CH	PLP	
		NS	8.3	4.0	NS	—	4.0	NS	4.2	8.0	
		EX	8.1	2.9	EX	10.8	5.7	EX	10.8	14.3	
		SM	25.4	31.5	SM	16.9	24.7	SM	26.8	31.5	
					Women						
		NS	—	4.0	NS	—	4.0	NS	3.5	8.0	
		EX	—	10.0	EX	—	5.0	EX	12.1	20.0	
		SM	20.3	31.7	SM	10.2	25.4	SM	25.4	30.2	

TABLE 2.—Continued

Author, year, country	Population	Cough		Phlegm	Other	Comments
Rawbone et al., 1978, Great Britain	10,498 secondary school children, aged 11-17, Hounslow	A little most days		With colds	Frequent colds	*EXPER (ex-smokers and experimental smokers combined); sex differences not significant; nonstandard questions; higher symptom prevalence in younger children not explained
		Age	NS	NS	NS	
		11	26.4	22.8	36.0	
		13	16.7	25.3	32.3	
		15	13.4	24.5	34.3	
			EXPER*	EXPER	EXPER	
		11	20.5	32.3	42.2	
		13	17.3	31.2	36.1	
		15	11.3	29.6	36.3	
			SM	SM	SM	
		11	24.3	56.1	51.1	
		13	25.9	49.6	50.4	
		15	27.4	53.6	39.8	
		A little every day				
			NS			
		11	7.3			
		13	4.2			
		15	4.7			
			EXPER			
		11	7.0			
		13	4.7			
		15	3.5			
			SM			
		11	29.2			
		13	17.8			
		15	13.4			

TABLE 2.—Continued

Author, year, country	Population	Cough	Phlegm	Other	Comments
Bouhuys et al., 1979, U.S.	7,203 residents, aged 7–65+, three communities	Usual cough LE* AN** WI† Men NS 8 10 15 SM 27 32 34 Women NS 7 12 9 SM 13 17 24			Smoking significantly associated with cough, phlegm, wheeze, and dyspnea; prevalence increased significantly with age, slightly higher in urban community; women had lower prevalence of phlegm and higher prevalence of dyspnea than men * LE = Lebanon ** AN = Ansonia † WI = Winnsboro
Burghard et al., 1979, France	29,138 students, aged 14–18, Bas-Rhin Department	Morning NS 13.7 SM 25.7 Day or night NS 16.9 SM 29.1 Chronic NS 2.7 SM 6.6		Breathlessness NS 14.1 SM 22.2	Prevalence of symptoms increased with increasing cigarette consumption; girls had higher prevalence of respiratory symptoms for each smoking category

TABLE 2.—Continued

Author, year, country	Population	Cough	Phlegm	Other	Comments
Gulsvik, 1979, Norway	19,988 people, aged 15–70, Oslo	Morning cough NS 11 EX 15 SM 36 Daytime cough NS 4 EX 7 SM 16 Cough 3 mos/yr NS 3 EX 5 SM 14	When coughing NS 10 EX 18 SM 28	Cough and phlegm periods NS 6 EX 8 SM 16	Cough and phlegm increased more with age for smokers (10–19 cig/day) than nonsmokers; no significant relationship between age and prevalence of periods of cough and/or phlegm; dose–response relationship between number of cigarettes and symptoms reported; data not given
Liard et al., 1980, France	899 men and women, aged 20–60+, (av. 39), Paris	Men NS 16.0 SM 25.4 Women NS 8.1 SM 26.5			Respiratory symptoms (cough and/or phlegm 3 mos/yr. for 2 years); not a random sample; male and female smokers had similar symptom prevalence; female nonsmokers had lower prevalence

TABLE 2.—Continued

Author, year, country	Population	Cough		Phlegm		Other		Comments
Park, 1981, Korea	856 university men and women, aged 18–29, Seoul		Morning		Morning	Breathlessness on exertion		Symptom prevalences apparently not age-adjusted; significance levels not reported; nonstandard questions; symptoms current
		NS	16.0	NS	20.1	NS	23.2	
		EX	31.3	EX	22.9	EX	25.0	
		SM	34.0	SM	26.1	SM	29.7	
			Daytime		Daytime			
		NS	4.2	NS	2.1			
		EX	8.3	EX	14.6			
		SM	10.9	SM	12.0			
			Nightime		Nightime			
		NS	13.5	NS	7.3			
		EX	18.8	EX	10.4			
		SM	19.9	SM	13.2			
Neukirch et al., 1982, France	2,266 secondary school students, aged ≤11–≥18 (mean 14.9), Paris		Usual cough and/or phlegm					21.8% of boys, 32.2% of girls were current smokers; girl smokers had higher symptom prevalence than boys if total lifetime cigarettes >4,000; results probably not age adjusted
			Boys					
		NS	26.1					
		SM	34.9					
			Girls					
		NS	26.9					
		SM	44.7					
Schenker et al., 1982, U.S.	5,686 women, aged 17–74 (mean 44.6), western Pennsylvania, telephone interviews		Chronic cough		Chronic phlegm		Wheeze most days or nights	Cough and phlegm most strongly related to current cigarettes/day; tar content had independent effects; age effect seen for nonsmokers, but not current smokers; symptom prevalences age adjusted
		NS	5.6	NS	4.5	NS	7.2	
		EX	7.5	EX	6.7	EX	8.3	
		SM		SM		SM		
		1–14	9.1	1–14	7.2	1–14	14.4	
		15–24	17.0	15–24	16.7	15–24	18.5	
		25+	31.8	25+	24.8	25+	28.0	

TABLE 3.—Prevalence (percent of cough, phlegm, and other symptoms for nonsmokers (NS), smokers (SM), and ex-smokers (EX), longitudinal studies

Author, year, country	Population	Smoking habits	Symptoms				Comments
			Cough		Phlegm		
		1973	1967	1973	1967	1973	
			Men				
Ferris et al., 1976, U.S.	1,201 men and women, aged 25–74 in 1961, Berlin New Hampshire	NS	6.0	8.5	8.9	7.6	72.3% of men, 78.4% of women followed up; 1973, symptom prevalences, age adjusted to compare with 1967, showed little change
		EX	20.5	9.7	23.3	15.9	
		SM					
		1–14	22.2	25.5	17.9	27.5	
		15–24	35.4	26.5	31.8	30.0	
		25–34	26.1	25.7	33.8	32.4	
		35+	50.6	56.4	37.1	51.9	
			Women				
		NS	4.4	6.2	8.1	7.4	
		EX	3.2	5.2	7.3	10.1	
		SM					
		1–14	10.7	10.0	11.6	9.8	
		15–24	19.5	16.3	21.8	9.8	
		25–34	27.2	16.1	22.5	21.8	
		35+	44.7	31.0	43.1	41.2	
			Cough day or night in winter				
		1966 1971	1966		1971		
Kiernan et al., 1976, Great Britain	2,738 men and women, aged 25, born in 1946, exams in 1966 and 1971	NS NS	5.5		4.9		Effects of chest illness before age 2, father's vocation, and current smoking significant; air pollution effect not significant; current smoking had largest effects *Prevalence, 1966 vs. 1972, $p < 0.05$
		NS SM	7.2		9.6*		
		SM SM	14.3		18.5*		
		SM EX	9.2		5.8		

TABLE 3.—Continued

Author, year, country	Population	Smoking habits		Symptoms				Comments
Leeder et al., 1977, Great Britain	2,130 fathers, mean age 31.0±6.1, 2,148 mothers, mean age 27.9±5.3, children born 1963–1965, London, 6 year followup			Cough/phlegm prevalence range				In male ex-smokers, prevalence of cough/phlegm decreased over time; no significant change in prevalence in female ex-smokers, but numbers were small
				Men				
		1st period	2nd period	1st 3-yr period		2nd 3-yr period		
		NS	NS	8.6–9.6		9.2–11.1		
		NS	SM	4.8–16.9		13.3–20.5		
		SM	SM	25.6–30.2		30.8–34.0		
		SM	EX	21.8–25.3		5.8–20.7		
				Women				
		NS	NS	4.9– 6.8		5.8– 7.3		
		NS	SM	8.2–10.2		13.3–18.4		
		SM	SM	16.3–22.4		23.0–28.4		
		SM	EX	4.1–22.5		12.2–14.3		
Woolf and Zamel, 1980, Canada	302 women, aged 25–54 at initial study, 5-year followup			Cough and/or phlegm		Breathlessness		60% followed up; all subjects maintained consistent smoking habits for 5 years
				1st exam	Final exam	1st exam	Final exam	
		NS		10	14	10	5	
		EX		3	13	18	8	
		SM		56	54	25	21	

TABLE 3.—Continued

Author, year, country	Population	Smoking habits		Symptoms				Comments
				Usual cough		Usual phlegm		
		1972	1978	1972	1978	1972	1978	
				Men				
Beck et al., 1982, U.S.	1,262 white residents, aged 7–55+, Lebanon, Connecticut, exams in 1972 and 1978	NS	NS	5	2	7	3	55% followed up; health indices of respondents and non-respondents similar; symptom prevalence tended to decline, but few changes were significant; *Prevalence, 1972 vs. 1978, $p < 0.5$
		NS	SM	0	0	0	4	
		SM	SM	23	21	22	26	
		SM	EX	25	2*	18	8	
		EX	EX	7	6	12	15	
				Women				
		NS	NS	7	4	5	6	
		NS	SM	0	0	0	9	
		SM	SM	20	14	15	11	
		SM	EX	28	12	8	16	
		EX	EX	10	3	4	1	

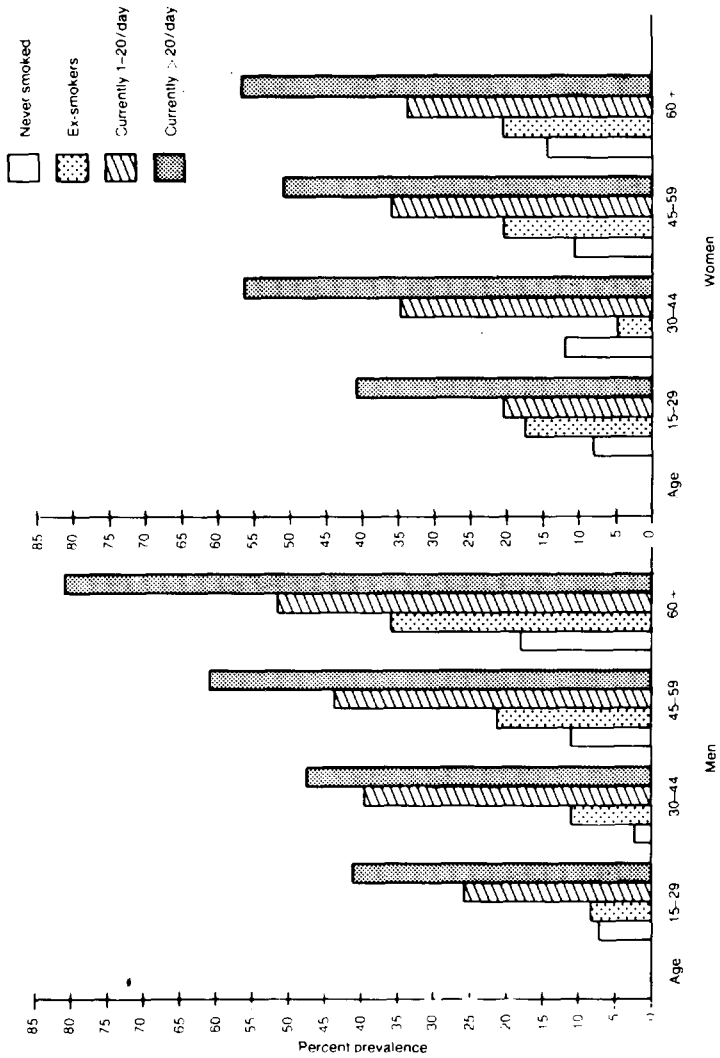

FIGURE 11.—Prevalence of chronic cough and/or chronic sputum among samples of men and women in Tucson, Arizona

SOURCE: Lebowitz and Burrows (1977).

Dose–Response Relationships

The most common measures of dose are the number of cigarettes currently smoked per day and the pack-years of cigarette consumption; the latter estimates lifetime exposure by integrating the number of cigarettes smoked (by pack) and the duration of cigarette use. Errors of memory compromise the accuracy of retrospective information, which may also be biased by differential recall in those

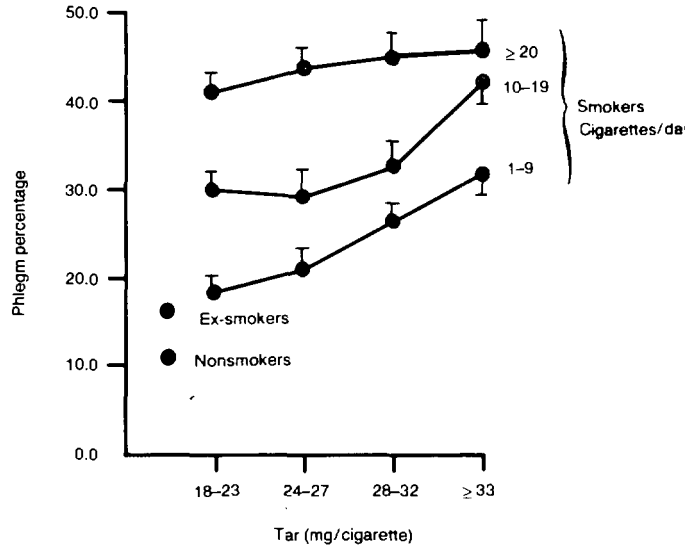

FIGURE 12.—Percentage of smokers with phlegm production (adjusted for age), according to tar yield of cigarettes

SOURCE: Higenbottam et al. (1980).

with and without smoking-related symptoms or diseases. Even accurate reports of current smoking habits fail to take into account all the sources of variation in exposure associated with the material used in cigarette manufacture or generated in the burning of cigarettes. The dose of noxious materials received is also influenced by human behavior, including the number, volume, and timing of puffs taken with each cigarette; retention of smoke in the mouth; depth of inhalation; disposition of the cigarette between puffs; and other aspects of smoking style that are not reproduced by the smoking-machines used to measure tar and nicotine yield.

Prevalence rates of cough or phlegm, or both, generally increase as the number of cigarettes smoked per day increases. The trends illustrated in Figures 11 and 12 were present in both sexes and all age groups (Lebowitz and Burrows 1977; Dean et al. 1978; Higgins et al. 1977; Huhti et al. 1978; Higenbottam et al. 1980; Schenker et al. 1982). Bland et al. (1978) found a dose–response relationship in secondary school children, among whom rates of reporting cough were higher in those who smoked most, even though levels of cigarette consumption were generally reported to be low. At the other extreme of the age range the trend is also apparent, even though symptomatic smokers are more likely than asymptomatic smokers to stop smoking or to reduce their cigarette consumption

(Higgins 1974; Fletcher 1976). Symptoms were more prevalent among heavier smokers of filter cigarettes as well as of nonfilter cigarettes (Dean et al. 1971). Prevalence rates of cough, phlegm, chronic bronchitis, and mucus hypersecretion show a similar pattern of association with pack-years of exposure (Tager and Speizer 1976; Lebowitz and Burrows 1977). Rates of incidence and remission observed in longitudinal studies add further support to the strong evidence that respiratory symptoms increase as exposure to cigarette smoke increases (Table 3).

In their study of more than 18,000 male civil servants in London, Higenbottam and colleagues (1980) found that the percentage of smokers who produced phlegm increased with increased daily cigarette consumption and also with increasing tar content of cigarettes among those who smoked less than 20 cigarettes a day. Symptoms were prevalent about equally among smokers of 20 or more cigarettes per day, regardless of the tar yield of the brands they used (Figure 12).

Schenker et al. (1982) reported the relationship of tar content of cigarettes to respiratory symptoms in a cross-sectional telephone survey of 5,686 adult women in rural Pennsylvania. The risk of chronic cough and phlegm was more strongly affected by the number of cigarettes smoked per day than by tar content. Cough and phlegm were reported least often by never smokers and with increasing frequency as the number of cigarettes smoked per day increased. Tar content of cigarettes was significantly associated with symptoms of chronic cough and phlegm—especially cough—and its effects were independent of the number of cigarettes smoked per day in a multiple logistic analysis. The risk (relative odds) of chronic cough for smokers of high tar cigarettes (20 or more mg) was approximately twice that for smokers of an equivalent number of low tar cigarettes (10 or less mg). A limitation of this cross-sectional study was the determination of tar content for current cigarettes only, rather than for lifetime smoking habits. Although the apparent relationship between tar content and symptoms could have been caused by changes in smoking habits, this was considered unlikely because symptomatic smokers tend to reduce their consumption of cigarettes more than asymptomatic smokers (Fletcher et al. 1976) and may also switch to low yield cigarettes. In this situation, any reported effect of tar content on symptoms would be an underestimate.

In summary, the prevalence of symptoms increases with dose of smoke exposure, when dose is measured by number of cigarettes smoked per day or tar content of the cigarette smoked.

Relationship of Cough and Phlegm to Sex and Age

Prevalence rates of cough and phlegm ascertained in epidemiological studies generally increase with age and are higher in men than

in women, as shown in Figure 11 and Tables 2 and 3. Rates also vary with smoking habits. Rates in nonsmokers better clarify associations of symptoms with age and sex than do rates in smokers, since they are less confounded by variations in exposure to cigarette smoke. However, recent evidence linking passive smoking with increased prevalence of respiratory symptoms suggests that rates in nonsmokers may be in excess of those that would be found in a population completely free of exposure to cigarette smoke (Lefcoe et al. 1983; Weiss et al. 1983).

Rates of reporting cough or phlegm or both were roughly equal in nonsmoking men and women in several cross-sectional studies (Bland et al. 1978; Higgins et al. 1977; Lebowitz and Burrows 1977; Manfreda et al. 1978; Neukirch et al. 1982; Rawbone et al. 1978). Rates were higher in nonsmoking men in some populations (Dean et al. 1977; Liard et al. 1980; Tager and Speizer 1976). Bouhuys et al. (1979) found no sex difference in the prevalence of cough, but a higher rate of reporting phlegm in male nonsmokers (Table 2). In most of these studies, the rates were not corrected for exposures to other respiratory irritants in the workplace or in the general environment.

In general, symptoms are more prevalent in male smokers than in female smokers (Table 3). However, differences in prevalence rates between the sexes are generally smaller or absent when comparisons are made between men and women who smoke similar numbers of cigarettes. Lebowitz and Burrows (1977) found that the excess prevalence of symptoms in male smokers compared with female smokers tended to be greatest at older ages, where there are also the greatest differences in smoking behavior. Men in these birth cohorts tend to have begun smoking earlier in life, smoke more cigarettes per day, inhale more deeply, and smoke higher tar and nicotine or unfiltered cigarettes. Two studies from France, Burghard et al. (1979) and Neukirch et al. (1982), concentrated on high school students. In general, the prevalence of smoking was similar for both boys and girls for the two studies, although the Neukirch group found a somewhat higher rate among the girls (46 percent versus 39 percent). Slightly more boys than girls, however, smoked more than 10 cigarettes per day. In these two studies, the prevalence of symptoms was higher among female smokers than among male smokers. These data suggest that the past differences in prevalence of symptoms between the sexes is largely attributable to differences in cigarette consumption. These differences were substantial in the past, and are still present among older adults, whereas current smoking practices are about the same in male and female adolescents and young adults.

Prevalence rates of cough, phlegm, and chronic bronchitis increased with increasing age in the U.S. population samples studied

by the National Center for Health Statistics (1981) and in several of the cross-sectional studies cited in Table 2. However, differences in rates of reporting symptoms among people of different ages may relate to effects of aging, differences in current exposures, or differences in exposure to cigarette smoke or other noxious agents in the past. It is therefore difficult or impossible to use cross-sectional data to separate effects of aging from effects of duration, dose, and nature of cigarette smoke exposure throughout life. Longitudinal studies provide information on time trends, both in exposure and in onset and course of disease. Nevertheless, conclusions may be incorrect if people who drop out of longitudinal studies are different from those who continue to participate.

Prevalence of symptoms increased with increasing age among men in cross-sectional data from Tucson (Figure 11), but the trend was more apparent among smokers and ex-smokers than among nonsmokers. However, Lebowitz and Burrows (1977) could not distinguish between an association caused by increasing age and an association due to increasing duration of exposure to cigarette smoke in smokers because the two were so highly correlated. Among women, symptoms were reported more frequently at ages 30 to 44 than at ages 15 to 29 (except by ex-smokers), but prevalence rates were essentially the same for the three groups over age 30. Higgins et al. (1977) found that there was no increase in cough and phlegm with increasing age in male or female nonsmokers in Tecumseh (Michigan), whereas prevalence rates increased with increasing age in male smokers. The pattern in female smokers was similar to that in Tucson and showed an increase with age up to age 30 or 40, but rates declined with increasing age after age 50. The extent to which these patterns related to amount smoked or duration of smoking was not reported, but these older birth cohorts of women probably began to smoke later in life and smoked fewer cigarettes per day, according to national smoking survey data.

In other cross-sectional studies cited in Table 2, symptom prevalence increased with age in the populations studied (Bouhuys et al. 1979; Dean et al. 1977; Gulsvik 1979; Huhti et al. 1978; Tager and Speizer 1976), but the trend was noted by Gulsvik to be less in nonsmokers. Huhti et al. found a significant increase with age among nonsmokers for phlegm and dyspnea only. Schenker et al. (1982) observed a trend for nonsmokers but not for smokers, and Tager and Speizer found that adjusting for smoking eliminated the trend with age.

Prevalence rates of cough and phlegm on two occasions 3 to 6 years apart are shown in Table 3 for five recent longitudinal studies of populations in the United States, Canada, and Great Britain. Kiernan et al. (1976), Leeder et al. (1977), Woolf and Zamel (1980), and Beck et al. (1982) found little change in the prevalence of

symptoms among continuing nonsmokers during the followup interval of up to 6 years. The rates among nonsmokers reported by Ferris et al. (1976) are similar on the two occasions, but symptoms were presented by smoking habits at followup only, and any effect of age was deliberately adjusted out because the authors' purpose was to evaluate effects of changes in smoking, changes in pollution, and trends over time independent of changes in age. Cough and phlegm appeared to be more frequent at followup in the persistent smokers studied by Kiernan et al. (1976) and Leeder et al. (1977), and about the same in women studied by Woolf and Zamel (1980) and in men studied by Beck et al. (1982). However, rates were slightly lower at followup in the female smokers followed by Beck. Even though starting to smoke or quitting can be eliminated as the explanation for increases or decreases in symptom prevalence over the course of these studies, it is possible that changes in the number or type of cigarettes smoked by persistent smokers influenced the prevalence of symptoms. The duration of followup in all these studies was relatively brief, and it is still difficult to distinguish between effects of aging and effects of duration, amount, and nature of exposure to cigarette smoke in smokers, even when major changes in smoking behavior are controlled. However, available data suggest that age itself is not the major factor responsible for differences in the frequency or distribution of symptoms in populations of nonsmokers and smokers.

Relationship of Cough and Phlegm to Airflow Obstruction

Many cross-sectional studies have found associations between cough, phlegm, chronic bronchitis, or mucus hypersecretion and reduced levels of pulmonary function. The forced expiratory volume at 1 second (FEV_1) has been measured in most clinical studies and in nearly all epidemiological studies, and mean levels of FEV_1 are generally slightly lower in groups of people who report respiratory symptoms (USPHS 1964, 1971; USDHEW 1979; USDHHS 1980a, 1981). Recent studies have compared other measures of pulmonary function in people with and without symptoms and have provided longitudinal data on pulmonary function for symptomatic and asymptomatic smokers and nonsmokers. Attention has been given to understanding the natural history of chronic airways obstruction and the interrelationships of respiratory symptoms, levels and rates of decline of pulmonary function, and their independent and interrelated associations with cigarette smoking. Several investigators have emphasized the desirability of identifying in advance those smokers who will develop severe COLD; symptoms and other characteristics have been evaluated as potential predictors of morbidity or mortality from COLD.

Fletcher and colleagues (1976) found that the age–height standardized FEV_1 at the initial survey of their population of working men in London was inversely related to the volume of sputum produced in the first hour after getting up. The regression of FEV_1 on age, given height, was steeper for symptomatic cigarette smokers than for asymptomatic smokers or nonsmokers. However, the authors caution that men may develop symptoms as they age and change from one regression slope to the other.

Burrows et al. (1977a) found that an index of cough or sputum was related to FEV_1 percent predicted when pack-years of smoking were controlled in a multiple regression analysis. Regressions of FEV_1 percent predicted on pack-years are shown for people with and without chronic cough and sputum in Figure 13; the intercept at 0 pack-years was lower and the decline in FEV_1 with increasing pack-years was significantly greater for those with chronic cough and sputum than for those with no cough or sputum. The authors calculated that values of FEV_1 were lower by about 10 percent in people with cough and sputum, regardless of smoking habits, and that values declined by about 4 percent of predicted for each 10 pack-years of smoking in people with cough and sputum and by about 2 percent in subjects without productive cough. There was a significant relationship between FEV_1 and pack-years of smoking in asymptomatic smokers in this population. A weaker relationship between cough and sputum and $\dot{V}_{max\,25\%}$ was also found to be independent of pack-years of smoking; however, prediction equations for flow rates have been revised substantially (Knudsen 1983), and the extent to which relationships between the revised flow rates and pack-years of smoking differ in symptomatic and asymptomatic subjects has not been reported.

Dosman et al. (1976) found poor correlations between respiratory symptoms and dynamic lung compliance, closing volume, closing capacity, slope of phase III, and helium flow-volume curves in a study of 49 smokers and 60 nonsmokers who were recruited from a smoking cessation clinic, a personnel department, and the staff of a laboratory.

In their community-based studies of children and adults, Bouhuys and colleagues (1977) studied relationships between respiratory symptoms and loss of lung function in smokers and nonsmokers. They found that residual values (observed–predicted) of FVC, FEV_1, PEF, $MEF_{50\%}$, and $MEF_{25\%}$ were not significantly different in people with no symptoms or only one symptom when analyses were done separately for adult white male smokers and nonsmokers. When a symptom score was used to combine information on usual cough, usual phlegm, wheeze, and dyspnea, decrements in lung function were greatest among those with most symptoms.

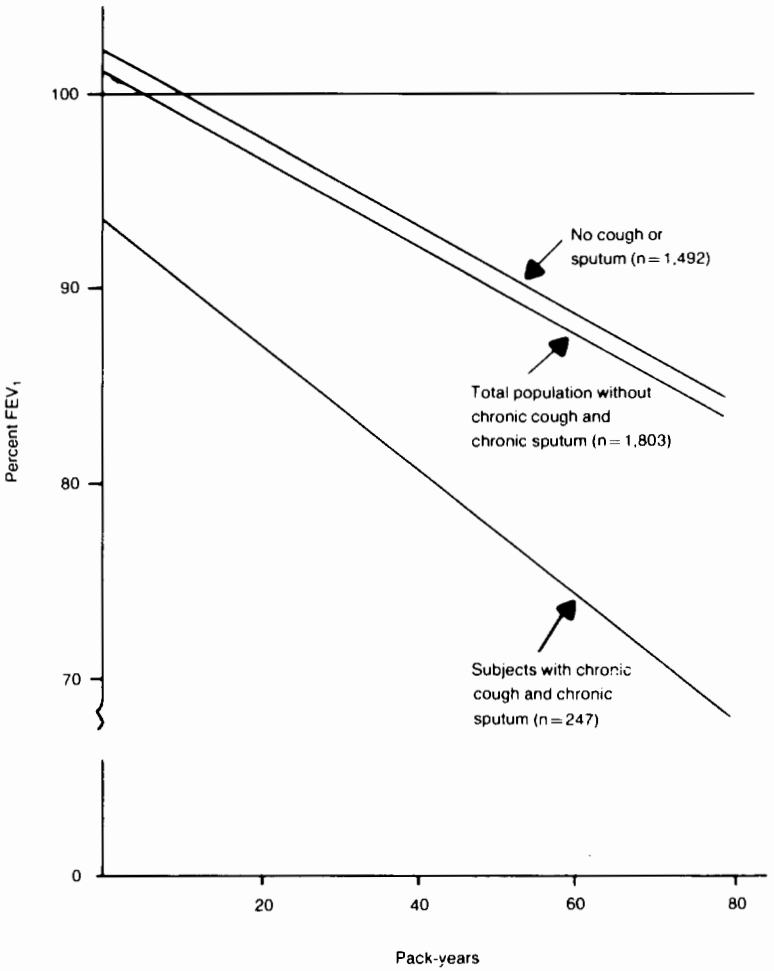

Figure 13.—Percentage distribution of predicted forced expiratory volume in 1 second (FEV_1) versus pack-year of cigarettes smoked, by cough and sputum history

SOURCE: Burrows et al. (1977a).

In a study (Detels et al. 1982) designed to assess the relative sensitivity and specificity of symptoms, the flow-volume curve (FV), the single breath nitrogen test (SBNT), and specific airway conductance (S_{Gaw}) for identifying COLD were compared with the FEV_1/FVC ratio and with one another in 1,201 residents of Los Angeles 25 to 29 years old. The tests were done in 1978–1979 at a followup examination of a previously defined cohort. Prevalence rates of cough and sputum were 9 percent in never smokers, 26

percent in current smokers, and 33 percent in smokers of 20 or more cigarettes a day. Prevalence rates of an abnormal FEV_1/FVC ratio in these groups were 8, 23, and 33 percent, respectively (the FEV_1/FVC ratio was considered abnormal if it was below the 95th percentile for never smokers without a history of respiratory illness). The researchers found that there was very little overlap between the presence of productive cough and abnormal tests, and that none of the tests of function showed reasonable concordance with this symptom. Lack of reasonable concordance meant that none of the other tests were abnormal in 50 percent or more of the individuals with productive cough. In this study, the FEV_1/FVC ratio was used as the standard against which the sensitivities of the other tests were judged; the sensitivity of the FEV_1/FVC itself was evaluated by its agreement with those tests found to be sensitive in the study. The lack of an independent method for identifying COLD, the cross-sectional nature of these data, and the way in which analyses were done restrict the ability to make biological inferences about the independence of the effects of cigarette smoking that lead to cough and sputum or to chronic airflow limitation. However, the authors note their findings are consistent with the hypothesis that effects of smoking on cough and sputum are independent of effects on airflow limitation.

Insights into the course and pathogenesis of COLD have been developed by Fletcher and his colleagues from observations made during their 8-year longitudinal studies of levels and rates of decline in lung function in middle-aged working men in London (Fletcher 1976; Fletcher et al. 1976). These investigators found that various measures of sputum production were correlated with FEV_1 standardized for height and age, and that this correlation was weakened only slightly by adjusting for smoking habits. The researchers maintained that the association between sputum production and pulmonary function could be due entirely to a common causation. Some men with mucus hypersecretion had normal FEV_1; conversely, some men with airflow obstruction did not report phlegm. Nevertheless, the relationship between phlegm and reduced FEV_1 was strong enough to give rise to an estimated reduction in FEV_1 of about 0.1 liters for every ml of sputum expectorated in the first hour after getting up. However, because decline in FEV_1 (FEV_1 slope) was not related to measures of sputum production when level of FEV_1 and smoking habits were controlled, the researchers concluded that mucus hypersecretion is not a cause of accelerated decline in FEV_1. Furthermore, there was no evidence that short-term changes in sputum production were associated with short-term changes in FEV_1. The researchers concluded that the association between expectoration and reduced FEV_1 is caused by the increased susceptibility of some people to both expectoration and excessive loss of FEV_1 when they are exposed to cigarette smoke or, presumably, to

other noxious materials. This study has made important contributions to understanding the natural history of chronic bronchitis and emphysema, but the duration of followup was only 8 years, the men were 30 to 59 years of age at the start of the study, and their mean age was 51 years at the midpoint. Similar studies of younger men and women and observations over longer periods of time are needed to extend these findings.

Johnston et al. (1976) found that sputum volume was not related to decline in FEV_1 in a 10-year followup study of chronic bronchitic patients. There was no difference in sputum volume between patients whose FEV_1 fell by more than 33 percent and controls (matched on initial FEV_1) whose FEV_1 did not fall. Furthermore, sputum volume was reduced in response to stopping smoking or to antibiotic treatment, whereas rate of decline of FEV_1 was unaffected. In this and other studies (Higgins et al. 1970; Fletcher et al. 1976; Peto et al. 1983) FEV_1 was strongly predictive of morbidity and mortality, whereas respiratory symptoms were not.

Woolf and Zamel (1980) studied "normal" employed women aged 25 to 54 in a longitudinal study designed to identify smokers at increased risk of developing COLD. Ventilatory function was measured at the beginning and at the end of a 5-year period during which smoking habits and symptoms were ascertained annually. Differences between initial and followup values of pulmonary function tests were expressed as a percentage of the initial value and compared in persistent nonsmokers and persistent smokers who either consistently reported or consistently denied cough or sputum. The decline in FEV_1, FEV_1/FVC, and $FEF_{25-75\%}$ was greater in symptomatic smokers than in asymptomatic nonsmokers, but not significantly different in asymptomatic smokers compared with either nonsmokers or symptomatic smokers. The average number of cigarettes smoked during the course of the study was greater for smokers with cough and sputum. Change in $FEF_{25-75\%}$ was evaluated in individual smokers, and no association was detected between cough and sputum and percentage change in this measure of lung function. The investigators identified one group of smokers whose decline in $FEF_{25-75\%}$ was similar to that in nonsmoking women and another group with a greater decline; cigarette consumption was similar in the two groups. The investigators concluded that individual susceptibility is an important determinant of the effect of cigarette smoking, because some women develop symptoms and others remain symptomless but experience rapid worsening of ventilatory function. However, they noted a tendency for both cough and sputum and rapid worsening of ventilatory function to coexist. The number of women in some groups was very small, and the measure of decline in lung function used by these researchers does not take into account regression to the mean or assess absolute

reduction; those with smaller initial values will have greater percentage reductions for a constant absolute reduction in function.

Followup studies at 10 and 15 years of the Tecumseh, Michigan, population showed that incidence rates of obstructive airways disease were higher in men and women who reported cough, phlegm, or both symptoms (chronic bronchitis) at entry compared with those who denied these symptoms (Figure 14) (Higgins et al. 1982). Both cough and chronic bronchitis were significant predictors of obstructive airways disease in men even when smoking habits were controlled in multiple logistic analyses. However, respiratory symptoms were poorer predictors of impaired pulmonary function at followup than were smoking habits and baseline levels of lung function. In a multiple logistic model with age, smoking habits, and level of lung function as risk factors, over 60 percent of the 10-year incidence cases developed among men and women in the top 10 percent of the risk distribution, whereas only 36 percent of incidence cases were in the top decile of risk when cough, rather than FEV_1, was used as a risk factor (Higgins 1984).

Summary

Cigarette smoking is associated with respiratory symptoms, including mucus hypersecretion, and with prevalence and incidence of COLD manifested by irreversibly impaired pulmonary function. While some smokers develop both conditions, and those with cough and phlegm are at increased risk of developing airways obstruction, the conditions can occur separately by mechanisms that are imperfectly understood but appear to be different. The excess risk of reduced FEV_1 or COLD in symptomatic smokers compared with asymptomatic smokers may be a reflection of increased susceptibility in some individuals. However, it may also be a measure of increased dose of cigarette smoke, in that smokers who report cough and phlegm tend to smoke more heavily than smokers who deny these symptoms, and measures such as numbers of cigarettes smoked per day are not precise enough to control adequately for the amount of smoke exposure. The rate, number, and volume of puffing as well as the depth of inhalation can vary substantially between smokers and are important additional measures of cigarette smoke exposure dose.

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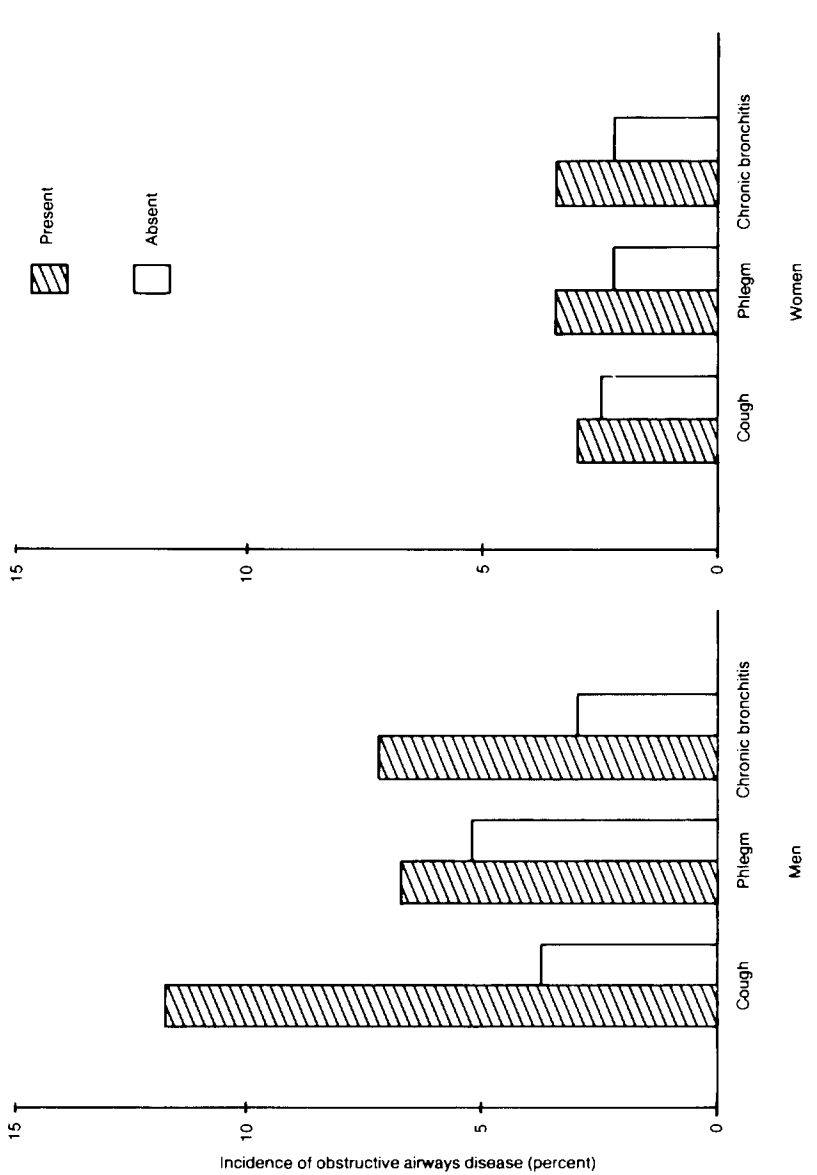

FIGURE 14.—Age-adjusted 15-year incidence of obstructive airways disease, by cough, phlegm, and chronic bronchitis status at entry to the study, Tecumseh, ages 16 to 64, 1962–1979

SOURCE: Higgins et al. (1982).

CHRONIC AIRFLOW OBSTRUCTION

Introduction

Airflow obstruction is the physiological consequence of disease processes that narrow the airway. In asthma the obstruction is reversible with pharmacologic bronchodilation, whereas the obstruction associated with airways damage and emphysema is often not reversible. The terminology with regard to permanent airflow obstruction has varied. The 1958 Ciba Foundation Guest Symposium proposed "generalized obstructive lung disease," which was subdivided into "asthma" and "irreversible or persistent obstructive lung disease" (1959); in the 1962 recommendations of the American Thoracic Society, "chronic obstructive bronchitis" was the only definition that mentioned abnormality of expiratory flow (American Thoracic Society 1962). In 1975, a joint committee of the American College of Chest Physicians and the American Thoracic Society recommended the term "chronic obstructive pulmonary disease" (American College of Chest Physicians and American Thoracic Society 1975). Thurlbeck (1976, 1977) has advocated the use of "chronic airflow obstruction," a functionally based definition that does not specify the underlying disease processes. Previous Reports of the Surgeon General have used varying terminology, including "chronic bronchopulmonary disease" in 1964, "chronic obstructive bronchopulmonary disease" in 1971, and "chronic obstructive lung disease" in 1979 (USPHS 1964, 1971; USDHEW 1979).

These definitions, however, cannot be readily applied to identify specific populations. Physiologists, epidemiologists, and clinicians often use differing approaches in determining whether airflow obstruction is present (Fletcher 1978). Physiologists, with the capability for making sophisticated laboratory measurements of airflow obstruction, may regard subtle early abnormalities of flow as definitive. In the community, epidemiologists have generally used spirometry as the primary method for assessing airflow obstruction. For epidemiologic purposes, airflow obstruction is usually defined by a forced expiratory volume in 1 second (FEV_1) less than a particular level after standardization for sex, age, and height, or by a ratio of the FEV_1 to the forced vital capacity (FVC) below a specified value. Tests of forced exhalation, such as the FEV_1, have the advantage of sensitivity to abnormalities of both the lung parenchyma and the airways (Mead 1979). Clinicians are more likely to detect and diagnose airflow obstruction when it is advanced and symptomatic. As would be anticipated, the differing approaches of physiologists, epidemiologists, and clinicians may lead to differing estimates of the frequency of airflow obstruction.

The natural history of chronic airflow obstruction in adults has been partially described by several recent prospective investigations:

Howard (1970), Bates (1973), Sharp et al. (1973), Fletcher et al. (1976), Fletcher and Peto (1977), Bosse et al. (1981), Beck et al. (1982), and Clement and van de Woestijne (1982). Although these investigations did not characterize the course of airflow obstruction across the entire human lifespan, the results provide a conceptual model for considering its development (Figure 15). Ventilatory function, generally measured by the FEV_1, increases during childhood and reaches a maximum level during early adulthood (Cotes 1979; Knudson et al. 1983). From this peak; the FEV_1 gradually and progressively declines with age. In people who develop airflow obstruction, a similar gradual loss of function occurs, but at a more rapid rate (Fletcher et al. 1976; Speizer and Tager 1979). Continued excessive loss of FEV_1 eventually results in symptomatic airflow obstruction when ventilatory function reaches a level at which activities are limited and dyspnea occurs. Evaluation by a physician for symptoms may lead to a clinical diagnosis at this point in the natural history of the disease process. This model may not satisfactorily describe the development of airflow obstruction in all individuals (Burrows 1981), but the accumulating evidence, reviewed below, indicates that a sustained excessive loss of ventilatory function most often leads to the development of clinically important chronic airflow obstruction.

In the conceptual model (Figure 15), there are three different measures of the frequency of airflow obstruction in a particular population: the prevalence of reduced ventilatory function as measured by the FEV_1, the FEV_1/FVC ratio, or other physiological parameters; the prevalence of physician-diagnosed airflow obstruction; and the frequency of excessive functional loss in a population followed over time. The first two measures can be determined from a single cross-sectional survey, whereas the third requires longitudinal observation. At present, scant data are available for the third category. The prevalence of physician-confirmed airflow obstruction is determined not only by the proportion of affected people in the population, but also by the patterns of medical care access and usage and the diagnostic practices of individual physicians. Furthermore, the clinical labels applied by physicians to people with airflow obstruction are variable and may include "chronic bronchitis," "emphysema," "COLD," and other terms. Thus, estimates of disease prevalence based on reported physician diagnoses may differ from those derived from physiological assessment.

Prevalence of Airflow Obstruction

Numerous populations throughout the world have been surveyed to assess the prevalence of airflow obstruction (Stuart-Harris 1968a, 1968b; Higgins 1974). Most often, the investigative techniques have included a respiratory symptoms questionnaire and measurement of pulmonary function, generally with a spirometer or peak flow meter.

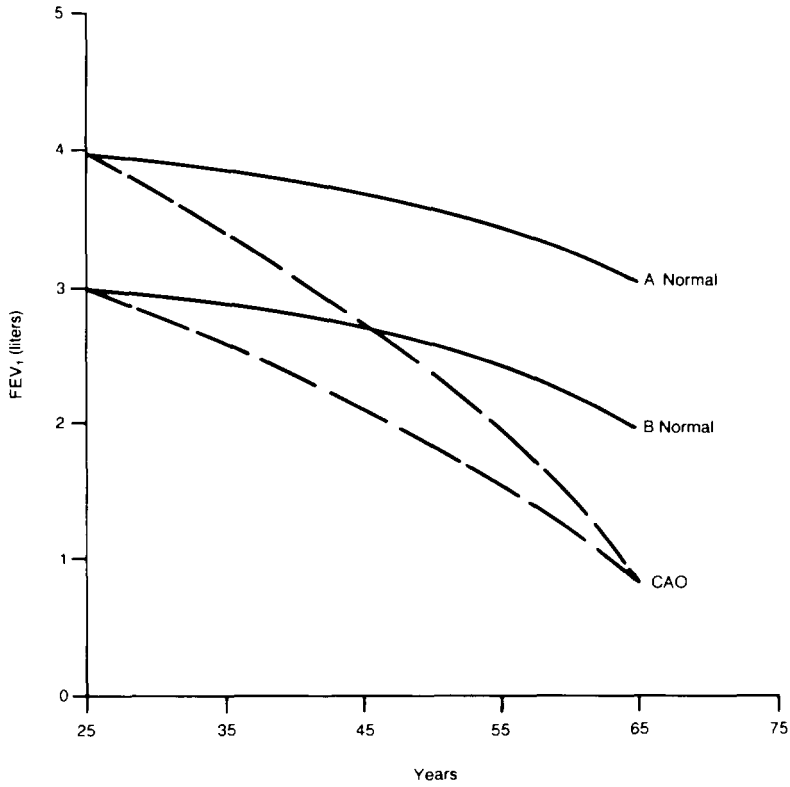

FIGURE 15.—Decline of FEV_1 at normal rate (solid line) and at an accelerated rate (dashed line)

NOTE: A: person who has attained a "normal" maximal FEV_1 during lung growth and development; B: person whose maximal FEV_1 has been reduced by childhood respiratory infection.

SOURCE: Samet et al. (1983).

The latter technique has the disadvantage of effort dependence. Early recognition of the potential problem of observer bias led to the development of standardized methods (Cochrane et al. 1951; Higgins 1974; Ferris 1978). Thus, most investigators throughout the world have used the British Medical Research Council questionnaire in the original form or with some modifications (Samet 1978). Standardization has been less uniform for lung function measurements, but minor variations in procedures would not introduce important differences in disease prevalence among the various populations examined.

Although many different populations have been surveyed since the 1950s, surprisingly few published reports provide data concerning the prevalence of airflow obstruction in the general population

(Tables 4 and 5). Comparisons among the available studies are limited by varying methodologies and inconsistent approaches in calculating rates. For example, only crude rates are available in some reports, and reference populations for age standardization also vary. The investigations summarized in Tables 4 and 5 were selected because they offer estimates of the prevalence of airflow obstruction in defined community-based samples. Those reports that describe mean levels of lung function parameters but not their distributions were excluded. Investigations of specific occupational groups were also excluded because prevalence estimates based on such populations may be biased by the overrepresentation of healthy persons (Monson 1980) and workplace exposures may have affected the frequency of disease.

For the United States, the available information spans the time period 1961 to 1979 and covers most geographic regions (Table 4). Regardless of the definition, it is apparent that airflow obstruction is common among adults in the United States. A higher proportion of men than women is affected, and the prevalence increases with age (Ferris and Anderson 1962; USPHS 1973; Lebowitz et al. 1975; Detels et al. 1979; Samet et al. 1982). Few minority populations have been studied. In New Mexico, Hispanic whites had a lower prevalence of physician-diagnosed current chronic bronchitis or emphysema than non-Hispanic whites (Samet et al. 1982). Although blacks have been included in several surveys (Bouhuys et al. 1979), prevalence estimates for this racial group have not been published. The available data (Table 4) do not permit a satisfactory assessment of changes in prevalence rates with time over the years 1961 to 1979.

The National Health and Nutrition Examination Surveys (NHANES 1) included spirometry in their evaluation of a representative sample of the U.S. population. The numerical values for these measures are reported by age, sex, and smoking status for the white population in the tables in the appendix to this chapter. The changes in mean values of these measures between age groups are also presented for white male and female smokers and nonsmokers in Figures 16 through 23. Differences between smokers and nonsmokers are evident for each of these spirometric measures. These differences are portrayed for successive age groups at one point in time, and therefore cannot be used to describe the changes with age or smoking status that one would expect in an individual or population followed sequentially. These data represent only those people in the study population who were willing and physically able to maximally exert themselves on the various spirometry tests. Others were disqualified by the examining physician because of existing medical conditions. The sampling nonresponse was higher among segments of the population expected to perform less well on the test, including people with existing airflow limitation. Therefore,

TABLE 4.—Prevalence of indices of airflow obstruction in selected U.S. adult populations

Author, year of study, location, reference	Number and type of population	Index	Prevalence (per 100)		
Higgins and Kjelsberg, 1959–1960, Tecumseh, Michigan (*1967*)	4,500 men and women, 20 years or older, community sample	Emphysema based on physician history and examination	Men Women		4.1[1] 1.1[1]
Higgins, 1962–1979, Tecumseh, Michigan (*1983*)	4,916, 4,443, and 4,930 men and women, 16 to 74 years old, in 1962–65, 1967–69, 1978–79	Obstructive airways disease: FEV_1 less than 65% predicted, and FEV_1/FVC ratio less than 80%		Men	Women
			1962–65	4.8[2]	2.5[2]
			1967–69	3.7[2]	1.4[2]
			1978–79	3.7[2]	2.2[2]
Ferris and Anderson, 1961, Berlin, New Hampshire (*1962*)	1,167 men and women, community sample	Irreversible obstructive lung disease, including wheezing, dyspnea, or FEV_1/FVC ratio less than 60%	Men Women		8.6[1] 8.1[1]
Mueller et al., 1967, Glenwood Springs, Colorado (*1971*)	609 men and women, community sample	Chronic airway obstruction: FEV_1/FVC ratio less than 60%	Men Women		13.2[1] 1.5[1]
U.S. Public Health Service, 1970, United States (*1973*)	116,000 men and women, nationwide sample	Presence of the condition during the previous year	Chronic bronchitis Men Women		3.1[1] 3.4[1]
			Emphysema Men Women		1.0[1] 0.3[1]

TABLE 4.—Continued

Author, year of study, location, reference	Number and type of population	Index	Prevalence (per 100)
Lebowitz et al., 1972–1973, Tucson, Arizona (*1975*)	3,805 men and women, adults and children, community sample	Physician-confirmed illness, current	Men over 44 years Chronic bronchitis 10.2 Emphysema 13.3[1] Women over 44 years Chronic bronchitis 9.0[1] Emphysema 4.3[1]
Knudson et al., 1972–1973, Tucson, Arizona (*1976*)	3,805 men and women, adults and children, community sample	FEV_1 and FEV_1/FVC ratio lower than 95th percentile for "normal"	Asymptomatic cigarette smokers FEV_1 7.8[1] FEV_1/FVC 8.1[1]
Detels et al., 1973–1974, Burbank and Lancaster, California (*1979*)	3,465 and 4,509 men and women, in Burbank and Lancaster, respectively, community samples	FEV_1 less than 50% of predicted value	Lancaster 18–59 yrs 0.8[2] 60 yrs 6.5[2] Burbank 18–59 yrs 1.0[2] 60 yrs 6.2[2]
Tager et al., 1973-1974, East Boston, Massachusetts (*1978*)	1,770 men and women, community sample of index subjects and their relatives	FEV_1 less than 65% of predicted	Men 5.6[1] Women 3.4[1]
Ferris et al., 1974–1977, six cities in the U.S. (*1979*)	7,909 men and women, community sample	FEV_1/FVC less than, equal to 60%	Men 5.0[1] Women 1.9[1]

TABLE 4.—Continued

Author, year of study, location, reference	Number and type of population	Index	Prevalence (per 100)	
Samet et al., 1978–1979, Albuquerque, New Mexico *(1982)*	1,722 men and women, community sample	Physician-diagnosed current chronic bronchitis or emphysema	Non-Hispanic whites	
			Men	3.6[2]
			Women	3.4[2]
			Hispanic whites	
			Men	0.8[2]
			Women	1.8[2]

[1] Crude rate.

[2] Age-adjusted rate.

[3] Age and sex-adjusted rate.

TABLE 5.—Prevalence of indices of airflow obstruction in selected adult non-U.S. populations

Author, year of study, location, reference	Number and type of population	Index	Prevalence (per 100)	
Anderson et al., 1963, Chilliwack, British Columbia (*1965*)	558 men and women, community sample	Obstructive lung disease, including wheezing, dyspnea, or FEV_1/FVC ratio less than 60%	Men Women	12.6[1] 8.7[1]
		FEV_1/FVC ratio less than 60%	Men Women	7.3[1] 3.5[1]
Mimica, 1969, Croatia, Yugoslavia (*1975*)	4,214 men and women, samples of six communities	FEV_1/FVC ratio less than 60%	Men Women	8.3[1] 1.9[1]
Sawicki, 1968, Krakow, Poland (*1977*)	4,355 men and women, community sample	FEV_1/FVC ratio less than 60%	Men Women	7.0[1] 5.0[1]
Huhti et al., 1968-1970, Hankasalmi, Finland (*1978*)	1,162 men, community sample	FEV_1/FVC ratio less than 60%	Men	7.6[1]
Brown and Gajdusek, year not stated, Western Caroline Islands (*1978*)	240 men and women, community sample	Chronic obstructive airway disease: clinical and spirometric criteria	Men and women	7.9[1]
Anderson, year not stated, Lufa, Papua New Guinea (*1979*)	770 men and women, 25 years or older, community sample	FEV_1/FVC ratio less than 60%	Men Women	9.0[1] 3.6[1]

[1] Crude rate.

the estimated means are probably overestimates of the true population values. Nevertheless, the figures clearly portray the magnitude of the effect that smoking exerts on expiratory flow rates in a national population sample.

Airflow obstruction is also prevalent outside the United States (Table 5). The disease can be identified in both technologically advanced and less developed populations. As in the United States, in other countries the prevalence of airflow obstruction is higher among men than among women.

Determinants of Airflow Obstruction

Introduction

Current understanding of the natural history of airflow obstruction suggests that risk factors operative during both childhood and adulthood may influence the development of disease. In the conceptual model proposed in Figure 15, childhood factors might increase the risk of airflow obstruction by lowering the maximum FEV_1 attained during lung growth and development, by predisposing to increased FEV_1 decline during adulthood, or by both mechanisms (Speizer and Tager 1979). During adulthood, in the model of Figure 15, risk factors for airflow obstruction must increase the rate at which lung function deteriorates.

Many endogenous and exogenous determinants of the development of airflow obstruction have been postulated (Tables 6 and 7). However, in spite of over 30 years of intensive investigation, the available data are definitive only for cigarette smoking and for α_1-antitrypsin deficiency (Speizer and Tager 1979; USDHHS 1980).

Cigarette Smoking and Chronic Airflow Obstruction

In nearly every population studied worldwide, cigarette smoking is the predominant determinant for the prevalence of airflow obstruction (Tables 8, 9, and 10). The uncommon exceptions primarily involve populations in whom severe chest infections or wood smoke exposure may have an etiological role (Woolcock et al. 1973; Anderson 1979a). The relationship between cigarette smoking and airflow obstruction has been variably described in the published reports. In some, the prevalence of airflow obstruction has been considered; in others, mean values of lung function parameters have been compared across categories of smoking use. In several more recent analyses, multiple regression or other multivariate techniques have been used for more careful characterization of dose–response relationships. Because the epidemiologic criteria for airflow obstruction are generally based on the FEV_1, this section focuses on studies that have included measurements of this parameter. The selected studies involve community samples (Tables 8 and 9) and

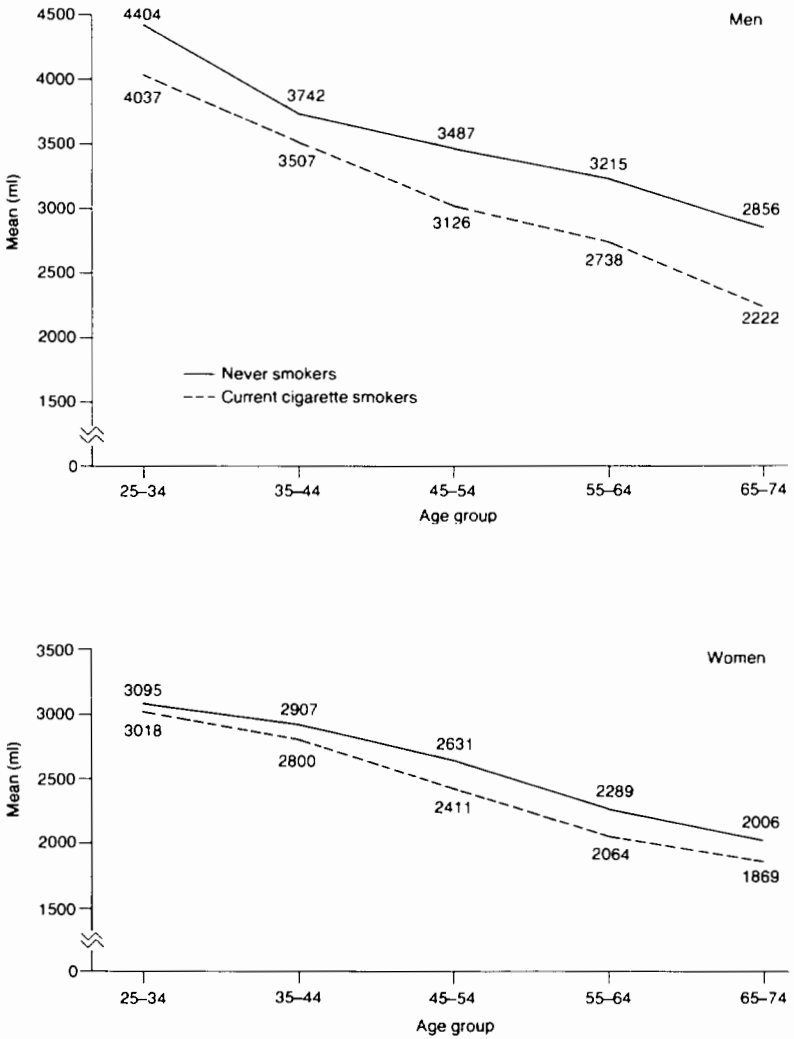

FIGURE 16.—Mean FEV_1 for white persons by smoking status, sex, and age, United States, 1971–1975

NOTE: Values adjusted by the direct method to reflect the age distribution of the U.S. population at the midpoint of the survey.

SOURCE: National Center for Health Statistics. Unpublished data from the first National Health Nutrition and Examination Survey (NHANES 1).

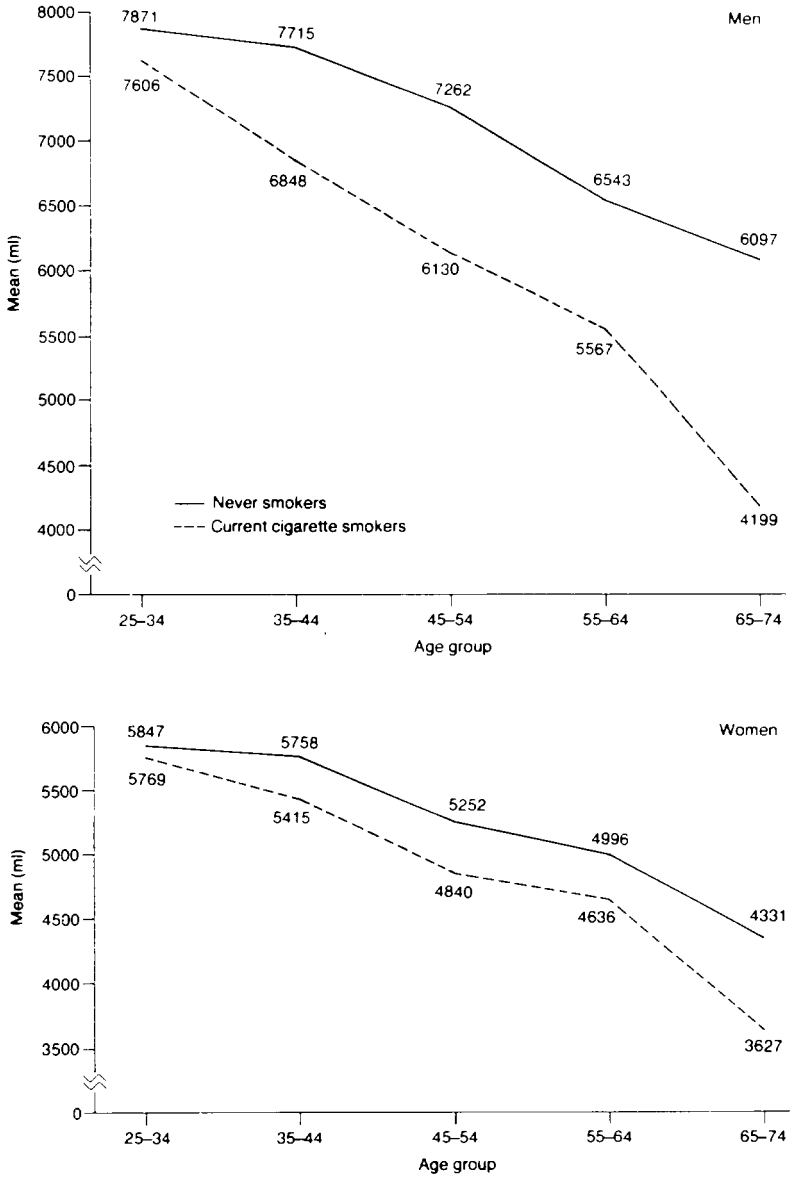

FIGURE 17.—Mean flow at 25 percent of FVC for white persons by smoking status, sex, and age, United States, 1971–1975

NOTE: Values adjusted by the direct method to reflect the age distribution of the U.S. population at the midpoint of the survey.

SOURCE: National Center for Health Statistics. Unpublished data from the first National Health Nutrition and Examination Survey (NHANES 1).

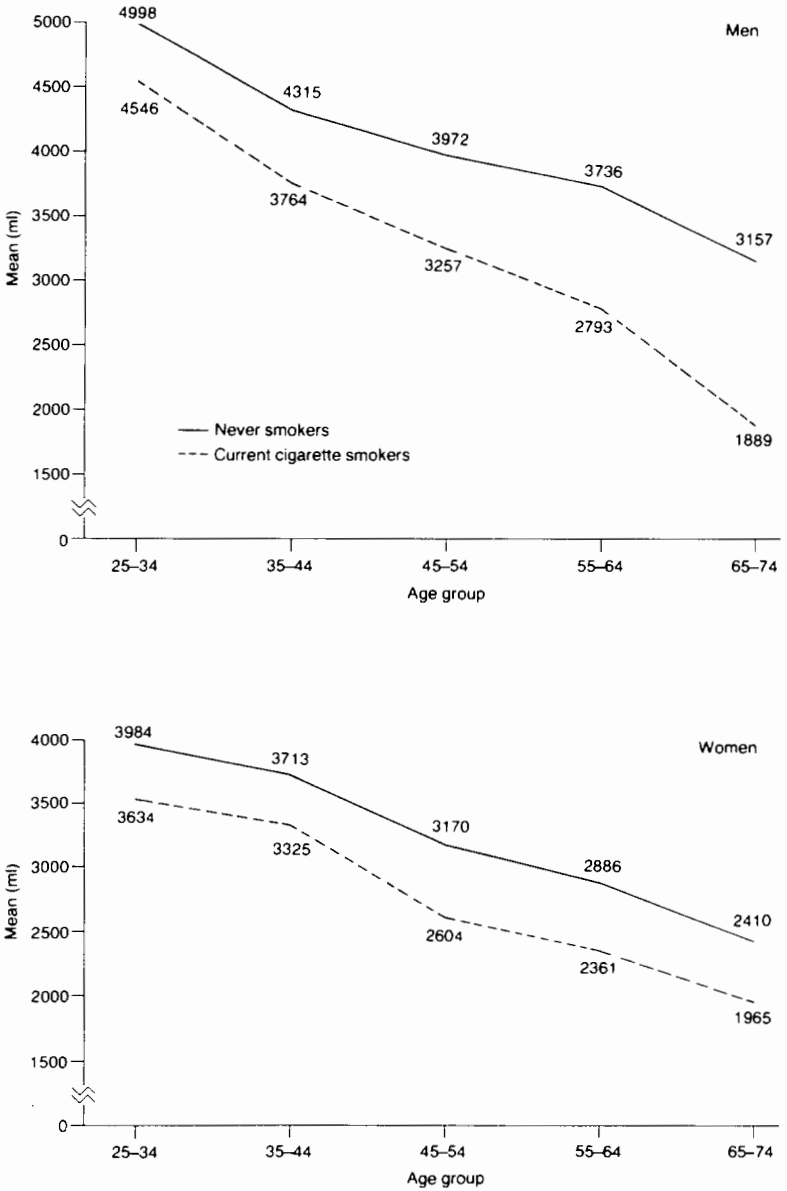

FIGURE 18.—Mean flow at 50 percent of FVC for white persons by smoking status, sex, and age, United States, 1971–1975

NOTE: Values adjusted by the direct method to reflect the age distribution of the U.S. population at the midpoint of the survey.

SOURCE: National Center for Health Statistics. Unpublished data from the first National Health Nutrition and Examination Survey (NHANES 1).

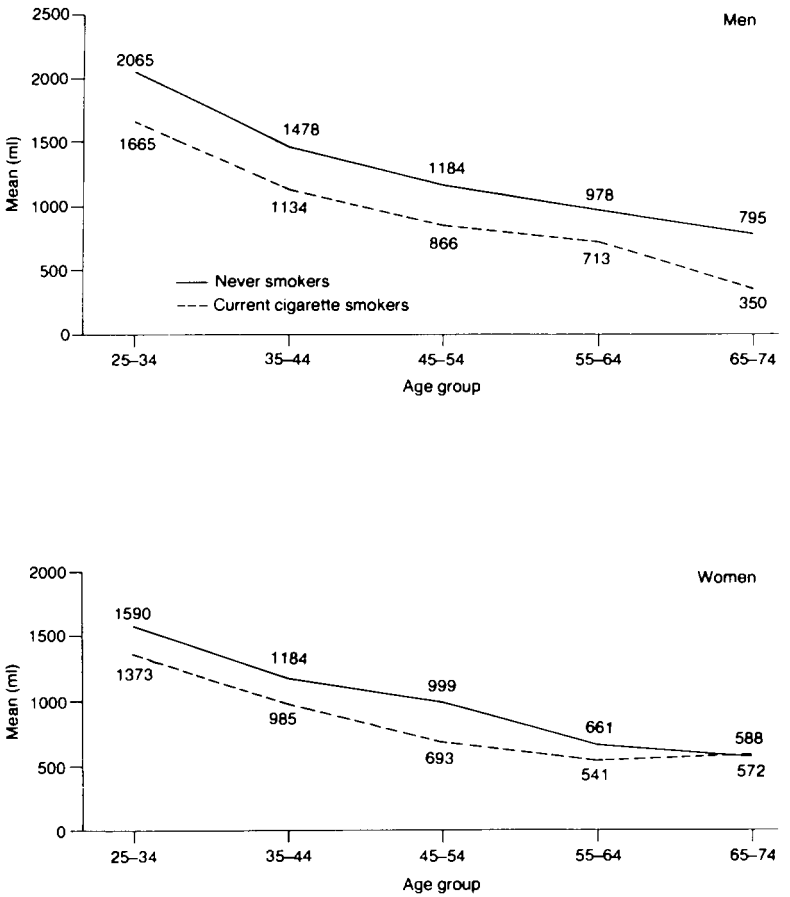

FIGURE 19.—Mean flow at 75 percent of FVC for white persons by smoking status, sex, and age, United States, 1971–1975

NOTE: Values adjusted by the direct method to reflect the age distribution of the U.S. population at the midpoint of the survey.

SOURCE: National Center for Health Statistics. Unpublished data from the first National Health Nutrition and Examination Survey (NHANES 1).

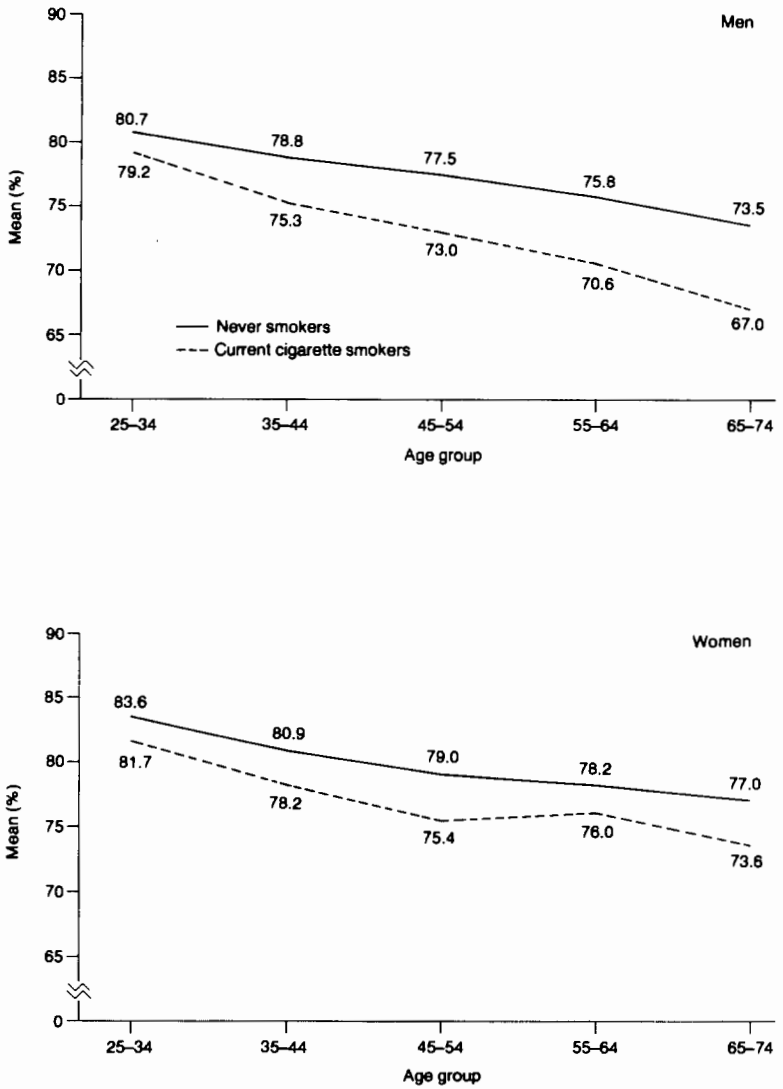

FIGURE 20.—Mean FEV_1/FVC ratio for white persons by smoking status, sex, and age, United States, 1971–1975

NOTE: Values adjusted by the direct method to reflect the age distribution of the U.S. population at the midpoint of the survey.

SOURCE: National Center for Health Statistics. Unpublished data from the first National Health Nutrition and Examination Survey (NHANES 1).

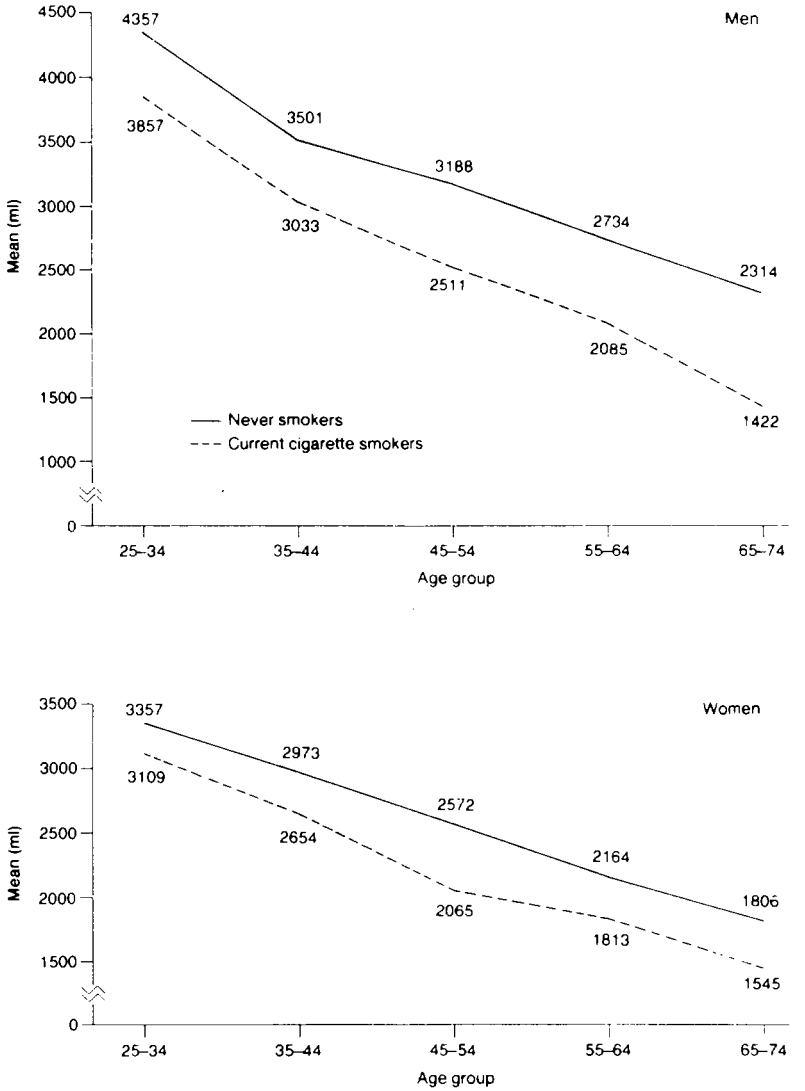

FIGURE 21.—Mean MMEF for white persons by smoking status, sex, and age, United States, 1971–1975

NOTE: Values adjusted by the direct method to reflect the age distribution of the U.S. population at the midpoint of the survey.

SOURCE: National Center for Health Statistics. Unpublished data from the first National Health Nutrition and Examination Survey (NHANES 1).

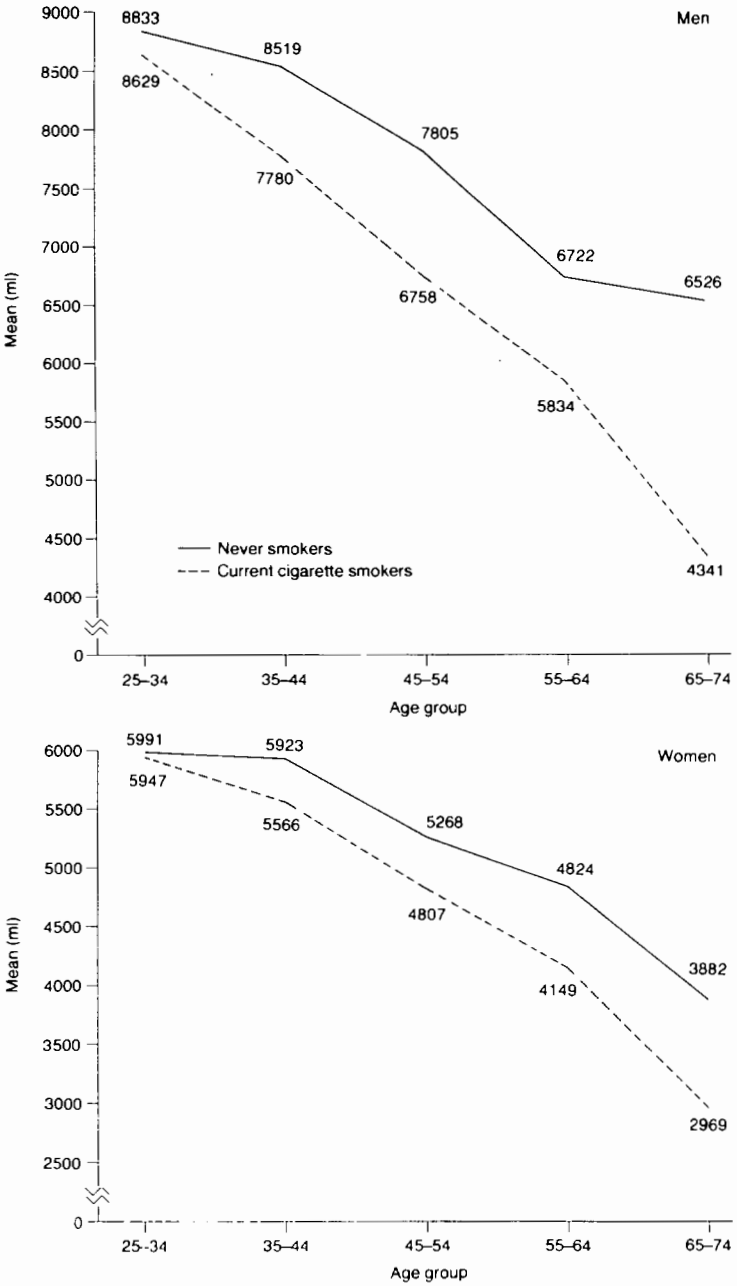

FIGURE 22.—Mean MEFR for white persons by smoking status, sex, and age, United States, 1971–1975

NOTE: Values adjusted by the direct method to reflect the age distribution of the U.S. population at the midpoint of the survey.

SOURCE: National Center for Health Statistics. Unpublished data from the first National Health Nutrition and Examination Survey (NHANES 1).

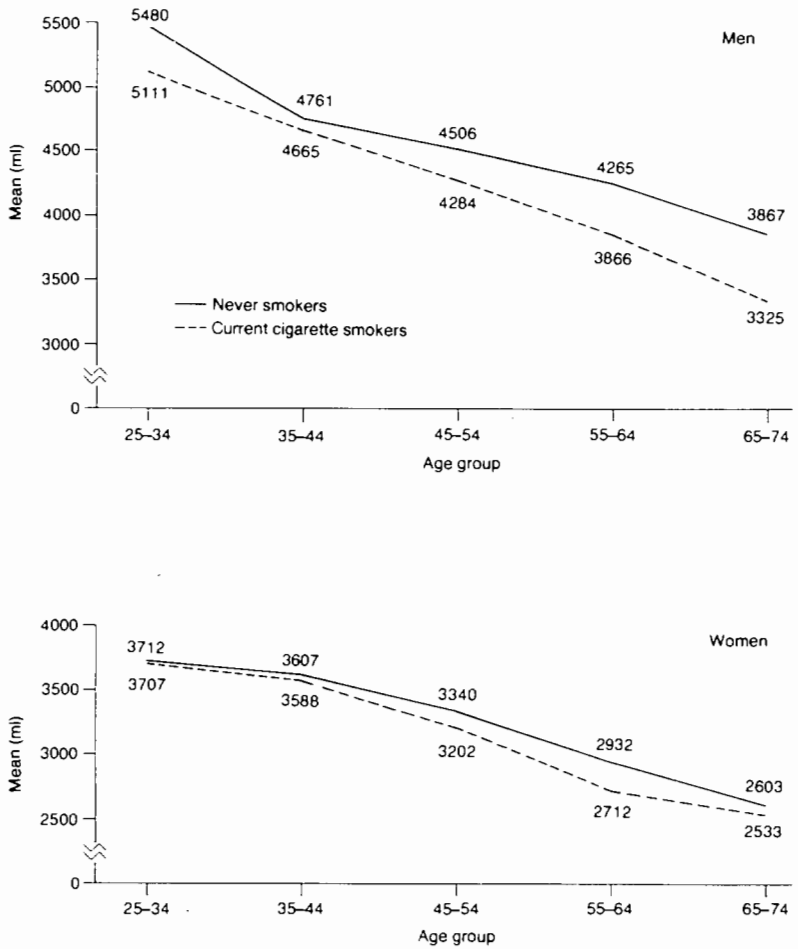

FIGURE 23.—Mean forced vital capacity for white persons by smoking status, sex, and age, United States, 1971–1975

NOTE: Values adjusted by the direct method to reflect the age distribution of the U.S. population at the midpoint of the survey.

SOURCE: National Center for Health Statistics. Unpublished data from the first National Health Nutrition and Examination Survey (NHANES 1).

TABLE 6.—Postulated risk factors for airflow obstruction during childhood

Active cigarette smoking
Air pollution, indoor and outdoor
Airways hyperreactivity
Atopy
Familial factors
Passive exposure to tobacco smoke
Respiratory illnesses
Socioeconomic status

TABLE 7.—Morbidity

ESTABLISHED RISK FACTORS FOR AIRFLOW OBSTRUCTION DURING ADULTHOOD
Active cigarette smoking
$Alpha_1$-antitrypsin deficiency
PUTATIVE RISK FACTORS FOR AIRFLOW OBSTRUCTION DURING ADULTHOOD
ABH secretor status
Air pollution
Airways hyperreactivity
Alcohol consumption
Atopy
Childhood respiratory illnesses
Familial factors
Occupation
Passive exposure to tobacco smoke
Respiratory illnesses
Socioeconomic status

occupational groups (Table 10) with exposures that have little or no effect on lung function. The selected studies are all cross sectional in design and thus describe the relationship between cigarette smoking and lung function level at only a single point in time.

Investigations in the United States, spanning the time period 1958 to 1977, convincingly demonstrate that cigarette smoking is a strong determinant of FEV_1 level and the prevalence of airflow obstruction (Table 8). In every population for which prevalence data are available, airflow obstruction is more common among smokers than among nonsmokers (Mueller et al. 1971; Knudson et al. 1976; Detels et al. 1979; Rokaw et al. 1980). In fact, in a multivariate analysis of determinants of airflow obstruction in East Boston, lifetime cigarette consumption was the only statistically significant predictor (Tager et al. 1978). Data from populations outside the United States (Table 9) and from a variety of occupational groups (Table 10) confirm the importance of cigarette smoking. Effects of cigarette smoking on FEV_1 level have been readily demonstrated in employed populations

TABLE 8.—Association between cigarette smoking and FEV_1 level in selected U.S. adult populations

Author, year of study, location, reference	Number and type of population	Findings		
Ashley et al., 1958, Framingham, Massachusetts, (*1975*)	1,238 men and women, 37 to 69 years of age	By linear regression, significant decline of FEV_1/FVC ratio with pack-years of cigarette consumption in men; similar decline demonstrated in women, but not significant for all age groups		
Higgins and Kjelsberg 1959–1960, Tecumseh, Michigan (*1967*)	5,140 men and women, 16 to 79 years of age	Age-adjusted mean FEV_1 (liters)		
			Men	Women
		Nonsmokers	3.32	2.34
		Ex-smokers	3.31	2.34
		Current smokers	3.12	2.28
Higgins et al., 1963, Marion County, West Virginia (1968a)	926 white men, 20 to 69 years of age	Mean FEV_1 (liters)		
		Nonsmokers	3.64	
		Ex-smokers	3.25	
		Current smokers		
		1–14/day	3.67	
		15–24/day	3.51	
		≥ 25/day	3.30	
Higgins et al., 1962–1965, Tecumseh, Michigan (*1977*)	4,669 men and women, 20 to 74 years of age	Mean normalized FEV_1 score		
			Men	Women
		Nonsmokers	10.2	10.1
		Ex-smokers	9.9	10.0
		Current smokers		
		< 20/day	9.8	9.9
		≥ 20/day	9.5	9.6

TABLE 8.—Continued

Author, year of study, location, reference	Number and type of population	Findings
Mueller et al., 1967, Glenwood, Colorado (*1971*)	609 men and women, 20 to 69 years of age	Prevalence of $FEV_1/FVC < 60\%$ Men / Women Nonsmokers 3 / 1 Current smokers 19 / 2
Ferris et al., 1967, Berlin, New Hampshire (*1973*)	848 men and women, 30 to 80 years of age	By multiple regression, in men and women, FEV_1 drops by 0.01 liters for each cigarette smoked per day
Burrows et al., 1972–1973, Tucson, Arizona (*1977*)	2,369 men and women, above 14 years of age	By multiple regression analysis, FEV_1 drops by 0.31 and 0.24 percent of predicted value per pack-year of smoking in men and women, respectively
Knudson et al., 1972–1973, Tucson, Arizona (*1976*)	2,735 men and women, all ages	Prevalence (%) of abnormal FEV_1 and/or FEV_1/FVC Asymptomatic nonsmokers 8.3 Asymptomatic smokers 13.3
Tager and Speizer, 1973–1974, East Boston, Massachusetts (*1976*)	633 men and women, 15+ years of age	By multiple regression, in men and women, significant reduction of an FEV_1 score with increasing lifetime consumption, and in smokers compared with nonsmokers
Tager et al., 1973–1974, East Boston, Massachusetts (*1978*)	1,251 men and women,	By multiple logistic analysis, lifetime cigarette consumption only significant predictor of airflow obstruction, defined as FEV_1 less than 65% predicted
Beck et al., 1972–1974, Lebanon and Ansonia, Connecticut, Winnsboro, South Carolina (*1981*)	4,690 men and women, 7+ years of age	By multiple regression analysis, significant dose–response relationships of adjusted residual FEV_1 with measures of cigarette smoking: duration, pack-years, and cigarettes per day

TABLE 8.—Continued

Author, year of study, location, reference	Number and type of population	Findings		
Ferris et al., 1974–1977, U.S. communities (*1979*)	8,480 men and women, 25 to 74 years of age	Mean residual FEV_1 (liters) after correction for height and age		
		Lifetime packs	Men	Women
		None	0.25	0.06
		< 3,000	0.21	0.04
		3,000–8,999	0.01	–0.05
		9,000–17,999	–0.19	–0.20
		≥ 18,000	–0.45	–0.28
Detels et al., Rokaw et al., 1973–1975, Burbank, Lancaster, Long Beach, California (Detels et al., 1979, Rokaw et al., 1980)	Approximately 8,000 men and women, 18 years or older	Prevalence (%) of FEV_1 below 75% predicted, age and sex-adjusted		
			Never smoked	Current smoker
		18–59 years old		
		Burbank	6.6	12.5
		Lancaster	3.4	6.6
		Long Beach	5.3	10.0
		≥ 60 years old		
		Burbank	15.9	23.5
		Lancaster	13.4	21.7

TABLE 9.—Association between cigarette smoking and lung function in selected non-U.S. populations

Author, year of study, location, reference	Number and type of population	Findings
Higgins, 1956, Vale of Glamorgan, Wales (*1957*)	581 men and women, 25 to 74 years of age	Ir men, reduced peak flow rates and indirect maximum voluntary ventilation in smokers compared with nonsmokers; no effect of smoking in women
Higgins et al., 1957 Stavely, England (*1959*)	776 men, aged 25 to 34 and 55 to 64	Mean indirect maximal breath capacity (liters) 25 to 34 yrs / 55 to 64 yrs Nonsmokers 145 / 101 Ex-smokers 143 / 89 Current smokers Light 140 / 87 Heavy 133 / 80
Higgins et al., 1958, Rhondda Fach, Wales (*1961*)	537 men, aged 35 to 64, and 173 women, aged 55 to 64	Mean indirect maximal breathing capacity (liters), men Miners / Nonminers Nonsmokers 93.1 / 114.6 Ex-smokers 93.6 / 105.9 Current smokers Light 89.0 / 104.1 Heavy 88.3 / 99.4 No effect of smoking in women

TABLE 9.—Continued

Author, year of study, location, reference	Number and type of population	Findings
College of General Practitioners, 1958, Britain (*1961*)	787 men and 782 women, aged 40 to 64	Age-adjusted mean PEFR[1] (liters/minute) Men / Women Nonsmokers: 448 / 318 Ex-smokers: 417 / 300 Current smokers 1–14/day: 412 / 314 15–24/day: 399 / 310 ≥25/day: 398 / 265
Sluis-Cremer and Sichel, 1962–1963, Carletonville, South Africa (*1968*)	533 men, 35 years or older	Reduced FEV_1 and PEFR[1] with increased tobacco consumption
Huhti, 1961, Harjavalta, Finland (*1967*)	420 men, 608 women, aged 40 to 64	All women, nonsmokers; in men, reduced FEV_1 and PEFR[1] in smokers compared with nonsmokers
Wilhelmsen et al., 1963, Göteborg, Sweden (*1969*)	339 men, aged 50	Mean FEV_1 (liters) Nonsmokers: 3.72 Ex-smokers: 3.71 Current smokers 1–14 g/day: 3.58 ≥15 g/day: 3.36
Huhti et al., 1968–1970, Hankasalmi, Finland (*1978*)	1,162 men, aged 25 to 69	Reduced FEV_1 in smokers compared with nonsmokers; increased prevalence of FEV_1/FVC ratio less than 60% in smokers

TABLE 9.—Continued

Author, year of study, location, reference	Number and type of population	Findings		
Mimica, 1969, Croatia, Yugoslavia (*1975*)	4,214 men and women, 35 to 54 years of age	Mean FEV_1 (liters)		
			Men	Women
		Nonsmokers	3.58	2.62
		Ex-smokers	3.57	2.70
		Current smokers		
		Light	3.42	2.64
		Heavy	3.42	2.60
Neri et al., 1969–1973, Sudbury and Ottawa, Canada (*1975*)	5,488 men and women, 14 years of age or older	Declining ratio of FEV_1/FVC with number of cigarettes smoked daily		
Manfreda et al., 1974, Portage la Prairie and Charleswood, Canada (*1978*)	502 men and women, 25 to 55 years of age	Significant regression of FEV_1/FVC ratio on number of cigarettes smoked daily		
Anderson, year not stated, Karkar Island, Papua New Guinea (*1976*)	548 men and women, 25 years of age or older	Age and height-adjusted mean FEV_1 (liters)		
			Men	Women
		Nonsmokers	2.56	2.13
		Smokers	2.40	2.01
Anderson, year not stated, Lufa, Papua New Guinea (*1979*)	733 men and women 25 years of age or older	Age and height-adjusted mean FEV_1 (liters)		
			Men	Women
		Nonsmoker	2.58	2.36
		Ex-smoker	2.62	2.27
		Occasional	2.57	2.29
		Regular	2.63	2.43

[1] Peak expiratory flow rate.

TABLE 10.—Association between cigarette smoking and lung function level in selected occupational groups

Author, year of study, location, reference	Number and type of population	Findings	
Sharp et al., 1960–1961, Chicago, U.S. (*1965*)	1,887 men, aged 43 to 58 years, employed at an electronics plant	Mean FEV_1 (liters)	
		Nonsmokers	3.15
		Smokers	
		<one pack per day	3.02
		≥one pack per day	2.90
Fletcher et al., 1961, London, England (*1976*)	1,136 men aged 30 to 59, employed at bank or in maintenance of transportation equipment	Adjusted FEV_1 (liters)	
		Nonsmokers	3.28
		Ex-smokers	3.16
		Current smokers	
		1–4 cigarettes/day	2.81
		5–14 cigarettes/day	3.05
		15–24 cigarettes/day	2.99
		≥25 cigarettes/day	2.94
Goldsmith et al., 1961, San Francisco, U.S. (*1962*)	3,311 longshoremen	Mean FEV_1 percent of predicted value	
		Never smokers	100
		Ex-smokers	97
		Current smokers	
		10 cigarettes/day	93
		11–39 cigarettes/day	93
		≥40 cigarettes/day	94

TABLE 10.—Continued

Author, year of study, location, reference	Number and type of population	Findings
Balchum et al., 1961, Los Angeles, U.S. (*1962*)	1,456 men employed in various industries	Prevalence (per 100) of FEV_1/FVC ratio less than 70 percent Nonsmokers 7.6 Smokers 18.8
Coates et al., 1962, Detroit, U.S. (*1965*)	1,584 male and female postal employees, aged 40 or older	Reduced FEV_1 and FEV_1/FVC ratio in smokers of 25 or more cigarettes daily compared with nonsmokers
Densen et al., 1961–1963, New York City, U.S. (*1969*)	12,500 males employed as postal or transit workers	Age- and height-adjusted FEV_1 (liters) Postal workers: White 3.29; Nonwhite 3.05 Transit workers: White 3.39; Nonwhite 3.08 Cigarette smokers <25 g per day: Postal White 3.14; Postal Nonwhite 2.95; Transit White 3.15; Transit Nonwhite 3.00 ≥ 25 g per day: Postal White 3.06; Postal Nonwhite 2.93; Transit White 3.02; Transit Nonwhite 2.95
Bandé et al., 1960–1975, Belgium (*1980*)	7,123 male military personnel, a few over age 45	By multiple regression, in cross-sectional analysis, significant effect of smoking on FEV_1 level after age 35
Comstock et al., 1962–1963 and 1967, U.S. and Japan (*1973*)	Three cross-sectional studies of men working for telephone company; U.S.—1,302 and 1,194 subjects, aged 40 to 65, 6% in study; Japan—592 subjects, aged 40 to 60	Mean FEV_1 level as percent predicted U.S. Study 1; U.S. Study 2; Japan Cigarettes per day None: 106; 103; 99 1–14: 104; 101; 100 15–24: 98; 92; 98 ≥ 25: 95; 93; 99

TABLE 10.—Continued

Author, year of study, location, reference	Number and type of population	Findings	
Khosla, 1964, Port Talbot, United Kingdom (*1971*)	7,701 males employees in the steel industry	Adjusted mean FEV_1 level (liters)	
		Never smokers	3.70
		Current smokers	
		<15 cigarettes/day	3.57
		15–24 cigarettes/day	3.48
		25–34 cigarettes/day	3.41
		≥35 cigarettes/day	3.37
Schlesinger et al., 1968, Israel (*1972*)	4,331 male civil servants, aged 45 or older	Mean value of the FEV_1/FVC ratio	
		Nonsmokers	76.0
		Ex-smokers	74.3
		Current smokers	
		1–19 cigarettes/day	73.9
		≥20 cigarettes/day	72.7
Kesteloot et al., 1968–1969, Belgium (*1976*)	4,961 males in the Belgian military, aged 15 to 59	By multiple regression, FEV_1 reduced by 0.14 liters in smokers of 1–19 cigarettes daily and by 0.23 liters in smokers of 20 or more daily	
O'Donnell and de Hamel, 1969–1970, New Zealand (*1976*)	1,079 male public servants, up to age 65	Reduced mean FEV_1 in smokers of 10 or more cigarettes daily; increased prevalence of FEV_1 below 80 percent of predicted in smokers of more than two packs daily	
Linn et al., 1973, San Francisco and Los Angeles, U.S. (*1976*)	644 male and female office workers, aged 17 to 60	By analysis of covariance, significant reduction of FEV_1 in smokers compared with nonsmokers	
Endelman et al., year not stated, Baltimore, U.S. (*1966*)	410 male volunteers, aged 20 to 103	By partial regression analysis, significant reduction of FEV_1 in current and former cigarette smokers	

TABLE 10.—Continued

Author, year of study, location, reference	Number and type of population	Findings		
Woolf and Suero, year not stated, Toronto (*1971*)	298 female volunteers employed at commercial firms, aged 25–54	Adjusted mean levels		
			FEV_1	FEV_1/FVC ratio
		Nonsmokers	2.65	86.7
		Ex-smokers	2.64	85.0
		Current smokers		
		70 cigarettes/week	2.63	85.2
		71–140 cigarettes/week	2.50	85.1
		≥140 cigarettes/week	2.45	84.1
Krumholz and Hedrick, year not stated, Dayton, U.S. (*1973*)	227 male executives, aged 35–64, selected to include nonsmokers (n=136) and long-term smokers (n=91)	Mean values		
			FEV_1	FEV_1/FVC
		Nonsmokers	3.80	77.3
		Smokers	3.42	73.6
Grimes and Hanes, year not stated, Los Angeles, U.S. (*1973*)	1,059 male and female insurance company employees	By multiple regression, significant reduction of FEV_1 level in male smokers but not in female smokers		
Lefcoe and Wonnacott, year not stated, western Ontario, Canada (*1974*)	1,072 males in four occupational groups	By multiple regression, significant reduction of FEV_1 in current cigarette smokers		
Higgenbottam et al., year not stated, London, England (*1980*)	18,403 male civil servants, aged 40 to 64	Reduced FEV_1 in cigarette smokers compared with nonsmokers, increased effect with increasing daily amount in current smokers		

(Table 10), even though people with symptomatic airflow obstruction may be likely to retire from their jobs.

Recently, predictors of the incidence of airflow obstruction have been examined with multivariate techniques in data from population samples in Tecumseh, Michigan (Higgins et al. 1982), and in Tucson, Arizona (Lebowitz et al. 1984). In Tecumseh, the strongest predictors of airflow obstruction (defined as an FEV_1 less than 65 percent of predicted) were age, the number of cigarettes smoked daily, changing smoking habits, and the initial FEV_1 level (Higgins et al. 1982). The addition of other variables to the predictive model did not greatly improve its validity. In Tucson, these same variables, along with certain symptoms and illnesses, and skin test reactivity were significant predictors (Lebowitz et al. 1984). During the 10 years of followup of a population sample in Finland, incidence cases of chronic airflow obstruction (defined as FEV_1/FVC ratio less than 60 percent) were observed only in those who continued to smoke (Huhti and Ikkala 1980). These studies of incidence highlight the importance of cigarette smoking in the etiology of airflow obstruction; new cases are rare among nonsmokers.

Dose–Response Relationships

Dose–response relationships between FEV_1 level and the amount of cigarette smoking have been described with simple descriptive statistics and further characterized by multiple regression analysis. In cross-sectional data, the FEV_1 level varies inversely with the amount smoked. Although the variation in mean FEV_1 levels among strata of smoking appears clinically unimportant, the distributions of values in smokers and nonsmokers are quite different (Figure 4). Cigarette smokers more often have abnormal lung function, regardless of the criteria applied to the population (Mueller et al. 1971; Knudson et al. 1976; Burrows et al. 1977a; Detels et al. 1979; Rokaw et al. 1980; Beck et al. 1981). This increased prevalence of abnormal function is a result of the skewed distribution of function in smokers, with a subgroup of the smokers showing a large decline rather than the entire group shifting by a small amount (Figure 4). As noted in this reference, however, there are decreasing numbers of smokers with FEV_1 above the mean for nonsmokers as pack-years increase, suggesting that all smokers are probably somewhat affected, even though only a minority eventually develop clinically significant airflow limitation.

In several populations, the relationship between cigarette smoking and FEV_1 level has been examined in greater detail. Burrows et al. (1977a) used linear multiple regression analysis to examine the relationship between cigarette smoking and ventilatory function in a population sample in Tucson, Arizona. Pack-years, a cumulative-dose measure, was the strongest predictor of FEV_1 level among the

smoking variables considered. In currently smoking men and women, the FEV_1 declined by approximately 0.25 percent of the predicted value for each pack-year of cigarette smoking; the effect was of a similar magnitude in ex-smokers. Using data from three separate U.S. communities, Beck and colleagues (1981) assessed the importance of six separate smoking variables: amount smoked daily, use of filters, inhalation, age started, age stopped for ex-smokers, and cumulative pack-years. For the FEV_1, the strongest predictors in male current smokers were the duration of smoking and the amount smoked; in female current smokers, only pack-year was statistically significant. The number of years of cessation was associated with FEV_1 in male but not in female ex-smokers.

However, in both the multiple regression analysis reported by Beck et al. (1981) and that reported by Burrows et al. (1977a), the measured cigarette smoke variables accounted for only about 15 percent of the variation of age- and height-adjusted FEV_1 levels. Unmeasured aspects of cigarette smoking, other environmental exposures, and the characteristics of the smokers must contribute to the unexplained variation. A role for the type of cigarette smoked has not yet been established (USDHHS 1981), and the impact of differences in depth or pattern of inhalation and other aspects of the pattern of smoking remains to be investigated; they are discussed in more detail in the chapter *on low tar and low nicotine cigarettes*. Further studies of these aspects of cigarette smoking are needed to monitor the consequences of changing cigarettes.

Factors Other Than Cigarette Smoking

A number of risk factors other than cigarette smoking have been postulated as contributing to the development of airflow obstruction (Table 7). Of these, a definite role for α_1-antitrypsin deficiency has been established, but only the small number of persons with homozygous deficiency incur markedly increased risk (Morse 1978). The current hypotheses on susceptibility to cigarette smoke postulate roles for childhood respiratory illnesses (USDHEW 1979; Burrows and Taussig 1980; Samet et al. 1983), for endogenously determined hypersensitivity of the lung, and for other genetic and familial factors (Speizer and Tager 1979; USDHHS 1980a). At present, these hypotheses remain largely untested. The data are similarly incomplete at present for the other factors listed as putative risk factors in Table 7. The status of each is briefly reviewed below.

ABH Secretor Status

Secretion of ABH antigens is a genetically determined trait that follows an autosomal dominant inheritance pattern; approximately

70 to 80 percent of the population excrete antigen into the body fluids (Cohen et al. 1980a). In a genetic-epidemiology study in Baltimore, Maryland (Cohen et al. 1980a), ABH nonsecretors had lower levels of FEV_1/FVC ratio and a higher proportion with FEV_1/FVC ratio below 69 percent. Studies in France (Kauffmann et al. 1982a, 1983) and in England (Haines et al. 1982) have confirmed reduced expiratory flow rates in ABH nonsecretors. In contrast, ABH secretor status did not predict the development of obstructive airways disease in the Tecumseh, Michigan, population (Higgins et al. 1982).

Air Pollution

Although exposure to air pollution at high levels may exacerbate the clinical condition of persons with chronic lung disease, a causal role for air pollution in the development of airflow obstruction has not been established (Tager and Speizer 1979; USDHHS 1980b). However, smoking is the major predictor for chronic airflow obstruction in areas of high as well as low atmospheric air pollution.

Airways Hyperreactivity

Orie and colleagues in the Netherlands (Orie et al. 1960) speculated that bronchial hyperreactivity and allergy may predispose to asthma and chronic bronchitis. Findings from two small longitudinal studies have suggested that airways reactivity may influence individual susceptibility to cigarette smoke. Barter and colleagues followed 56 patients with mild chronic bronchitis during a 5-year period (Barter et al. 1974; Barter and Campbell 1976). The rate of decline of FEV_1 increased with the degree of airways reactivity, as measured by reversibility with isoproterenol or responsiveness to methacholine. Britt et al. (1980) measured change of FEV_1 in 20 young adult male relatives of patients with chronic obstructive pulmonary disease. The decline of FEV_1 was approximately five times larger in the nine subjects with a positive methacholine challenge test. In patients with clinically diagnosed airflow obstruction, airways reactivity is also associated with more rapid decline of lung function (Kanner et al. 1979). Because airway reactivity would affect the FEV_1 directly as well as possibly influence the susceptibility to smoke, it is difficult to ascertain from these data whether the relationship between airway reactivity and COLD is direct or spurious.

Alcohol Consumption

The epidemiological data on alcohol consumption are conflicting. A study of former alcoholics demonstrated an excess prevalence of lung function abnormalities, including airflow obstruction (Emergil

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and Sobol 1977). In the Tucson population, alcohol consumption was a significant predictor of ventilatory function after the effect of smoking was controlled (Lebowitz 1981). The findings of an investigation in Yugoslavia were similar (Saric et al. 1977). However, two large U.S. investigations did not demonstrate adverse effects of alcohol intake (Cohen et al. 1980b; Sparrow et al. 1983a).

Atopy

Cross-sectional data from the Tucson population suggest increased susceptibility to cigarette smoke in atopic people (Burrows et al. 1976). In subjects aged 15 to 54, the prevalence of an FEV_1/FVC ratio below 90 percent of predicted value increased with skin test reactivity among both smokers and nonsmokers. Subsequent reports from this same study have not confirmed an overall relationship between FEV_1 level and atopy, but indicate that atopy may predispose to airflow obstruction in a subset of the population (Burrows et al. 1977a, 1983). Burrows and coworkers (1981) also reported an increased level of IgE in smokers independent of their allergy skin test reactions, and the interrelationship of these factors is currently being examined.

Childhood Respiratory Illness

In a longitudinal investigation of 792 English working men, Fletcher and coworkers (Fletcher et al. 1976) found a cross-sectional association between childhood illness history and FEV_1 level. The decline of FEV_1 level during the study's longitudinal phase was not correlated with childhood illness variables. In contrast, analyses of cross-sectional data from a population sample in Tucson suggested that childhood respiratory illnesses may increase susceptibility to cigarette smoke (Burrows et al. 1977b). In this population, people with a history of respiratory trouble before age 16 demonstrated excessive decline of ventilatory function with increasing age and with increasing cigarette consumption.

Familial Factors

Familial aggregation of lung function level, adjusted for age, height, and sex, has been demonstrated in populations in the United States and elsewhere (Higgins and Keller 1975; Tager et al. 1976; Schilling et al. 1977; Mueller et al. 1980). However, a recent report suggests that the familial aggregation of lung function may be a reflection of the familial aggregation of body habitus (Lebowitz et al. 1984). Relatively modest correlations of FEV_1 level have been demonstrated between siblings and between parent–child pairs. The role of familial factors is further supported by investigations demonstrating increased prevalence of airflow obstruction in rela-

tives of diseased subjects (Kueppers et al. 1977; Tager et al. 1978; Cohen 1980). This familial factor cannot be explained by familial resemblance of α_1-antitrypsin phenotype or of ABH secretor status (Kueppers et al. 1977; Cohen 1980). In the Tecumseh population, however, family history of airflow obstruction did not predict the incidence of this disease. The results of twin studies are also consistent with genetic influences on FEV_1 level and suggest that genetic factors may influence susceptibility to cigarette smoke (Webster et al. 1979; Hankins et al. 1982; Hubert et al. 1982).

Occupation

Several population-based investigations suggest that occupational exposures other than those recognized as causing lung injury may have some effect on lung function level. In Tecumseh, mean age and height-adjusted FEV_1 scores in men were highest in farmers and lowest in laborers; the differences were not explained by smoking and were present in nonsmokers (Higgins et al. 1977). Similarly, in Tucson, men reporting employment in certain high risk industries or exposure to specific harmful agents had a higher prevalence of abnormal lung function (Lebowitz 1977a). In a Norwegian case–control study, men employed in workplaces characterized as polluted were at increased risk for clinically diagnosed emphysema (Kjuus et al. 1981). Longitudinal studies of industrial populations also show that occupational exposures may increase the rate of decline of FEV_1 (Jedrychowski 1979; Kauffmann et al. 1982b; Diem et al. 1982). For example, Kauffmann et al. (1982b) found that FEV_1 change during a 12-year period varied with job exposures in an employed industrial population. Effects of dust, gas, and heat were present, as was evidence for a dose–response relationship between increasing exposure and a greater rate of decline. In these studies, however, smoking effects were generally much greater than the occupational effects.

Passive Exposure to Tobacco Smoke

Passive exposure is discussed in detail elsewhere in this Report.

Respiratory Illnesses

In an 8-year followup study of London men, chest infections were not associated with a rate of FEV_1 decline (Fletcher et al. 1976). The findings of several smaller longitudinal studies were similarly negative with regard to respiratory infection (Howard 1970; Johnston et al. 1976). It is now apparent that mucus hypersecretion and airflow obstruction are separate pathophysiological entities that have a common cause—cigarette smoking (Fletcher et al. 1976; Peto et al. 1983).

Socioeconomic Status

Weak effects of socioeconomic status on lung function level have been demonstrated in community samples in Tecumseh (Higgins et al. 1977) and in Tucson (Lebowitz 1977b). In both populations, lung function appeared to be influenced independently by socioeconomic status indicators, even after controlling for cigarette smoking. In the Tecumseh study, FEV_1 increased slightly with increasing income and education level (Higgins et al. 1977); in the Tucson study, the proportion of people with an abnormal FEV_1 varied in a similar pattern with these indices (Lebowitz 1977a). Effects of socioeconomic status were present in nonsmokers in both investigations. Stebbings (1971), in a sample of nonsmokers in Hagerstown, Maryland, also demonstrated an association between lung function level and socioeconomic status.

In summary, there is evidence that a number of factors other than cigarette smoke may influence lung function, but the influence of these factors is small relative to the effect of smoking, and the major question is whether they can influence susceptibility to cigarette-induced lung injury rather than whether they, of themselves, result in lung disease in nonsmokers.

Development of Airflow Obstruction

At this time, the natural history of airflow obstruction has been only partially described; a population has not yet been followed from childhood to the development of airflow obstruction during adulthood. However, the available data from separate investigations cover the entire course of the disease and support the conceptual model proposed in Figure 15.

With aging, measures of function begin to deteriorate after age 25 to 30. In nonsmokers without respiratory disease, cross-sectional data generally show that the FEV_1 declines by 20 to 30 ml per year (Dickman et al. 1969; Morris et al. 1971; Cotes 1979; Crapo et al. 1981). Longitudinal data have been confirmatory (Tables 11 and 12). For example, Tockman (1979) measured the FEV_1 loss during an 8-year period in 399 male nonsmokers. In most, the FEV_1 declined at 25 ml annually; a few, with an initial FEV_1 lower than 2.5 l, lost 34 ml annually.

Sufficient excessive loss leads to the development of airflow obstruction. However, many questions remain unanswered concerning this process of functional deterioriation. It is unclear whether the loss always occurs uniformly or if it develops in stages with intermittent and relatively steep declines (Bates 1979; Burrows 1981). The concept that the decline is nearly always gradual receives strong support from the findings of the 8-year longitudinal study conducted by Fletcher and coworkers (1976). In this investigation of

TABLE 11.—Association between cigarette smoking and longitudinal change in lung function in selected population samples

Author, years of study, location, reference	Number and type of population	Findings		
Higgins and Oldham, 1954–1959 Rhondda Fach, Wales (*1962*)	253 male miners, ex-miners, and nonmining controls	Annual decline of indirect maximal breathing capacity (liters/min)		
			Controls	Miners, ex-miners without pneumoconiosis
		Nonsmokers	1.6	0.8
		Ex-smokers	0.7	1.8
		Current smokers		
		1–14 g/day	1.3	1.7
		≥ 15g/day	1.6	2.2
Ashley et al., 1958–1968, Framingham, U.S. (*1975*)	399 men and 636 women, aged 37 to 69 in 1958	10-year change in FEV_1/FVC ratio (age-standardized to overall distribution for each sex)		
			Men	Women
		Nonsmokers	0.21	−3.6
		Continued smokers	−1.3	−4.1
		Stopped, 1958–1968	0.51	−4.6
Higgins et al., 1957–1966, Stavely, England (1968b)	594 men, aged 25–34 or 55–64 in 1957	Annual decline of $FEV_{75\%}$ (ml/year) by age and smoking in 1957		
			25–34 yrs	55–64 yrs
		Nonsmokers	21	32
		Ex-smokers	29	44
		Current smokers		
		1–14g/day	37	54
		≥ 15g/day	38	37

TABLE 11.—Continued

Author, years of study, location, reference	Number and type of population	Findings		
Huhti and Ikkala, 1961–1971, Harjavalta, Finland (*1980*)	492 men and 671 women, aged 40 to 64 in 1961	Annual decline of FEV_1 (ml/year)	Men	Women
		Nonsmokers	33	27
		Ex-smokers	45	27
		Continued smokers	44	39
		Stopped, 1961–1971	51	35
Wilhelmsen et al., 1963–1967, Göteborg, Sweden (*1969*)	313 men, aged 50 in 1963	Annual decline of FEV_1 (ml/year)		
		Nonsmokers	43	
		Ex-smokers	33	
		Current smokers		
		1–14g/day	70	
		≥ 15g/day	70	
		Stopped, 1963–1967	40	

TABLE 11.—Continued

Author, years of study, location, reference	Number and type of population	Findings		
Oxhoj et al., 1963–1973, Göteborg, Sweden (same population as Wilhelmsen et al. 1969) (*1976*)	269 men, aged 50 in 1963	Annual decline of FEV_1 (ml/year)		
		Nonsmokers	40	
		Ex-smokers	37	
		Current smokers	58	
		Stopped, 1963–1973	49	
Van der Lende et al., Vlaardingen, 1967–1978, and Vlagtwedde, 1967–1976, Netherlands (*1981*)	894 men and women, aged 25 and older	Mean annual decline of FEV_1	Unadjusted	Adjusted
		Nonsmokers	13.3	16.6
		Ex-smokers	15.8	13.4
		Pipe/cigar	24.4	22.6
		≤4 g/cig	3.6	8.7
		5–14 g/cig	22.2	20.9
		15–24 g/cig	31.4	28.2
		≥25 g/cig	35.8	34.0
Krzyzanowski, 1968–1973, Cracow, Poland (*1980*)	2,572 men and women, aged 19 to 70	Annual decline of FEV_1 (ml/year)	Men	Women
		Nonsmokers	56	44
		Continued smokers	73	53

TABLE 12.—Association between cigarette smoking and longitudinal change in lung function in selected occupational or other groups

Author, years of study, location, reference	Number and type of population	Findings	
Comstock et al., 1962-1963 to 1967 or 1969, various locations U.S. (*1970*)	670 male telephone company employees, aged 40 to 65	Decline in FEV_1 (liters) between surveys	
		Nonsmokers	0.28
		Ex-smokers	0.17
		All smokers	0.41
Howard, 1956 to 1967, Sheffield, England (*1970*)	159 male employees of an engineering works	Annual decline in $FEV_{75\%}$ (ml/year)	
		Nonsmokers	0.036
		Ex-smokers	0.025
		Current smokers	0.031
DeMeyere and Vuylsteek, 1967 to 1970, Ghent, Belgium (*1971*)	627 male railroad workshop employees	Annual decline in FEV_1 (ml/year)	
		Nonsmokers	92
		Ex-smokers	96
		Current smokers	
		1-14 g/day	96
		≥ 15 g/day	88
		Stopped, 1961-1971	80

TABLE 12.—Continued

Author, years of study, location, reference	Number and type of population	Findings	
Fletcher et al., 1961 to 1969, London, England (*1976*)	792 male transport maintenance or bank workers, aged 30 to 59 at entry	Annual decline of FEV_1 (ml/year)	
		Nonsmokers	36
		Ex-smokers	31
		Continued smokers	
		< 5 cigs/day	44
		5–15 cigs/day	46
		15–25 cigs/day	54
		≥ 25 cigs/day	54
Kauffmann et al., 1960 to 1972, Paris, France (*1979*)	575 male factory workers, aged 30 to 54 in 1960	Annual decline of FEV_1 (ml/year), adjusted for initial level	
		Nonsmokers	40
		Ex-smokers	44
		Current smokers	
		< 15 g/day	46
		≥ 15 g/day	51
Jedrychowski, 1968 to 1973, Cracow, Poland (*1979*)	186 male employees of a fertilizer factory	5-year decline of FEV_1 as percent of mean, by 1973 smoking	
		Nonsmokers	3
		Ex-smokers	5
		Current smokers	7
Poukkula et al., 1967 to 1977, Oulu, Finland (*1982*)	659 male pulp mill employees, aged 18 to 64 in 1967	Annual decline of FEV_1 (ml/year)	
		Nonsmokers	37
		Ex-smokers	39
		Continued smokers	49
		Stopped, 1967–1977	48

TABLE 12.—Continued

Author, years of study, location, reference	Number and type of population	Findings	
Woolf and Zamel, years not given, Toronto, Canada (*1980*)	302 female volunteers, aged 25 to 54 at entry	5-year change in FEV_1 as percent of initial value	
		Nonsmokers	-1.5
		Ex-smokers	-0.8
		Smokers	
		≤70 cigs/week	-0.4
		71-140 cigs/week	-3.0
		>140 cigs/week	-4.6
Bosse et al., 1963-1968 to 1969-1974, Boston, U.S. (*1981*)	850 male volunteers	Annual decline of FEV_1 (ml/year), adjusted for age and initial level	
		Nonsmokers	0.053
		Ex-smokers	0.057
		Current smokers	0.085
Love and Miller, 1957 to 1973 (average followup, 11 years), United Kingdom (*1982*)	1,677 male coalminers	11-year decline in FEV_1 (liters)	
		Nonsmokers	0.41
		Ex-smokers	0.48
		Intermittent smokers	0.52
		Current smokers	0.53

792 employed men, the individual patterns of temporal change of the FEV_1 were strongly variable, but the loss generally occurred gradually. Fletcher et al. further demonstrated that FEV_1 level correlated with FEV_1 slope, a finding that they termed the "horse-racing effect." Correlation between slope and level would be anticipated, if functional loss occurs gradually. This correlation has important implications for intervention; those losing FEV_1 more rapidly should become identifiable early as they develop a reduced FEV_1 level. Other studies, however, do not agree with either the pattern of FEV_1 decline or the "horse-racing" effect. Rapid declines to levels compatible with clinical disease or followed by a prolonged plateau have been described (Howard and Astin 1969; Howard 1970; Johnston et al. 1976). In a followup study of Canadian men with chronic bronchitis, steep declines of FEV_1 without subsequent improvement were frequently observed (Bates 1973). Additionally, correlation of FEV_1 level and slope has been found in most other longitudinal investigations (Howard 1970; Petty et al. 1976; Huhti and Ikkala 1980; Bosse et al. 1981; Clement and van de Woestijne 1982; Kauffmann et al. 1982b), but not in all (Barter et al. 1974; Krzyzanowski 1980).

Another unanswered question concerning functional deterioration is whether gradual decline occurs in a linear or a nonlinear fashion (Fletcher et al. 1976). Sufficient numbers of people have not yet been followed to distinguish alternative patterns, although the available data indicate acceleration of the decline with aging (Emergil et al. 1971; Fletcher et al. 1976).

In spite of these uncertainties concerning the development of airflow obstruction, the available data indict cigarette smoking as the primary risk factor for excessive loss of FEV_1 (Tables 11 and 12). The findings in both general population samples (Table 11) and occupational and volunteer cohorts (Table 12) have been similar. Recent reports from Belgium (Bande et al. 1980; Clement and van de Woestijne 1982) and from Connecticut (Beck et al. 1982), not readily summarized in tabular form, also described a strong effect of smoking on FEV_1 decline. A few studies have not shown increased loss in cigarette smokers (Howard 1970; De Meyere and Vuylsteek 1971). Even in people with clinically diagnosed airflow obstruction, continued smoking maintains the excess decline of FEV_1 (Hughes et al. 1982), although not all findings are consistent (Ogilvie et al. 1973; Johnston et al. 1976).

Dose–response relationships have been found in many investigations between the amount smoked during followup and the FEV_1 decline (Tables 11 and 12). The reported increases from the lowest to the highest smoking categories range up to 10 to 15 ml annually. Although this additional loss in heavier smokers appears small, if sustained for long periods of time it would shorten the time interval

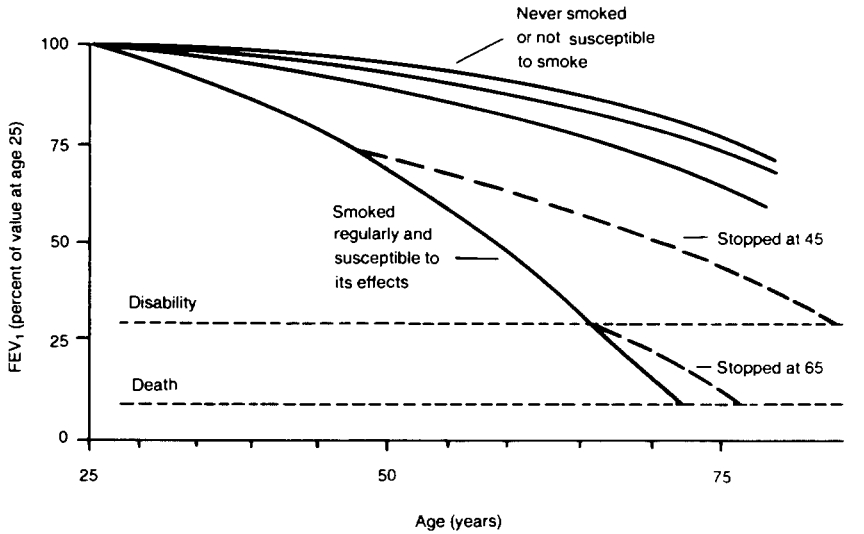

FIGURE 24.—Risks for men with varying susceptibility to cigarette smoke and consequences of smoking cessation

NOTE: + = death.
SOURCE: Fletcher and Peto (1977).

to the development of functional impairment. So far, favorable effects of filter tip smoking and declining tar content on the rate of decline have not been shown (Fletcher et al. 1976; Sparrow et al. 1983b).

Generally, sustained smokers experience a greater loss than those who stop during followup. In the study by Fletcher et al. (1976) of London men, subjects who stopped smoking at the beginning of the followup period lost FEV_1 at the same rate as never smokers. The results of two U.S. studies of ex-smokers are similar (Bosse et al. 1981; Beck et al. 1982). This reduced loss in ex-smokers emphasizes the importance of active smoking and the immediate benefits of smoking cessation (Figure 24). Smokers with reduced FEV_1 may be protected from developing clinically significant loss by timely smoking cessation (Fletcher and Peto 1977).

The distribution of FEV_1 decline has been characterized and described for some populations, including patient groups (Burrows and Earle 1969; Howard 1974; Barter et al. 1974), population samples (Milne 1978), and occupational cohorts (Howard 1970; Fletcher et al. 1976). Similar data are also available for the mid-maximum expiratory flow, another measure of ventilatory function (Bates 1973; Woolf and Zamel 1980). In each of these investigations, the distribution of FEV_1 decline is unimodal (Figure 25); that is, a distinct population with more rapid decline is not sharply separated from those with lesser rates. The modes and medians of the distributions

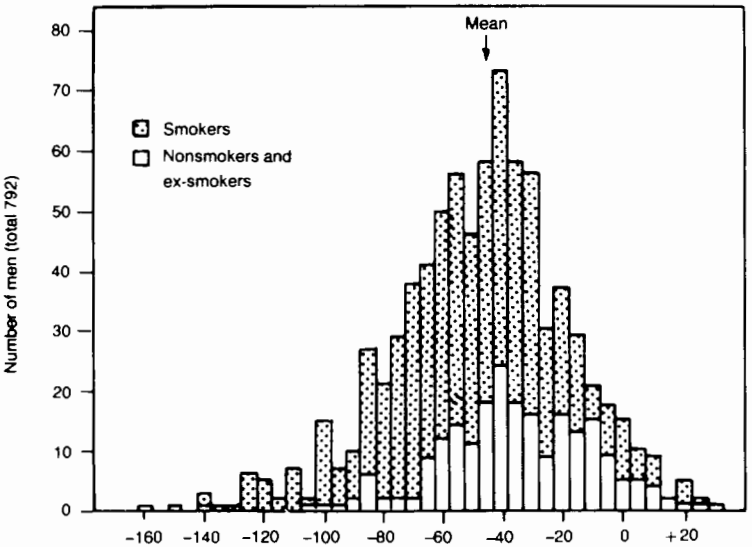

FIGURE 25.—Distribution of 8-year FEV_1 slope in 792 London men

SOURCE: Fletcher et al. (1976).

are generally negative, but some subjects have had positive slopes during the relatively brief followup period of investigations conducted up to this time.

The distributions tend to be skewed by subjects losing FEV_1 more rapidly. The proportion of cigarette smokers is increased among those in the tail of excess loss (Figure 25). For example, Clement and van de Woestijne (1982) examined subjects with excess FEV_1 decline in a prospective study of 2,406 members of the Belgian Air Force. Losses beyond those expected from nonsmokers affected 6 percent of nonsmokers, 7.5 percent of light smokers (<20 cigarettes/day), and 12 percent of heavy smokers (>20 cigarettes/day).

The shape of the distribution of FEV_1 decline has important implications for the development of airflow obstruction. Smokers are not sharply separated from nonsmokers (Figure 25), but more often lose FEV_1 at a rapid rate. Because of this spectrum of severity, not all smokers develop significant airflow obstruction. Although the factors that lead to excessive loss in individual smokers remain uncertain, they may include differences in the pattern of smoking. It is apparent, however, that this susceptible minority can be protected by smoking cessation.

Summary

During the 20 years that have elapsed since the 1964 Surgeon General's Report, the relationship between cigarette smoking and airflow obstruction has been intensively investigated. Surveys of community samples and other groups have established that airflow obstruction is a common condition in the United States and elsewhere. In some populations, as high as 10 percent of adults are affected.

Determinants of lung function level and of the prevalence of airflow obstruction have now been examined in many populations throughout the world. Cigarette smoking is the strongest predictor of abnormal measures of ventilatory function. A causal relationship between cigarette smoking and airflow obstruction is supported by the consistency of the many published reports, the strength of the association, and the evidence for dose–response.

Many risk factors for airflow obstruction other than cigarette smoking have been postulated, including other harmful environmental exposures and the inherent susceptibility of the smoker. Homozygous α_1-antitrypsin deficiency can explain only a minute proportion of the disease burden. The development of airflow obstruction by only a minority of smokers indicates that the interaction of smoking with other factors may influence the risk for specific smokers. Current research emphasizes the potential roles of childhood respiratory illness and airways hyperresponsiveness.

Longitudinal studies have now partially described the prolonged natural history of airflow obstruction. Excessive loss of ventilatory function, beyond that expected from aging alone, results in the development of disease in cigarette smokers. Only a susceptible minority of cigarette smokers lose function at a rate that will eventually cause clinically significant impairment. For this group, timely smoking cessation can prevent the development of disease.

EMPHYSEMA

Introduction

Pulmonary emphysema is frequently present in the lungs of individuals with chronic obstructive lung disease. This section has three purposes: (1) to review the definition, types, and quantification of emphysema; (2) to summarize the physiological and radiographic feature of emphysema; and (3) to discuss critically the relationship of smoking to emphysema, based upon observations in people and in experimental animals. Current concepts of the pathogenesis of emphysema are reviewed elsewhere.

Definition of Emphysema

The generally accepted definition of emphysema is an anatomic condition of the lung characterized by abnormal dilation of air spaces distal to the terminal bronchioles accompanied by destruction of air space walls (American Thoracic Society 1962; Heard et al. 1979). Difficulties with this definition have been discussed by Thurlbeck (1983). Normal air space dimensions have not been determined, and criteria of destruction have not been defined. These limitations hamper attempts to investigate the earliest lesions of emphysema and the subtle effects of environmental agents on lung structure.

Types of Emphysema

British pathologists pointed out in the forties and fifties that emphysematous lesions in certain people involved the respiratory bronchioles, which appeared as grossly enlarged airspaces in the center of the primary lung lobules surrounded by normal lung. In other individuals, the alveolar ducts were involved early, and even mild involvement appeared grossly as a coarsening of the architecture of the entire lobule. They designated the two polar patterns of emphysema as centrilobular emphysema (CLE) and panlobular emphysema (PLE) (Heppleston and Leopold 1961). Many lungs either show both types of emphysema or are unclassifiable. Of 122 lungs with emphysema examined by one pulmonary pathologist, 73 were considered mixed or unclassifiable and 49 were clearly CLE or PLE (Mitchell et al. 1970). When the agreement of three pathologists was required, only 27 of the original 122 lungs remained classifiable and 95 were mixed or could not be classified. There were no statistically significant differences between the groups classified as PLE or CLE in any clinical variables. The only nonsmokers in either group had CLE, and the proportion of light smokers (less than 25 pack-years) was very similar between groups. In this study and others (Anderson and Foraker 1973), CLE was most severe in the upper lobes and PLE was uniformly distributed. According to Thurlbeck (1976), a common

combination is CLE in the upper lobes and PLE in the lower lobes; where lobectomies are used for correlation, typing of emphysema is therefore a particularly empty exercise. When emphysema is far advanced, it is often impossible to recognize the site of the initial involvement. Thus, it is not clear whether the differences in prevalence of CLE and PLE are real or represent differences in interpretation by different observers.

Several localized types of emphysema occur in areas around scar tissue (paracicatricial), along interlobar and interlobular septa (paraseptal), and as bullous lesions (which represent the most advanced and extreme distortion of normal lung structure). Bullous deformities occur with any type of emphysema, including CLE and PLE. Occasionally, bullous lesions occupy huge intrapulmonary volumes.

Detection of Emphysema

The detection of emphysema requires suitably prepared lung specimens. At a minimum, this means the lung must be fixed in inflation (Thurlbeck 1964). Fume fixation or fixation by instillation of liquid fixative through the airways is satisfactory, but for optimal evaluation of the latter group, barium impregnation or paper-mounted whole-lung sections should be used. Because lungs with emphysema frequently also have some degree of intrinsic airways disease, the severity of emphysema and the clinical state of the patient may not correlate directly. Pathologists can easily recognize mild degrees of emphysema that are rarely associated with clinical disability.

Quantification of Emphysema

There are a number of techniques for quantifying the volume of lung involved with "obvious" emphysema that are adequately reproducible and correlate well with one another (Thurlbeck 1976; Bignon 1976). Semi-quantitative or subjective scoring methods as well as point counting have been used. These approaches all require lungs inflated to a relevant volume, usually one approximating total lung capacity during life. This can be achieved by a distending pressure of 25 cm H_20 (Thurlbeck 1979; Berend et al. 1980).

In the scoring method, the lung is divided into a number of units and the severity of emphysema in each unit is scored (mild, moderate, or severe receive 1, 2, or 3 points, respectively). The scores for each unit are summed to give a total score for the lung (Ryder et al. 1969). Alternatively, lung slices may be matched by visual comparison to a set of graded standards to achieve an emphysema score (Thurlbeck et al. 1970). These methods include both severity and extent of emphysema, and although they involve subjective judgments, they have proved to be remarkably reproducible.

In the point counting approach, regularly spaced points are superimposed on a lung slice. Each point is recorded as falling on normal parenchyma, emphysematous parenchyma, or nonparenchyma (conducting airways or vessels). The volume proportion of emphysematous lung is recorded. This method can be objective (e.g., if an emphysematous space is taken to be one greater than 1 mm in diameter), but it includes only extent and not severity of emphysema.

Morphometric methods carried out on histologic sections, exemplified by the mean linear intercept (Lm) (Thurlbeck 1967a, b), are strictly objective, but they require careful attention to problems of sampling and are time consuming and insensitive to focal disease. For measurements of the Lm, histologic sections are made of blocks selected by stratified random sampling. The average distance between alveolar walls is determined from the number of intersections of alveolar walls with a line of known length. The internal surface area of the lung can be calculated when the volume of the lung is known (Hasleton 1972).

Pulmonary Function in Emphysema

Because unequivocal proof of the presence of emphysema requires direct examination of lung tissue, the strategies used to characterize the pulmonary function abnormalities associated with emphysema have either involved comparison of functional data collected during life with autopsy or surgical material or have used measurements made exclusively on post-mortem specimens. Two important conclusions from these studies should be noted at the outset. First, impaired air flow during maximal expiratory maneuvers, as reflected in reduced values for the FEV_1, $FEV_{1\%}$, and $FEF_{25-75\%}$, is neither sensitive nor specific for emphysema. It is possible to have severe emphysema without clinical obstructive lung disease (Thurlbeck 1977). It is also possible to have severe chronic obstructive lung disease without having emphysema, even though most patients with advanced chronic obstructive lung disease have some degree of emphysema (Mitchell et al. 1976). Second, none of the tests used to identify early obstructive lung disease, such as closing volume, the single breath N_2 curve, or frequency dependence of compliance, distinguish diminished elastic recoil that may be related to emphysema (see below) from increased resistance in small airways (Buist and Ducic 1979). Even the determination of density dependence of maximum expiratory airflow, once felt to be specific for detecting abnormalities in the caliber of small airways, is not immune to the effects of lung elastic recoil. A decreased effect on maximal expiratory air flow of using low density gas can be caused by decreased elastic recoil (Gelb and Zamel 1981).

Pulmonary function testing of individuals with proven emphysema often shows increases of residual volume, functional residual capacity, and total lung capacity and decreases of maximal expiratory air flow (Boushy et al. 1971; Park et al. 1970; reviewed in Kidokoro et al. 1977). However, because individuals with emphysema commonly also have intrinsic airway disease (Cosio et al. 1978) affecting the results of these pulmonary function tests in the same direction as emphysema, it is clear that these tests are not specific for emphysema. Accordingly, there has been interest in other, more distinctive tests. Among readily applicable tests, the diffusing capacity has proved to be directly related to the extent of emphysema (Park et al. 1970; Boushy et al. 1971; Berend et al. 1979), presumably reflecting a diminution of internal surface area available for gas exchange. The usefulness of the diffusing capacity to identify and estimate emphysema is limited, however, because the measurement is not sensitive to low grades of emphysema (Symonds et al. 1974) or specific for emphysema. Moreover, the results must be interpreted carefully in smokers because the values for diffusing capacity are lower than in nonsmokers, and the difference extends even to young smokers who are not likely to have emphysema (Enjeti et al. 1978; Miller et al. 1983).

Mechanical Properties of the Lungs in Emphysema

Measurements of the pressure–volume characteristics of the lung have generally been regarded as a reliable means of physiologically detecting and quantifying emphysema because (a) patients with emphysema often have increased lung distensibility and correspondingly low transpulmonary pressures (loss of elastic recoil) and (b) the severity of emphysema has seemed to correlate with the change in elastic recoil. It has also been assumed that the regions of lung with emphysema are the cause of the decreased lung elastic recoil, an assumption that appears reasonable because elastic recoil results in part from surface forces at the air-liquid interface and there is less surface area in emphysema.

Recent observations challenge these concepts. Berend and Thurlbeck (1982), using lungs obtained post mortem, could not demonstrate a relationship between indices of lung elasticity and the grade of emphysema in 48 lungs ranging in grade from 2 to 80 (on a scale of 100), and observed (Berend et al. 1981) in emphysematous lungs that the relative increase in compliance of the lower lobes was greater than the upper lobes, even though the emphysema was worse in the upper lobes. Others have also reported poor correlations between emphysema and elastic recoil. Silvers et al. (1980) found decreased elastic recoil and increased total lung capacity in excised human lungs with minimal emphysema, and Schuyler et al. (1978) noted in hamsters given small doses of elastase intravenously that there was

decreased lung elastic recoil at low lung volumes, although the lungs did not show morphometric changes. Guenter et al. (1981) noted that mild emphysema produced by pepsin caused greater changes in lung elasticity than similar degrees of lung destruction produced by endotoxin-induced repetitive leukocyte sequestration. They suggested that these differences may be due to differences in the location of the connective tissue injury within the lung.

Even among those who have reported an association between emphysema and elastic recoil, the correlations have been best when the emphysema was severe (Greaves and Colebatch 1980). Pare et al. (1982) found a correlation between emphysema grade and elastic properties of the lungs in 55 persons; however, in 5 whose surgically removed lung tissue received emphysema scores between 20 and 70 (out of a maximum of 100), the elastic properties of the lungs tested preoperatively were indistinguishable from normal. While such discrepancies probably reflect the limitations of relating the overall elastic properties of both lungs to the morphology of a single lobe, it must also be recognized that the sensitivity of the pressure–volume diagram is limited, since a narrow range of pressure (to 20 cm H_20) depicts the average retractive force from millions of air spaces and the connective tissue network of the lung.

From these recent findings it must be concluded that the relationship between elastic recoil and morphologic measures of emphysema is not highly predictable, and that the decrease of elastic recoil and increase of total lung capacity commonly seen in emphysematous lungs may not result entirely from abnormal mechanical properties in the areas showing emphysema. The mechanical abnormalities may also derive from areas that appear normal, although the possible reasons for this are obscure (reviewed by Thurlbeck 1983). An alternate explanation for this discordance between elastic recoil and morphologic emphysema may be the problems of sampling and grading intrinsic to these morphologic measures.

The work of Michaels et al. (1979) introduces a further complexity to the use of pressure–volume curves as an indicator of emphysema. They found that inhalation of a bronchodilator shifted the curve of smokers in the direction of increased compliance, but had no effect in nonsmokers (Figure 26). Cessation of smoking had the same effect as a bronchodilator. These results were interpreted as indicating that smoking causes some peripheral airway units to constrict and become effectively closed. Thus, pressure–volume studies to detect early changes compatible with emphysema in smokers may give false negative results unless accompanied by studies with bronchodilators.

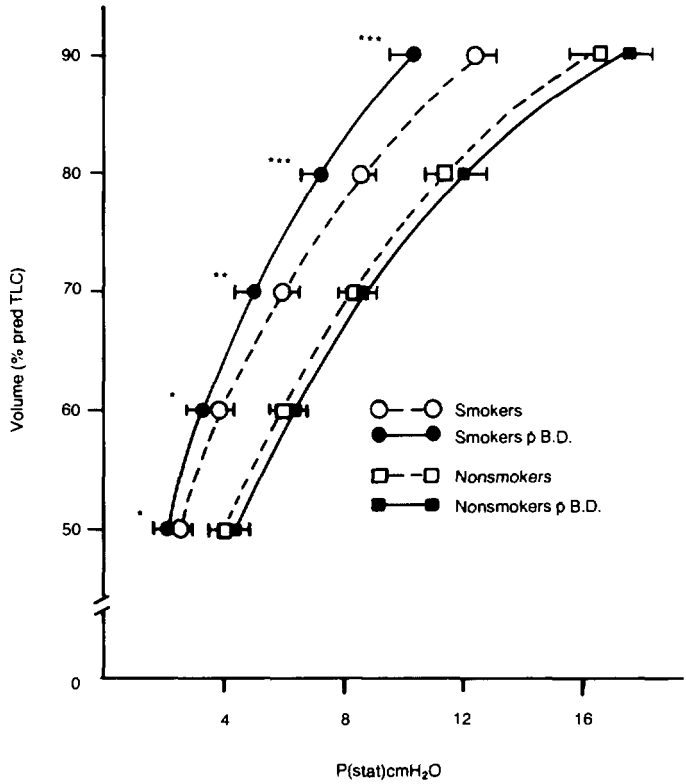

FIGURE 26.—The effect of nebulized bronchodilator on the pressure–volume characteristics of the lungs in 19 smokers (6 men and 13 women) and 16 nonsmokers (9 men and 7 women)

NOTE: The mean age was approximately 40 years (range, 19 to 56) and smokers used approximately 30 cigarettes per day. Male smokers showed borderline significant differences in indices of expiratory airflow and single breath N_2 test data as compared with the male nonsmokers, but there was no difference in these tests between female smokers and nonsmokers. As shown, smokers had significantly less elastic recoil than nonsmokers. After the bronchodilator, the difference between smokers and nonsmokers increased further, particularly at high lung volume.

B.D. = broncodilator; % pred. TLC = percent predicted total lung capacity; P(stat) = transpulmonary pressure.
$^{*}p<0.05$; $^{**}p<0.01$; $^{***}p<0.005$.
SOURCE: Michaels et al. (1979).

Aging and Lung Structure

With advancing age, structural and functional changes occur in the lungs of virtually all adults, even those who have no known exposure to specific inhalants through occupation or personal habits (Fishman 1982; Campbell and Lefrak 1983). The elastic recoil of the lungs declines with aging, and the residual volume to total lung capacity ratio increases. These changes are seen even in people who have never smoked, do not have signs or symptoms of cardiorespiratory disease, and have the normal (MM) phenotype of α_1-antiprotein-

ase (Knudson et al. 1977). Also with aging, the average distance between alveolar walls increases (Thurlbeck 1967a; Hasleton 1972), the proportion of lung volume that is composed of alveoli decreases, and the proportion of alveolar ducts increases (Ryan et al. 1965).

Whether the differences in the lungs that occur with aging are a consequence only of the passage of time or are the result of subtle environmental insults summed over many years is unanswerable. They are "normal" or "abnormal" depending on whether one regards "normal" as a statistical concept or as the optimal state for the tissue. In either case, the aging lung has some features similar to emphysema. Age changes alone will not, however, contribute to or obscure the diagnosis of centrilobular emphysema, which involves mainly respiratory bronchioles, recognized macroscopically as focal lesions against a background of normal lung. The age changes may overlap with early panlobular emphysema (Anderson et al. 1970). However, since smokers usually die at an earlier age than nonsmokers, aging cannot account for the differences observed between the lungs of smokers and nonsmokers at autopsy.

Emphysema and Cigarette Smoking

Studies of people and of experimental animals conclusively link cigarette smoking to the development and extent of emphysema. This information is summarized in the following discussion.

Observations in People

Post-mortem material, used to approach the problem in the 1960s and 1970s, clearly established an association between smoking and emphysema. Post-mortem lung tissue has continued to be used to study emphysema, but the main goal of recent studies has been to identify those physiologic features that correlate with emphysema rather than to quantify the relationship between smoking and emphysema. Studies of emphysema using surgically removed lung tissue, a more recent approach to studying emphysema, have aimed mainly at elucidating the physiology of the emphysematous lung. The results of these studies have involved smokers almost exclusively because of the rarity of emphysema in nonsmokers.

Studies Using Post-Mortem Material

A number of studies have examined the relationship between cigarette smoking and emphysema (Anderson et al. 1964, 1966; Thurlbeck 1963; Thurlbeck et al. 1974; Ryder et al. 1971; Auerbach et al. 1972, 1974; Spain et al. 1973). These data emphasize that not only is cigarette smoking closely associated with the development and extent of emphysema, but also it is extremely rare for the forms

of emphysema found in patients with COLD to be present to a significant degree in nonsmokers.

Thurlbeck (1963) reported 19 patients who had severe emphysema at autopsy. All 19 were cigarette smokers, in contrast to 18 smokers out of 38 patients who did not have significant emphysema at autopsy. Anderson et al. (1964) conducted a more systematic evaluation of the relationship between cigarette smoking and the degree of emphysema at autopsy. They found that 12 of 23 patients without emphysema were cigarette smokers, whereas 55 of 84 with mild emphysema, 30 of 33 with moderate emphysema, and 14 of 15 with severe emphysema were cigarette smokers. Petty et al. (1967) reported similar findings, with 6 of 57 patients with moderate emphysema at autopsy being nonsmokers and only 1 of 61 patients with severe emphysema being a nonsmoker. Ryder et al. (1971) found that of 21 patients whose lungs showed more than 25 percent emphysema, only 1 was a nonsmoker.

Thurlbeck et al. (1974) examined the relationship of age to extent of emphysema in smokers compared with nonsmokers in the combined autopsy populations of the teaching hospitals in three separate cities. The severity of emphysema was quantified using a panel grading method, with a score under 25 representing mild emphysema. They found that the degree of emphysema increased slightly in nonsmokers beginning in the fifth decade and reached an average score of 10 to 15 in men and 4 to 6 in women by the eighth and ninth decades. In contrast, male smokers had an average score of 25 to 30 by the seventh decade and maintained this level for the next two decades.

Sutinen et al. (1978) (Table 13) examined the relationship between prevalence and extent of emphysema and duration of the smoking habit. As would be expected from previous studies, moderate or severe emphysematous changes were limited to smokers. However, these changes were also limited to those smokers who had smoked for 20 or more years, and severe emphysema was reported only in those who had smoked for 40 years or more. These data, coupled with that of Thurlbeck et al. (1974) describing only mild emphysematous changes in nonsmokers with advancing age, suggest that emphysema is a late pathologic change in cigarette-induced lung disease. This correlates well with the clinical experience of severe emphysema being rare prior to the fifth decade. It also suggests that cessation, even among middle-aged smokers, may have substantial impact on emphysema morbidity and mortality.

Dose–Response Relationships

Some studies have reported the extent of emphysematous change in smokers of different numbers of cigarettes per day. Spain et al. (1973) examined the lungs of 134 subjects who died suddenly and

TABLE 13.—Correlation between the severity of emphysema at autopsy and total smoking duration

Grade of emphysema	Prevalence of emphysema (percent) by total smoking years				
	0	1–19	20–39	40 or more	Total
No emphysema	61.6	81.6	21.2	8.8	43.1
Mild (grades 5 to 20)	38.4	15.4	69.7	50.0	45.8
Moderate (grades 30 to 50)	–	–	9.1	26.5	7.8
Severe (grade 60 or more)	–	–	–	14.7	3.3
All grades	38.4	15.4	78.8	91.8	56.9
Total number	73	13	33	34	153

NOTE: $P < 0.0005$; X^2 test, with groups of moderate and severe emphysema and of smoking times 1–19 and 20–39 years combined.

SOURCE: Sutinen et al. (1978).

who had no previous history of lung disease. They found emphysematous changes greater than grade 20 (mild emphysema) in 10 percent of nonsmokers, 36 percent of smokers of less than one pack per day, and 39 percent of smokers of more than one pack.

A much larger study was conducted by Auerbach et al. (1972, 1974), who examined whole lung sections from 1,443 men and 388 women autopsied between 1963 and 1970. Table 14 describes the relationship of age, smoking habits, and degree of emphysema graded on a scale of 0 to 9, with 9 representing severe emphysema. It is clear that severe emphysema is limited to smokers, and that the severity of emphysematous change at autopsy increases with increasing number of cigarettes smoked per day during life. This study also found that almost all (94.5 percent) smokers of more than one pack per day had some degree of emphysema (slight, moderate, advanced, or far advanced) (Table 15). In contrast, 93.8 percent of nonsmokers had either none or minimal emphysema. This evidence would suggest that emphysematous change is a nearly universal phenomenon in heavy smokers, but is rare in nonsmokers, and that it is the large ventilatory reserve of the lungs that restricts clinically manifest disease to those individuals with far advanced emphysema. Similar results were reported in a more limited number of autopsies done on female smokers (Auerbach et al. 1974) (Table 16).

A study of microscopic lung sections from the autopsies of 1,436 men and 388 women was also reported by Auerbach et al. (1974), and closely paralleled the results of the whole lung study. However, they also reported the results in smokers who had quit for more than or less than 10 years prior to death (Table 17). The degree of emphysematous change was still related to the amount smoked, but

TABLE 14.—Degree of emphysema in current smokers[a] and in nonsmokers, according to age groups

Age group	Degree of emphysema	Subjects who never smoked regularly	Current pipe or cigar smokers	Current cigarette smokers†			
				<½†	½–1†	1–2†	2+ †
<60	0–0.75	53	18	12	3	2	—
	1–1.75	2	11	4	9	24	5
	2–2.75	—	1	2	17	130	56
	3–3.75	—	1	5	12	50	38
	4–4.75	—	—	—	4	8	7
	5–6.75	—	—	—	—	4	5
	7–9.00	—	—	—	—	3	1
	Totals	55	31	23	45	221	112
	Mean	0.10	0.83	1.29	2.37	2.56	2.86
	SD	0.04	0.13	0.26	0.16	0.07	0.10
60–69	0–0.75	35	17	4	—	—	—
	1–1.75	1	8	1	—	4	1
	2–2.75	2	3	4	5	37	23
	3–3.75	2	2	2	9	42	24
	4–4.75	—	—	1	3	11	9
	5–6.75	—	—	—	1	8	1
	7–9.00	—	—	—	1	5	4
	Totals	40	30	12	19	107	62
	Mean	0.39	0.95	1.90	3.59	3.39	3.37
	SD	0.13	0.16	0.34	0.35	0.15	0.20
70 or older	0–0.75	68	21	2	—	—	—
	1–1.75	4	28	10	8	2	2
	2–2.75	5	22	13	23	40	9
	3–3.75	4	8	5	10	38	18
	4–4.75	—	2	1	7	11	7
	5–6.75	—	1	—	2	9	3
	7–9.00	—	—	—	1	12	5
	Totals	81	82	31	51	112	44
	Mean	0.50	1.66	2.15	2.98	3.68	3.91
	SD	0.39	0.11	0.17	0.20	0.17	0.27

[a] Subjects who smoked regularly up to time of terminal illness.
†Packages/day.

SOURCE: Auerbach et al. (1972).

was less in those who had quit for more than 10 years prior to death, suggesting that the cessation of smoking results in a slowing of the

TABLE 15.—Age-standardized percentage distribution of male subjects in each of four smoking categories, according to degree of emphysema

Degree of emphysema	Subjects who never smoked regularly (%)	Current pipe or cigar smokers (%)	Current cigarette smokers (%)	
			<1*	1+ *
0–0.75 (none)	90.0	46.5	13.1	0.3
1–1.75 (minimal)	3.8	33.0	16.4	5.2
2–2.75 (slight)	3.3	13.0	33.7	42.6
3–3.75 (moderate)	2.9	6.3	25.1	32.7
4–9.00 (advanced to far advanced)	0	1.2	11.7	19.2
Totals	100.0	100.0	100.0	100.0

*Packages/day.

SOURCE: Auerbach et al. (1972).

TABLE 16.—Means of the numerical values given lung sections at autopsy of female current smokers, standardized for age

	Subjects who never smoked regularly	Current cigarette smokers	
		<1 Pk.	≥1 Pk.
Number of subjects	252	33	64
Emphysema	0.05	1.37	1.70
Fibrosis	0.37	2.89	3.46
Thickening of arterioles	0.06	1.26	1.57
Thickening of arteries	0.01	0.40	0.64

NOTE: Numerical values were determined by rating each lung section on scales of 0–4 for emphysema and thickening of the arterioles, 0–7 for fibrosis, and 0–3 for thickening of the arteries.

SOURCE: Auerbach et al. (1974).

rate of progression of emphysematous change in those who quit compared with those who continue to smoke.

Studies of Alpha$_1$-Proteinase-Inhibitor-Deficient Individuals

The deficiency of α_1-proteinase inhibitor is an experiment of nature with broad implications for understanding the pathogenesis of emphysema (Idell and Cohen 1983). Discovery of homozygous-deficient subjects (type PiZZ) with only 10 percent of normal plasma

TABLE 17.—Means of the numerical values given lung sections at autopsy of male former cigarette smokers, standardized for age

	Never smoked regularly	Stopped ≥10 years		Stopped <10 years	
		Formerly smoked			
		<1 Pack	>1 Pack	<1 Pack	>1 Pack
Number of subjects	175	35	66	51	131
Emphysema	0.09	0.24	0.70	1.08	1.69
Fibrosis	0.40	1.14	1.74	2.44	3.30
Thickening of arterioles	0.10	0.57	0.93	1.25	1.59
Thickening of arteries	0.02	0.04	0.16	0.36	0.61

NOTE: Numerical values for each finding were determined by rating each lung section on scales of 0–4 for emphysema and thickening of the arterioles, 0–7 for fibrosis, and 0–3 for thickening of the arteries.
SOURCE: Auerbach et al. (1974).

proteinase inhibitory activity and the demonstration of the frequent early development of emphysema in such subjects (Orell and Mazodier 1972) called attention to the critical step of fibrous tissue proteolysis in the remodeling of lung structure. It also pointed to at least one potential explanation for the variability in extent of emphysema among smokers.

Together with data from animal experiments, the discovery of the PiZZ defect and its association with emphysema has led to general acceptance of a theory of imbalance between the extracellular levels of proteinase and proteinase inhibitor in the lung as the cause of panacinar emphysema in subjects with this deficiency. The pathogenetic lessons learned from α_1-proteinase-inhibitor deficiency also afford plausible explanations for other forms of emphysema, especially emphysema associated with cigarette smoking.

Homozygous Deficient—PiZZ

In his classic description of the severe (PiZZ) deficiency of the α_1-proteinase inhibitor, Eriksson (1965) did not indicate an effect of cigarette smoking on the development of emphysema. Later studies, however, did recognize smoking as a potential aggravating factor (Kueppers and Black 1974; Larsson 1978) and reported that PiZZ persons who smoked cigarettes were destined to experience shortness of breath 10 to 15 years earlier (Figure 27) and to die sooner than PiZZ persons who did not smoke (Figure 28).

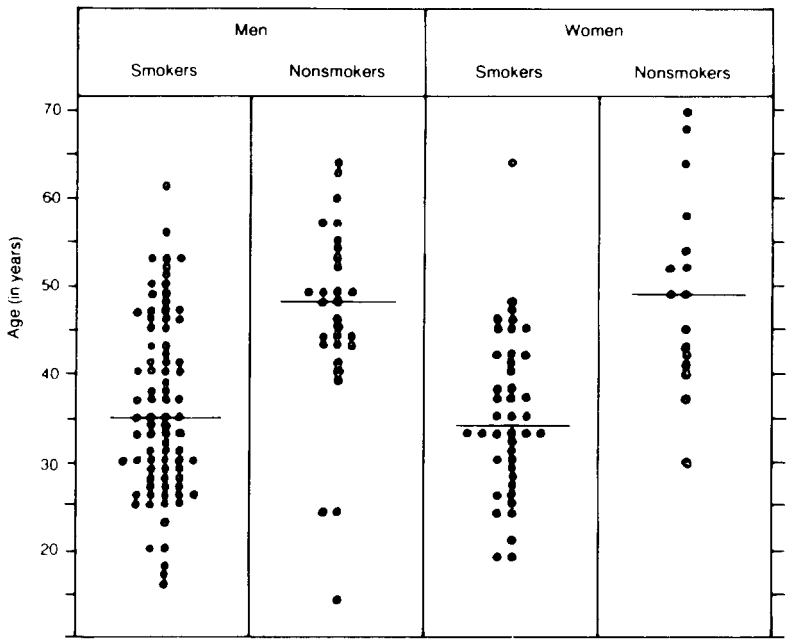

FIGURE 27.—Age at onset of dyspnea in 169 PiZZ individuals separated according to sex and smoking history

NOTE: The horizontal lines show the median values. The difference between nonsmokers and smokers was highly significant for both sexes and was 13 and 15 years for men and women, respectively.

SOURCE: Larsson (1978).

More recent studies, however, have shown considerable variation in the rate of decline of lung function among middle-aged PiZZ adults (Buist et al. 1983). In a comparison of 22 persons with PiZZ phenotype who had never smoked with 36 PiZZ smokers, Black and Kueppers (1978) found variability in symptoms and lung function abnormalities in both groups. Smokers generally sought medical attention earlier, and those who reached the older age groups, such as 60 to 69, had smoked less and started to smoke later in life. There was overlap in these characteristics between the age groups, however, and some smokers did live into the 50 to 69 age range. In this analysis, the correlations between pulmonary function test abnormalities and pack-years of cigarette smoking were small.

The British Thoracic Society, in a multicentered study of PiZZ individuals (Tobin et al. 1983), reported an association between

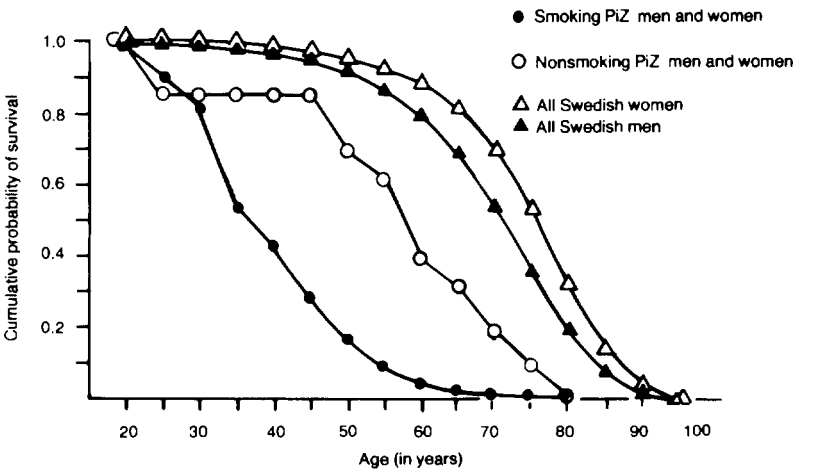

FIGURE 28.—The cumulative probability of survival, given that 20 years of age is reached, in smoking and nonsmoking Swedish PiZZ individuals, compared with all Swedish men and women

NOTE: Survival was higher for PiZZ nonsmokers than for PiZZ smokers in both sexes above age 35.
SOURCE: Larsson (1978).

cigarette smoking and the onset of pulmonary symptoms and deterioration of lung function, but demonstrated no significant correlation between the quantity of tobacco consumed and the extent of pulmonary dysfunction. A notable finding in this study, applicable to other studies of the natural history of disease related to α_1-proteinase-inhibitor deficiency, was the impressive difference between individuals found because of medical complaints (index cases) and those detected by surveys (nonindex cases). Nonindex cases had better pulmonary function and survived longer than index cases, irrespective of other variables such as age and smoking history. The distinction between these two categories of subjects suggests the importance of factors besides the PiZZ phenotype in the development of symptomatic lung disease in PiZZ persons.

PiZZ individuals who smoke increase their risk for early onset of symptomatic chronic obstructive lung disease and for a shortened lifespan, compared with nonsmoking PiZZ individuals. However, pulmonary function data have shown only limited differences in diffusing capacity and elastic recoil between the smokers and the nonsmokers (Black and Kueppers 1978).

Heterozygous Deficient—PiMZ

The PiMZ phenotype of α_1-antiproteinase inhibitor occurs in approximately 3 percent of the population. Because of the high frequency of emphysema in PiZZ persons, it is important to establish whether PiMZ individuals also have an increased risk of emphysema and chronic obstructive lung disease. From the unpredictability of obstructive lung disease even among those with the PiZZ phenotype, however, one might expect difficulty in discerning the effect of the PiMZ phenotype.

Among adults with symptomatic chronic obstructive lung disease, the PiMZ phenotype is more prevalent than expected (Mittman 1978). It is uncertain whether this means of subject identification is appropriate, as was noted concerning index and nonindex PiZZ individuals. Madison et al. (1981) emphasized the complexity of this issue by noting that the PiMZ phenotype was only one of several factors that appeared to be related to the risk of obstructive lung disease. Other factors identified as relevant included smoking, a family history of lung diseases, and being male.

From studies of children and young adults it is evident that the PiMZ phenotype does not strongly predispose to chronic pulmonary disease. Thus, PiMZ children (Buist et al. 1980) failed to show any early changes of lung dysfunction analogous to what has been observed in some young PiZZ individuals; PiMZ adults below the age of 40 had the same results by spirometry and the single breath N_2 test as PiMM individuals matched for smoking history (Buist et al. 1979b).

Numerous studies involving older subjects indicate that PiMZ individuals preserve their lung function, as measured by spirometry, compared with controls matched for smoking (Tattersall et al. 1979, de Hamel and Carrell 1981). The elastic properties of the lungs may be different in PiMZ persons, but if there are differences, they are small. Larsson et al. (1977) reported that 50-year-old PiMZ men who smoked had reduced elastic recoil at total lung capacity compared with PiMZ nonsmokers, even though they had no evidence of impaired air flow. The PiMZ nonsmokers were indistinguishable from PiMM nonsmokers. Tattersall et al. (1979) also found no effect upon airflow in PiMZ middle-aged men, and a statistically nonsignificant decrease in elastic recoil. Using an index of the slope of the pressure–volume curve, Knudson and Kaltenborn (1981) found no significant reduction in elastic recoil of PiMZ subjects compared with matched PiM controls.

There is little direct information about the occurrence of emphysema among PiMZ individuals. In an autopsy study, Eriksson et al. (1975) found emphysema among 13 of 26 subjects with diastase-resistant PAS-positive inclusions in the liver, compared with an incidence of emphysema of only 18 percent in the controls. Although

these findings suggest an increased occurrence of emphysema with the PiMZ phenotype, this study should be interpreted cautiously because the smoking histories of the subjects and the quantification of the emphysema were not included. Moreover, the significance of the PAS-positive inclusions is not certain, because one recent study found that such inclusions represented immunoreactive α_1-proteinase inhibitor in only half of the tissue studied (Qizilbash and Young-Pong 1983).

It may be concluded from the studies involving α_1-proteinase-inhibitor-deficient people that for those with the PiMZ phenotype, smoking has not been shown to promote a greater risk of emphysema than it does in PiMM persons. In the rare individual with PiZZ, the risk of emphysema is extremely high in both smokers and nonsmokers, but PiZZ smokers experience an earlier onset and more severe chronic obstructive lung disease than PiZZ nonsmokers.

Observations in Experimental Animals

Experimental animals have been subjected to cigarette smoke to examine whether changes typical of emphysema result. As noted below, it appears that cigarette smoke exposure can produce emphysematous-like changes in the lungs under experimental conditions, but the exposure must be quite prolonged and intense, or additional factors must be employed to "sensitize" the lungs to the effects of cigarette smoke.

Pioneering studies in dogs exposed to cigarette smoke, by Hernandez et al. (1966) and by Auerbach et al. (1967), indicated effects consistent with emphysema, but these reports did not include quantitative morphology or data about the mechanical properties of the lungs. Moreoever, the exposures may have created problems of hypoxemia and infection that may have influenced the responses to cigarette smoke. Contrary to these findings, in later studies, beagles that inhaled cigarettes by face mask in four sessions per day for up to 1 year—an inhalation sufficient to raise the blood carboxyhemoglobin saturation to 5.4 $\pm$ 0.9 percent—had no statistically significant changes in mean linear intercept or internal surface area, although their large airways showed epithelial cell hyperplasia, proliferation of goblet cells, and peribronchial inflammation (Park et al. 1977).

Recently, Hoidal and Niewoehner (1983) presented data suggesting that cigarette smoke may be an important cofactor in the development of elastase-induced emphysema. They found that inhalation of cigarette smoke led to severe emphysema in hamsters if used in conjunction with doses of elastase that did not produce emphysema when used alone. In this study, hamsters were exposed to cigarette smoke for 15 minute periods, six times per day, 6 days per week for 7 weeks in standardized chambers. The animals were challenged with small doses of elastase given intratracheally; controls consisted of

animals given either elastase or smoke exposure or neither. Animals receiving only smoke or only elastase showed no changes of mean linear intercept or volume–pressure relationship of the excised lungs, compared with animals given neither elastase nor smoke exposure. The combinations of smoking followed by elastase or smoking both before and after elastase produced statistically significant increases of mean linear intercept, displacement upward and to the left of the volume–pressure curves (Figure 29), and marked emphysema by light microscopy of inflation-fixed lungs. The mechanism of the synergism between elastase and smoking was not elucidated. One possibility considered was that cigarette smoke impaired the repair mechanism normally triggered by elastase exposure, a possibility supported by Osman et al. (1982), who found that hamsters exposed to cigarette smoke after intratracheal elastase did not show the heightened lung elastin synthesis typically seen after lung injury produced by elastase.

Summary

Clinically significant degrees of emphysematous lung destruction are commonly present in individuals with COLD. Severe emphysema occurs almost exclusively in cigarette smokers and those with homozygous α_1-antitrypsin deficiency. The extent of emphysematous change increases with increasing numbers of cigarettes smoked per day and with the duration of the smoking habit. While clinically significant emphysema is limited to a minority of those who smoke, most heavy smokers have some degree of emphysematous change by the sixth decade of life.

Individuals with homozygous α_1-antitrypsin deficiency have an exceptionally high risk of developing emphysema. This risk is present for both smokers and nonsmokers, but smokers with α_1-antiprotease deficiency develop clinical symptoms earlier in life. It is unclear whether individuals with heterozygous antiprotease phenotypes are at increased risk of developing COLD.

Summary and Conclusions

1. Cigarette smoking is the major cause of COLD morbidity in the United States; 80 to 90 percent of COLD in the United States is attributable to cigarette smoking.
2. In population-based studies in the United States, cigarette smoking behavior is often the only significant predictor for the development of COLD. Other factors improve the predictive equation only slightly, even in those populations where they have been found to exert a statistically significant effect.
3. In spite of over 30 years of intensive investigation, only cigarette smoking and α_1-antiprotease deficiency (a rare genet-

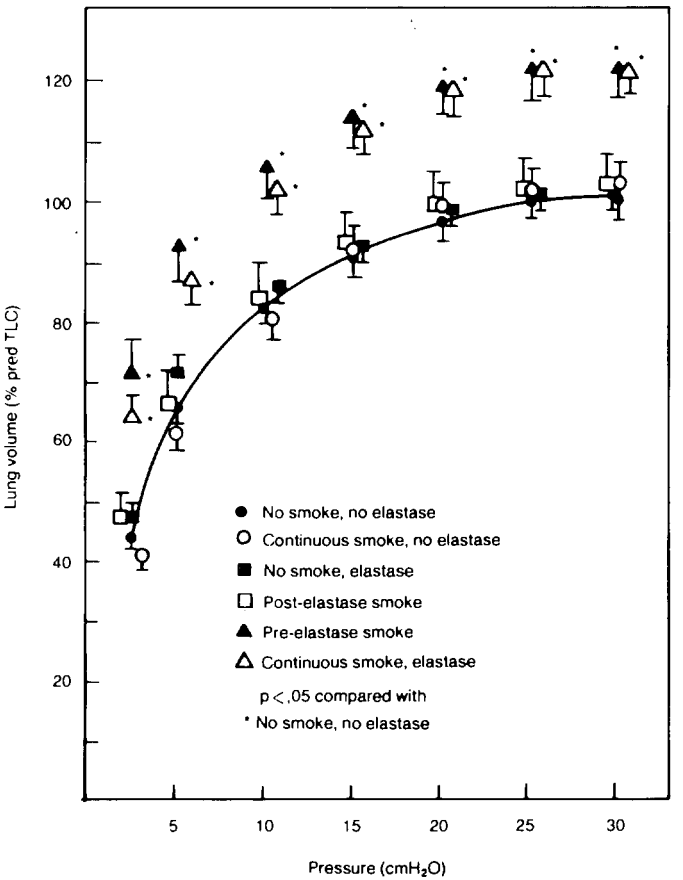

FIGURE 29.—The effects of combining cigarette smoking and elastase upon the pressure–volume characteristics of the lungs of experimental animals

NOTE: The in vitro measurements of lung volume are shown as percentage of predicted total lung capacity (TLC) relative to transpulmonary pressure of hamster lungs following in vivo exposure to various combinations of cigarette smoke and intratracheally administered pancreatic elastase. Values are the mean ± SEM of measurements made during deflation. The animals that smoked and then received elastase (Pre-Elastase Smoke) and those that smoked both before and after elastase (Continous Smoke, Elastase) had significant changes in the elastic properties of the lungs. There were no changes from control if elastase or smoking were used separately or when smoking occurred only after elastase.

SOURCE: Hoidal and Niewoehner (1983).

ic defect) are established causes of clinically significant COLD in the absence of other agents.

4. Within a few years after beginning to smoke, smokers experience a higher prevalence of abnormal function in the small airways than nonsmokers. The prevalence of abnormal small airways function increases with age and the duration of the

smoking habit, and is greater in heavy smokers than in light smokers. These abnormalities in function reflect inflammatory changes in the small airways and often reverse with the cessation of smoking.

5. Both male and female smokers develop abnormalities in the small airways, but the data are not sufficient to define possible sex-related differences in this response. It seems likely, however, that the contribution of sex differences is small when age and smoking exposure are taken into account.
6. There is, as yet, inadequate information to allow a firm conclusion to be drawn about the predictive value of the tests of small airways function in identifying the susceptible smoker who will progress to clinical airflow obstruction.
7. Smokers of both sexes have a higher prevalence of cough and phlegm production than nonsmokers. This prevalence increases with an increasing number of cigarettes smoked per day and decreases with the cessation of smoking.
8. Differences between smokers and nonsmokers in measures of expiratory airflow are demonstrable by young adulthood and increase with number of cigarettes smoked per day.
9. The rate of decline in measures of expiratory airflow with increasing age is steeper for smokers than for nonsmokers; it is also steeper for heavy smokers than for light smokers. After the cessation of smoking, the rate of decline of lung function with increasing age appears to slow to approximately that seen in nonsmokers of the same age. Only a minority of smokers will develop clinically significant COLD, and this group will have demonstrated a more extensive decline in lung function than the average smoker. The data are not yet available to determine whether a rapid decline in lung function early in life defines the subgroup of smokers who are susceptible to developing COLD.
10. Clinically significant degrees of emphysema occur almost exclusively in cigarette smokers or individuals with genetic homozygous α_1-antiprotease deficiency. The severity of emphysema among smokers increases with the number of cigarettes smoked per day and the duration of the smoking habit.

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Appendix Tables

TABLE A.—FEV_1 for white adults, by smoking status, sex, and age, United States, 1971–1975

Cigarette smoking status (by age)	Both sexes					Men					Women				
	N	n	Mean	SD	SE	N	n	Mean	SD	SE	N	n	Mean	SD	SE
Never smokers															
25–74			3140[1]		21[1]			3669[1]		39[1]			2664[1]		19[1]
25–34	6733	394	3607	791	51	2633	130	4404	584	63	4099	264	3095	372	26
35–44	5278	291	3171	607	49	1669	81	3742	591	73	3609	210	2907	397	40
45–54	4942	353	2840	594	35	1206	85	3487	626	72	3736	268	2631	401	29
55–64	3660	251	2511	589	31	880	59	3215	531	81	2781	192	2289	401	29
65–74	2875	235	2148	549	36	481	43	2856	627	96	2394	192	2006	402	36
Ex-smokers															
25–74			3112		24			3623		37			2651		28
25–34	2811	160	3677	810	80	1359	66	4303	627	92	1452	94	3091	441	55
35–44	3086	171	3566	767	69	1828	94	4013	643	70	1258	77	2916	361	44
45–54	3323	213	3155	742	65	2345	143	3414	683	69	978	70	2535	454	65
55–64	2669	181	2845	693	63	1826	130	3087	649	63	843	51	2319	456	90
65–74	1769	157	2388	686	66	1270	121	2533	699	78	499	36	2020	487	92
Smokers															
25–74			2878		20			3281		32			2514		27
25–34	8885	487	3567	752	44	4792	239	4037	639	51	4093	248	3018	435	41
34–44	5849	320	3166	655	47	3027	158	3507	639	71	2822	162	2800	439	43
45–54	5606	374	2761	623	37	2743	182	3126	579	49	2863	192	2411	437	40
55–64	3251	192	2416	631	50	1700	108	2738	632	63	1551	84	2064	400	50
65–74	933	84	2071	653	86	534	56	2222	556	79	400	28	1869	714	155

TABLE A.—Continued

Cigarette smoking status (by age)	Both sexes					Men					Women				
	N	n	Mean	SD	SE	N	n	Mean	SD	SE	N	n	Mean	SD	SE
Light smokers															
25–74			2951		38			3311		57			2626		52
25–34	2162	113	3425	650	97	879	43	3914	508	102	1283	70	3089	508	88
35–44	1267	72	3106	618	93	308	17	3775[2]	515	139	859	55	2891	479	83
45–54	1090	76	2683	490	73	383	24	3009	409	95	707	52	2507	437	76
55–64	1043	57	2408	573	83	313	18	2919[2]	660	150	730	39	2190	350	62
65–74	304	21	2150	737	185	131	11	2222[2]	426	130	172	10	2095[2]	901	305
Moderate smokers															
25–74			2878		23			3335		40			2466		25
25–34	4269	235	3671	810	60	2534	123	4136	684	69	1735	112	2991	393	51
35–44	2413	130	3217	646	68	1214	66	3593	624	99	1199	64	2836	395	47
45–54	2715	179	2679	634	53	1145	75	3106	622	79	1570	104	2368	429	51
55–64	1287	82	2406	589	68	690	45	2776	455	60	597	37	1977	408	70
65–74	464	44	2023	609	105	261	28	2279	572	126	203	16	1693[2]	484	124
Heavy smokers															
25–74			2785		32			3202		52			2409		38
25–34	2417	136	3514	699	70	1363	72	3927	597	82	1054	64	2979	393	80
35–44	2148	116	3143	684	71	1505	75	3382	646	89	643	41	2582	373	64
45–54	1779	118	2930	649	70	1193	82	3184	579	75	586	36	2411	440	92
55–64	922	53	2440	741	118	697	45	2619	737	133	224	8	1883[2]	398	121
65–74	154	18	2038[2]	606	151	130	16	2096[2]	638	172	24	2	1733[2]	215	150

NOTE: N = weighted population estimate in thousands; n = number of people in sample; SD = standard deviation; SE = standard error.

[1] Adjusted by the direct method to reflect the age distribution of the U.S. population at the midpoint of the survey.

[2] Does not meet standards of reliability.

SOURCE: National Center for Health Statistics. Unpublished data from the first National Health Nutrition and Examination Survey (NHANES 1).

TABLE B.—Flow at 25 percent of FVC for white adults, by smoking status, sex, and age, United States, 1971–1975

Cigarette smoking status (by age)	Both sexes					Men					Women				
	N	n	Mean	SD	SE	N	n	Mean	SD	SE	N	n	Mean	SD	SE
Never smokers															
25–74			6253[1]		47[1]			7261[1]		91[1]			5343[1]		36[1]
25–34	6733	394	6639	1591	98	2633	130	7871	1513	157	4099	264	5847	1042	89
35–44	5278	291	6377	1484	114	1669	81	7715	1545	176	3609	210	5758	952	80
45–54	4942	353	5742	1586	90	1206	85	7262	1796	213	3736	268	5252	1141	70
55–64	3660	251	5368	1397	101	880	59	6543	1593	265	2781	192	4996	1091	83
65–74	2875	235	4626	1576	102	481	43	6097	1951	298	2394	192	4331	1303	108
Ex-smokers															
25–74			6093		62			7095		107			5188		67
25–34	2811	160	6835	1855	203	1359	66	8042	1715	285	1452	94	5705	1126	165
35–44	3086	171	7020	2041	176	1828	94	7956	2059	232	1258	77	5659	965	116
45–54	3323	213	6270	1896	164	2345	143	6765	1919	185	978	70	5084	1176	151
55–64	2669	181	5783	1764	144	1826	130	6261	1820	160	843	51	4749	1058	197
65–74	1769	157	4918	1948	207	1270	121	5194	2091	265	499	36	4213	1278	197
Smokers															
25–74			5647		47			6362		88			5002		52
25–34	8885	487	6760	1694	102	4792	239	7606	1663	126	4093	248	5769	1081	83
35–44	5849	320	6157	1740	123	3027	158	6848	1875	180	2822	162	5415	1200	102
45–54	5606	374	5471	1658	92	2743	182	6130	1783	137	2863	192	4840	1233	106
55–64	3251	192	5123	1815	132	1700	108	5567	2041	223	1551	84	4636	1372	169
65–74	933	84	3954	1586	181	534	56	4199	1745	238	400	28	3627	1274	255

TABLE B.—Continued

Cigarette smoking status (by age)	Both sexes					Men					Women				
	N	n	Mean	SD	SE	N	n	Mean	SD	SE	N	n	Mean	SD	SE
Light smokers															
25–74			5834		91			6569		142			5171		112
25–34	2162	113	6549	1652	209	879	43	1688	1690	293	1283	70	5769	1071	140
35–44	1267	72	6045	1481	211	308	17	7250[2]	1634	369	959	55	5658	1193	188
45–54	1090	76	5545	1476	217	383	24	6373	1572	311	707	52	5096	1203	193
55–64	1043	57	5222	1534	238	313	18	6096[2]	1616	399	730	39	4849	1333	249
65–74	304	21	3779	1272	345	131	11	3742[2]	1279	482	172	10	3807[2]	1266	489
Moderate smokers															
25–74			5661		66			6430		118			4967		76
25–34	4269	235	6909	1719	136	2534	123	7647	1667	164	1735	112	5831	1120	132
35–44	2413	130	6384	1786	194	1214	66	7348	1738	236	1199	64	5408	1212	170
45–54	2715	179	5269	1490	111	1145	75	5821	1661	183	1570	104	4867	1202	137
55–64	1287	82	5065	1787	202	690	45	5576	1897	334	597	37	4475	1439	265
65–74	464	44	3950	1717	304	261	28	4356	1892	404	203	16	3427[2]	1285	319
Heavy smokers															
25–74			5485		85			6219		151			4822		111
25–34	2417	136	6691	1659	166	1363	72	7468	1640	225	1054	64	5685	1018	176
35–44	2148	116	5964	1815	198	1505	75	6363	1902	261	643	41	5031	1084	186
45–54	1779	118	5712	1940	207	1193	82	6326	1920	251	586	36	4458	1257	260
55–64	922	53	5090	2117	321	697	45	5322	2288	434	224	8	4370[2]	1202	353
65–74	154	18	4155[2]	1653	401	130	16	4180[2]	1758	463	24	2	4023[2]	904	629

NOTE: N = Weighted population estimate, in thousands; n = number of people in sample; SD = standard deviation; SE = standard error.

[1] Adjusted by the direct method to reflect the age distribution of the U.S. population at the midpoint of the survey.

[2] Does not meet standards of reliability.

SOURCE: National Center for Health Statistics. Unpublished data from the first National Health Nutrition and Examination Survey (NHANES 1).

TABLE C.—Flow at 50 percent of FVC for white adults, by smoking status, sex, and age, United States, 1971–1975

Cigarette smoking status (by age)	Both sexes					Men					Women				
	N	n	Mean	SD	SE	N	n	Mean	SD	SE	N	n	Mean	SD	SE
Never smokers															
25–74			3743[1]		38[1]			4083[1]		86[1]			3342[1]		34[1]
25–34	6733	394	4381	1194	69	2633	130	4998	1255	128	4099	264	3984	963	78
35–44	5278	291	3904	1164	84	1669	81	4315	1221	152	3609	210	3713	989	91
45–54	4942	353	3366	1212	84	1206	85	3972	1287	150	3736	268	3170	1119	90
55–64	3660	251	3090	1087	74	880	59	3736	1220	180	2781	192	2886	955	72
65–74	2875	235	2535	1045	73	481	43	3157	1060	174	2394	192	2410	996	84
Ex-smokers															
25–74		3579	59		4188	67		3123	81						
25–34	2811	160	4329	1292	120	1359	66	5029	1243	195	1452	94	3674	949	114
35–44	3086	171	4249	1384	129	1828	94	4702	1410	180	1258	77	3590	1037	160
45–54	3323	213	3474	1404	114	2345	143	3749	1428	143	978	70	2816	1091	147
55–64	2669	181	3110	1411	118	1826	130	3294	1362	127	843	51	2711	1432	293
65–74	1769	157	2524	1296	121	1270	121	2578	1364	153	499	36	2384	1092	167
Smokers															
25–74			3169		39			3475		59			2892		54
25–34	8885	487	4126	1268	74	4792	239	4546	1296	103	4093	248	3634	1037	90
35–44	5849	320	3552	1298	87	3027	158	3764	1399	140	2822	162	3325	1137	98
45–54	5606	374	2924	1208	76	2743	182	3257	1278	92	2863	192	2604	1040	94
55–64	3251	192	2587	1248	107	1700	108	2793	1364	148	1551	84	2361	1062	144
65–74	933	84	1922	1220	159	534	56	1889	1174	175	400	28	1965	1279	252

TABLE C.—Continued

Cigarette smoking status (by age)	Both sexes					Men					Women				
	N	n	Mean	SD	SE	N	n	Mean	SD	SE	N	n	Mean	SD	SE
Light smokers															
25–74			3313		74			3676		110			2984		102
25–34	2162	113	3964	1230	169	879	43	4617	1248	222	1283	70	3516	994	162
35–44	1267	72	3630	1076	151	308	17	4190[2]	943	226	959	55	3450	1054	168
45–54	1090	76	2911	864	107	383	24	3150	969	197	707	52	2781	771	103
55–64	1043	57	2756	1375	205	313	18	3542[2]	1643	395	730	39	2420	1080	200
65–74	304	21	2056	1252	292	131	11	1706[2]	883	366	172	10	2321[2]	1415	425
Moderate smokers															
25–74			3207		57			3561		79			2888		71
25–34	4269	235	4246	1239	96	2534	123	4640	1297	126	1735	112	3671	872	47
35–44	2413	130	3781	1182	124	1214	66	4039	1198	171	1199	64	3520	1107	142
45–54	2715	179	2775	1205	111	1145	75	3079	1243	124	1570	104	2553	1125	140
55–64	1287	82	2665	1186	167	690	45	2873	1191	207	597	37	2425	1134	245
65–74	464	44	1881	1239	218	261	28	2131	1316	279	203	16	1558[2]	1047	266
Heavy smokers															
25–74			3043		68			3283		92			2828		110
25–34	2417	136	4067	1333	153	1363	72	4326	1305	197	1054	64	3733	1295	247
35–44	2148	116	3239	1469	166	1505	75	3456	1550	227	643	41	2731	1103	185
45–54	1779	118	3152	1355	147	1193	82	3458	1377	168	586	36	2526	1062	222
55–64	922	53	2286	1123	173	697	45	2379	1222	221	224	8	1997[2]	651	232
66–74	154	18	1760[2]	1113	285	130	16	1559[2]	1059	274	24	2	2834[2]	703	490

NOTE: N = weighted population estimate, in thousands; n = number of people in sample; SD = standard deviation; SE = standard error.

[1] Adjusted by the direct method to reflect the age distribution of the U.S. population at the midpoint of the survey.

[2] Does not meet standards of reliability.

SOURCE: National Center for Health Statistics. Unpublished data from the first National Health Nutrition and Examination Survey (NHANES 1).

TABLE D.—Flow at 75 percent of FVC for white adults, by smoking status, sex, and age, United States, 1971–1975

Cigarette smoking status (by age)	Both sexes					Men					Women				
	N	n	Mean	SD	SE	N	n	Mean	SD	SE	N	n	Mean	SD	SE
Never smokers															
25–74			1230[1]		28[1]			1329[1]		42[1]			1073[1]		24[1]
25–34	6733	394	1776	714	52	2633	130	2065	649	72	4099	264	1590	691	62
35–44	5278	291	1277	621	49	1669	81	1478	843	129	3609	210	1184	456	32
45–54	4942	353	1044	636	44	1206	85	1184	664	74	3736	268	999	620	53
55–64	3660	251	737	511	36	880	59	978	612	83	2781	192	661	449	34
65–74	2875	235	609	463	32	481	43	795	408	64	2394	192	572	465	38
Ex-smokers															
25–74			1152		29			1403		41			992		37
25–34	2811	160	1695	678	61	1359	66	1925	664	109	1452	94	1480	616	72
35–44	3086	171	1460	664	62	1828	94	1623	693	92	1258	77	1224	538	59
45–54	3323	213	1026	625	48	2345	143	1148	666	59	978	70	734	378	53
55–64	2669	181	734	541	54	1826	130	778	446	41	843	51	638	694	156
65–74	1769	157	588	506	43	1270	121	592	516	47	499	36	578	481	87
Smokers															
25–74			967		22			1053		29			889		34
25–34	8885	487	1530	688	41	4792	239	1665	655	60	4093	248	1373	692	65
35–44	5849	320	1062	552	34	3027	158	1134	599	57	2822	162	985	486	35
45–54	5606	374	778	511	31	2743	182	866	530	41	2863	192	693	478	43
55–64	3251	192	631	536	42	1700	108	713	580	63	1551	84	541	468	56
65–74	933	84	452	689	100	534	56	350	445	77	400	28	588	901	199

TABLE D.—Continued

Cigarette smoking status (by age)	Both sexes					Men					Women				
	N	n	Mean	SD	SE	N	n	Mean	SD	SE	N	n	Mean	SD	SE
Light smokers															
25–74			1049		44			1120		64			985		67
25–34	2162	113	1480	679	94	879	43	1647	606	113	1283	70	1366	703	127
35–44	1267	72	1122	534	63	308	17	1294[2]	484	101	959	55	1067	537	73
45–54	1090	76	837	431	57	383	24	840	500	137	707	52	836	388	42
55–64	1043	57	706	540	85	313	18	931[2]	652	182	730	39	609	450	88
65–74	304	21	660	1040	264	131	11	393[2]	587	231	172	10	864[2]	1244	414
Moderate smokers															
25–74			970		28			1107		41			846		32
25–34	4269	235	1603	685	57	2534	123	1755	686	82	1735	112	1382	620	76
35–44	2413	130	1134	499	52	1214	66	1265	517	78	1199	64	1000	443	58
45–54	2715	179	717	480	49	1145	75	801	416	47	1570	104	656	514	67
55–64	1287	82	643	598	72	690	45	784	637	119	597	37	481	503	69
65–74	464	44	373	366	68	261	28	381	375	85	203	16	363[2]	353	103
Heavy smokers															
25–74			882		47			956		38			815		82
25–34	2417	136	1447	689	95	1363	72	1503	593	101	1054	64	1374	790	172
35–44	2148	116	940	595	63	1505	75	995	647	85	643	41	811	422	69
45–54	1779	118	836	589	57	1193	82	941	624	73	586	36	620	438	79
55–64	922	53	529	410	57	697	45	545	416	62	224	8	479[2]	388	160
65–74	154	18	297[2]	453	112	130	16	258[2]	408	98	24	2	505[2]	603	420

NOTE: N = weighted population estimate, in thousands; n = number of people in sample; SD = standard deviation; SE = standard error.

[1] Adjusted by the direct method to reflect the age distribution of the U.S. population at the midpoint of the survey.

[2] Does not meet standards of reliability.

SOURCE: National Center for Health Statistics. Unpublished data from the first National Health Nutrition and Examination Survey (NHANES 1).

TABLE E.—FEV_1/FVC ratio for white adults, by smoking status, sex, and age, United States, 1971–1975

Cigarette smoking status (by age)	Both sexes					Men					Women				
	N	n	Mean	SD	SE	N	n	Mean	SD	SE	N	n	Mean	SD	SE
Never smokers															
25–74			79.1[1]		0.21[1]			77.9[1]		0.34[1]			80.2[1]		0.23[1]
25–34	6733	394	82.5	6.08	0.34	2633	130	80.7	5.91	0.69	4039	264	83.6	5.93	0.44
35–44	5278	291	80.3	5.67	0.37	1669	81	78.8	5.25	0.64	3609	210	80.9	5.73	0.45
45–54	4942	353	78.7	5.84	0.38	1206	85	77.5	5.95	0.77	3736	268	79.0	5.75	0.41
55–64	3660	251	77.6	5.03	0.35	880	59	75.8	5.13	0.81	2781	192	78.2	4.85	0.39
65–74	2875	235	76.5	6.41	0.52	481	43	73.5	7.59	1.14	2394	152	77.0	5.97	0.55
Ex-smokers															
25–74			77.7		0.30			76.6		0.44			78.7		0.41
25–34	2811	160	81.7	5.92	0.53	1359	66	80.9	5.94	0.94	1452	94	82.4	5.81	0.78
35–44	3086	171	79.5	6.26	0.56	1828	94	78.8	6.78	0.83	1258	77	80.4	5.26	0.69
45–54	3323	213	76.2	6.58	0.50	2345	143	75.9	7.10	0.66	978	70	77.0	5.04	0.69
55–64	2669	181	73.7	7.79	0.70	1826	130	72.7	8.07	0.79	843	51	76.0	6.60	1.36
65–74	1769	157	71.5	9.34	1.05	1270	121	70.0	9.83	1.20	499	36	75.3	6.58	1.05
Smokers															
25–74			75.9		0.26			74.0		0.36			77.5		0.39
25–34	8885	487	80.3	6.78	0.38	4792	239	79.2	6.50	0.52	4093	248	81.7	6.85	0.61
35–44	5849	320	76.7	7.28	0.46	3027	158	75.3	7.92	0.71	2822	162	78.2	6.16	0.47
45–54	5606	374	74.2	7.05	0.41	2743	182	73.0	7.55	0.59	2863	192	75.4	6.32	0.52
55–64	3251	192	73.1	8.73	0.59	1700	108	70.6	9.59	1.03	1551	84	76.0	6.61	0.75
65–74	933	84	69.8	9.40	1.44	534	56	67.0	8.94	1.54	400	28	73.6	8.67	2.09

TABLE E.—Continued

Cigarette smoking status (by age)	Both sexes					Men					Women				
	N	n	Mean	SD	SE	N	n	Mean	SD	SE	N	n	Mean	SD	SE
Light smokers															
25–74			77.3		0.47			75.7		0.76			78.7		0.60
25–34	2162	113	80.9	7.43	0.84	879	43	80.3	7.10	1.11	1283	70	81.4	7.62	1.30
35–44	1267	72	78.4	6.18	0.79	308	17	77.1[2]	6.14	1.54	959	55	78.8	6.13	1.30
45–54	1090	76	76.5	4.94	0.66	383	24	75.1	6.06	1.58	707	52	77.3	4.01	0.54
55–64	1043	57	76.9	7.06	0.97	313	18	74.8[2]	9.00	2.25	730	39	77.8	5.81	0.87
65–74	304	21	71.4	10.59	2.65	131	11	64.6[2]	10.84	4.17	172	10	76.5[2]	6.90	2.64
Moderate smokers															
25–74			75.8		0.36			74.6		0.48			76.9		0.47
25–34	4269	235	80.4	6.36	0.53	2534	123	79.3	6.29	0.70	1735	112	81.9	6.16	0.73
35–44	2413	130	77.9	6.18	0.65	1214	66	77.3	6.61	0.85	1199	64	78.6	5.64	0.77
45–54	2715	179	73.6	7.48	0.69	1145	75	71.3	7.87	0.96	1570	104	75.3	6.67	0.80
55–64	1287	82	73.2	7.46	0.81	690	45	72.1	8.00	1.38	597	37	74.3	6.58	1.07
65–74	464	44	69.3	8.30	1.48	261	28	68.4	7.63	1.58	203	16	70.4[2]	8.98	2.42
Heavy smokers															
25–74			75.1		0.58			72.8		0.57			77.2		1.06
25–34	2417	136	79.1	6.85	0.73	1363	72	78.0	6.33	0.89	1054	64	81.9	6.90	1.16
35–44	2148	116	74.2	8.24	0.92	1505	75	73.3	8.68	1.21	643	41	76.2	6.64	1.15
45–54	1779	118	73.7	7.21	0.74	1193	82	74.0	7.34	0.86	586	36	73.2	6.91	1.30
55–64	922	53	68.9	10.08	1.42	697	45	67.1	10.09	1.81	224	8	74.6[2]	7.63	2.40
65–74	154	18	68.0[2]	9.78	2.65	130	16	65.9[2]	8.75	2.42	24	2	79.4[2]	6.66	4.63

NOTE: N = weighted population estimate, in thousands; n = number of people in sample; SD = standard deviation; SE = standard error.

[1] Adjusted by the direct method to reflect the age distribution of the U.S. population at the midpoint of the survey.

[2] Does not meet standards of reliability.

SOURCE: National Center for Health Statistics. Unpublished data from the first National Health Nutrition and Examination Survey (NHANES 1).

TABLE F.—MMEF for white adults, by smoking status, sex, and age, United States, 1971–1975

Cigarette smoking status (by age)	Both sexes					Men					Women				
	N	n	Mean	SD	SE	N	n	Mean	SD	SE	N	n	Mean	SD	SE
Never smokers															
25–74			3020[1]		29[1]			3392[1]		52[1]			2684[1]		26[1]
25–34	6733	394	3748	1023	64	2633	130	4357	1008	106	4199	264	3357	820	58
35–44	5278	291	3140	827	58	1669	81	3501	911	106	3609	210	2973	727	58
45–54	4942	353	2724	837	50	1206	85	3198	1021	119	3736	268	2572	703	48
55–64	3660	251	2301	730	43	880	59	2734	763	104	2781	192	2164	663	51
65–74	2875	235	1891	679	51	481	43	2314	827	130	2394	192	1806	611	56
Ex-smokers															
25–74			2910		41			3324		66			2537		51
25–34	2811	160	3753	1066	102	1359	66	4321	1014	162	1452	54	3222	809	103
35–44	3086	171	3500	1165	106	1828	94	3882	1237	157	1258	77	2944	765	104
45–54	3323	213	2800	1111	91	2345	143	3021	1171	114	978	70	2270	714	102
55–64	2669	181	2318	948	75	1826	130	2463	953	87	843	51	2005	857	180
65–74	1769	157	1826	873	82	1270	121	1865	922	99	499	36	1728	723	115
Smokers															
25–74			2553		31			2786		49			2343		41
25–34	8885	437	3512	1069	66	4792	239	3857	1101	93	4093	248	3109	872	77
35–44	5849	320	2850	970	65	3027	158	3033	1073	107	2822	162	2654	800	63
45–54	5606	374	2283	896	54	2743	182	2511	1007	78	2863	192	2065	709	66
55–64	3251	192	1955	854	67	1700	108	2065	985	106	1551	84	1813	654	78
65–74	933	84	1474	831	118	534	56	1422	677	104	400	28	1545	995	220

TABLE F.—Continued

Cigarette smoking status (by age)	Both sexes					Men					Women				
	N	n	Mean	SD	SE	N	n	Mean	SD	SE	N	n	Mean	SD	SE
Light smokers															
25–74			2736		57			2985		93			2510		77
25–34	2162	113	3457	1034	144	879	43	3923	1044	196	1283	70	3137	807	153
35–44	1267	72	2936	839	110	308	17	3400[2]	760	184	959	55	2787	808	124
45–54	1090	76	2334	641	84	383	24	2521	806	173	707	52	2232	502	68
55–64	1043	57	2252	894	124	313	18	2694[2]	1239	321	730	39	2063	605	87
65–74	304	21	1667	1023	257	131	11	1339[2]	568	238	172	10	1917[2]	1206	404
Moderate smokers															
25–74			2542		41			2848		64			2266		40
25–34	4269	235	3605	1106	93	2534	123	3960	1132	123	1735	112	3087	828	98
35–44	2413	130	2993	907	99	1214	66	3257	968	145	1199	64	2725	752	92
45–54	2715	179	2169	823	74	1145	75	2345	891	92	1570	104	2041	744	95
55–64	1287	82	1894	811	103	690	45	2144	848	162	597	87	1604	655	106
65–74	464	44	1395	738	126	261	28	1535	746	159	203	16	1214[2]	687	157
Heavy smokers															
25–74			2404		53			2620		72			2210		87
25–34	2417	136	3389	1018	120	1363	72	3614	1045	167	1054	64	3122	911	187
35–44	2148	116	2628	1063	119	1505	75	2777	1144	157	643	41	2280	735	123
45–54	1779	118	2421	1087	125	1193	82	2663	1145	150	536	36	1926	786	185
55–64	922	53	1706	764	166	697	45	1754	828	136	224	8	1557[2]	439	169
65–74	154	18	1313[2]	591	151	130	16	1247[2]	601	160	24	2	1665[2]	369	257

NOTE: N = weighted population estimate, in thousands; n = number of people in sample; SD = standard deviation; SE = standard error.

[1] Adjusted by the direct method to reflect the age distribution of the U.S. population at the midpoint of the survey.

[2] Does not meet standards of reliability.

SOURCE: National Center for Health Statistics. Unpublished data from the first National Health Nutrition and Examination Survey (NHANES 1).

TABLE G.—MEFR for white adults, by smoking status, sex, and age, United States, 1971–1975

Cigarette smoking status (by age)	Both sexes					Men					Women				
	N	n	Mean	SD	SE	N	n	Mean	SD	SE	N	n	Mean	SD	SE
Never smokers															
25–74			6545[1]		62[1]			7894[1]		114[1]			5327[1]		41[1]
25–34	5733	394	7103	1895	123	2633	130	8833	1551	167	4099	264	5991	1081	94
35–44	5278	291	6744	1774	144	1669	81	8519	1710	223	3609	210	5923	1058	103
45–54	4942	353	5887	1825	110	1206	85	7805	2106	268	3736	268	5268	1185	86
55–64	3660	251	5280	1559	98	880	59	6722	1527	228	2781	192	4824	1264	98
65–74	2855	234	4317	1776	112	472	42	6526	1863	289	2394	192	3882	1394	118
Ex-smokers															
25–74			6453		72			7809		120			5229		83
25–34	2811	160	7521	2246	232	1359	66	9184	1911	295	1452	94	5964	1153	167
35–44	3086	171	7554	2241	212	1828	94	8789	2006	239	1258	77	5759	1017	131
45–54	3323	213	6773	2056	202	2345	143	7451	1901	213	978	70	5146	1398	191
55–64	2669	181	5944	2002	194	1826	130	6532	1997	220	843	51	4671	1297	245
65–74	1769	157	4986	2187	221	1270	121	5425	2267	280	499	36	3867	1463	220
Smokers															
25–74			5914		52			7041		96			4897		55
25–34	8885	487	7393	2019	122	4792	239	8629	1728	133	4093	248	5847	1216	101
35–44	5849	320	6712	1974	152	3027	158	7780	1922	211	2822	162	5566	1256	94
45–54	5606	374	5762	1864	104	2743	182	5758	1819	137	2863	192	4807	1332	113
55–64	3251	192	5030	1952	147	1700	108	5834	2022	211	1551	84	4149	1421	171
65–74	933	84	3753	1862	216	534	56	4341	1961	260	400	28	2969	1373	263

TABLE G.—Continued

Cigarette smoking status (by age)	Both sexes					Men					Women				
	N	n	Mean	SD	SE	N	n	Mean	SD	SE	N	n	Mean	SD	SE
Light smokers															
25–74			6068		104			7085		177			5150		114
25–34	2162	113	7006	1792	233	879	43	8347	1559	246	1283	70	6088	1294	193
35–44	1267	72	6450	1784	275	308	17	8275[2]	1918	530	959	55	5864	1270	192
45–54	1090	76	5656	1632	232	383	24	6718	1445	269	707	52	5080	1425	249
55–64	1043	57	4979	1611	240	313	18	6142[2]	1903	478	730	39	4482	1154	208
65–74	304	21	3585	1295	350	131	11	4054[2]	1318	457	172	10	3228[2]	1157	388
Moderate smokers															
25–74			5921		76			7165		120			4798		89
25–34	4269	235	7616	2146	154	2534	123	8755	1864	176	1735	112	5952	1263	164
35–44	2413	130	6819	1992	230	1214	66	8112	1734	264	1199	64	5511	1241	150
45–54	2715	179	5513	1755	137	1145	75	6533	1799	181	1570	104	4769	1286	144
55–64	1287	82	5100	1996	243	690	45	6122	1687	261	597	37	3917	1640	299
65–74	464	44	3701	2084	373	261	28	4495	2122	466	203	16	2681[2]	1512	376
Heavy smokers															
25–74			5755		98			6902		155			4720		115
25–34	2417	136	7356	1925	204	1363	72	8573	1544	192	1054	64	5781	1010	170
35–44	2148	116	6751	2053	223	1505	75	7412	1995	289	643	41	5205	1164	196
45–54	1779	118	6167	2034	214	1193	82	6945	1909	239	586	36	4581	1280	254
55–64	922	53	4989	2221	366	697	45	5410	2285	433	224	8	3679[2]	1327	395
65–74	154	18	4136[2]	2060	496	130	16	4249[2]	2187	571	24	2	3535[2]	964	671

NOTE: N = weighted population estimate, in thousands; n = number of people in sample; SD = standard deviation; SE = standard error.

[1] Adjusted by the direct method to reflect the age distribution of the U.S. population at the midpoint of the survey.

[2] Does not meet standards of reliability.

SOURCE: National Center for Health Statistics. Unpublished data from the first National Health Nutrition and Examination Survey (NHANES 1).

TABLE H.—Forced vital capacity for white adults, by smoking status, sex, and age, United States, 1971–1975

Cigarette smoking status (by age)	Both sexes					Men					Women				
	N	n	Mean	SD	SE	N	n	Mean	SD	SE	N	n	Mean	SD	SE
Never smokers															
25–74			3978[1]		29[1]			4708[1]		52[1]			3320[1]		24[1]
25–34	6733	394	4403	1052	67	2633	130	5480	759	89	4099	264	3712	464	32
35–44	5278	291	3972	814	65	1669	81	4761	759	98	3609	210	3607	530	54
45–54	4942	353	3624	782	45	1206	85	4506	795	92	3736	268	3340	522	39
55–54	3660	251	3252	820	47	880	59	4265	758	123	2780	192	2932	526	38
65–74	2875	235	2815	719	48	481	43	3867	774	127	2394	192	2603	482	43
Ex-smokers															
25–74			3996		30			4703		46			3357		32
25–34	2811	150	4522	1043	101	1359	66	5335	816	118	1452	94	3760	533	68
35–44	3086	171	4500	972	91	1828	94	5096	753	86	1258	77	3633	450	49
45–54	3323	213	4143	915	78	2345	143	4499	796	76	978	70	3291	543	79
55–64	2669	181	3862	898	94	1826	130	4239	786	95	843	51	3044	489	79
65–74	1769	157	3335	864	86	1270	121	3594	821	92	499	36	2675	568	99
Smokers															
25–74			3790		26			4405		38			3236		35
25–34	8885	487	4464	977	55	4792	239	5111	784	59	4093	248	3707	539	50
35–44	5849	320	4146	851	59	3027	158	4665	750	81	2822	162	3588	546	55
45–54	5606	374	3731	814	49	2743	182	4284	678	65	2863	192	3202	532	45
55–64	3251	192	3315	845	66	1700	108	3866	730	71	1551	84	2712	467	59
65–74	933	84	2985	870	118	534	56	3325	747	117	400	28	2533	815	185

TABLE H.—Continued

Cigarette smoking status (by age)	Both sexes					Men					Women				
	N	n	Mean	SD	SE	N	n	Mean	SD	SE	N	n	Mean	SD	SE
Light smokers															
25–74			3824		54			4358		81			3342		64
25–34	2162	113	4260	857	116	879	43	4892	641	118	1283	70	3828	705	118
35–44	1267	72	3986	875	135	308	17	4922[2]	768	235	959	55	3686	671	119
45–54	1090	76	3521	680	103	383	24	4022	555	155	707	52	3249	580	107
55–64	1043	57	3135	704	108	313	18	3866[2]	636	141	730	39	2822	457	87
65–74	304	21	3042	917	237	131	11	3470[2]	555	159	172	10	2717[2]	1001	347
Moderate smokers															
25–74			3789		30			4454		50			3190		38
25–34	4269	235	4584	1020	74	2534	123	5217	793	80	1735	112	3660	447	55
35–44	2413	130	4145	846	90	1214	66	4671	812	125	1199	64	3612	457	66
45–54	2715	179	3658	852	73	1145	75	4357	737	111	1570	104	3147	521	57
55–64	1287	82	3312	854	99	690	45	3881	696	89	597	37	2654	453	80
65–74	464	44	2928	820	149	261	28	3327	734	172	203	16	2414[2]	614	173
Heavy smokers															
25–74			3710		43			4364		61			3120		54
25–34	2417	136	4440	968	91	1363	72	5055	818	102	1054	64	3644	404	69
35–44	2148	116	4244	832	82	1505	75	4609	679	94	643	41	3392	440	73
45–54	1779	118	3971	758	81	1193	82	4304	638	84	586	36	3292	480	95
55–64	922	53	3524	928	151	697	45	3851	798	142	224	8	2508[2]	438	143
65–74	154	18	3036[2]	938	240	130	16	3189[2]	925	252	24	2	2223[2]	472	328

NOTE: N = weighted population estimate, in thousands; n = number of people in sample; SD = standard deviation; SE = standard error.

[1] Adjusted by the direct method to reflect the age distribution of the U.S. population at the midpoint of the survey.

[2] Does not meet standards of reliability.

SOURCE: National Center for Health Statistics. Unpublished data from the first National Health Nutrition and Examination Survey (NHANES 1).

TABLE I.—Recurring persistent cough attacks for adults, by sex, age, and smoking status, United States, 1971–1975

	Men Smoking status						Women Smoking status					
	Never	Former	Current	Light	Moderate	Heavy	Never	Former	Current	Light	Moderate	Heavy
25–34												
P	3.2	4.4	6.7	7.6	5.7	7.7	4.4	6.0	8.4	5.7	7.1	15.2
SE	1.85	2.23	1.57	4.01	1.98	2.79	1.21	2.48	1.63	1.92	2.27	4.93
n	168	78	327	72	160	94	399	121	367	119	164	81
N	3319	1593	6608	1383	3335	1875	6416	1873	6304	2239	2642	1393
35–44												
P	4.9	8.0	13.8	9.0	5.9	22.1	5.4	5.0	8.9	2.3	8.0	25.8
SE	2.59	3.47	3.17	6.39	2.69	6.40	1.60	2.46	1.89	1.21	2.85	7.37
n	101	117	226	33	93	100	310	107	270	103	114	51
N	2114	2384	4412	614	1769	2029	5197	1771	4563	1776	1968	799
45–54												
P	4.3	9.2	10.3	6.4	12.0	10.6	4.9	3.0	11.5	7.8	9.9	21.8
SE	1.61	2.28	2.07	2.73	3.65	3.53	1.55	1.97	2.16	2.61	2.99	4.04
n	114	204	296	61	122	112	435	101	329	109	163	57
N	1568	3290	4282	810	1705	1745	5989	1458	4800	1497	2413	890
55–64												
P	1.1	14.6	20.5	2.4	14.4	25.9	6.8	9.9	15.7	6.4	14.8	50.1
SE	1.06	3.21	3.27	8.88	4.33	5.87	1.65	3.35	3.46	3.17	3.93	15.8
n	94	192	205	50	91	64	394	86	178	76	82	20
N	1320	2791	2990	708	1305	976	5599	1501	3014	1268	1369	378

TABLE I.—Continued

	Men Smoking status						Women Smoking status					
	Never	Former	Current	Light	Moderate	Heavy	Never	Former	Current	Light	Moderate	Heavy
65–74												
P	7.5	17.5	23.7	3.6	34.4	25.4	8.7	5.4	23.1	17.2	24.8	59.9[2]
SE	3.16	3.44	4.55	2.31	6.90	10.1	1.52	2.85	4.93	6.05	8.02	22.37
n	98	232	135	39	60	35	461	81	83	46	32	5
N	864	2232	1199	318	574	295	5487	958	952	523	362	66
25–74												
P[1]	3.9	9.6	13.4	10.2	12.0	16.7	5.7	5.8	12.4	7.1	11.6	31.1
SE[1]	0.92	1.51	1.30	2.22	1.66	2.31	0.66	1.25	1.19	1.32	1.84	5.63

NOTE: P = proportion; SE = standard error; n = number of people in sample; N = weighted population estimate, in thousands.

[1] Adjusted by direct method to reflect the age distribution of the U.S. population at the midpoint of the survey.

[2] Does not meet standards of reliability.

SOURCE: National Center for Health Statistics. Unpublished data from the first National Health Nutrition and Examination Survey (NHANES 1).

TABLE J.—Three-week periods of increased cough or phlegm for adults, by sex, age, and smoking status, United States, 1971–1975

	Men Smoking status						Women Smoking status					
	Never	Former	Current	Light	Moderate	Heavy	Never	Former	Current	Light	Moderate	Heavy
25–34												
P	6.9	2.9	7.2	6.9	7.9	6.5	4.2	5.6	10.7	5.4	11.1	18.0
SE	2.39	1.67	1.83	4.04	2.63	2.33	1.07	2.39	1.91	2.05	2.97	5.18
n	168	78	327	72	160	94	399	121	367	119	164	81
N	3319	1593	6608	1383	3335	1875	6416	1873	6304	2239	2642	1393
35–44												
P	6.0	3.3	5.2	1.2	3.9	7.6	3.8	1.9	8.1	5.1	10.9	8.3
SE	2.43	1.98	1.68	1.20	2.08	2.86	1.54	1.37	2.01	1.89	3.67	4.20
n	101	117	226	33	93	100	310	107	270	103	114	51
N	2114	2384	4412	614	1769	2229	5197	1771	4563	1776	1968	799
45–54												
P	1.7	3.9	6.3	0.3	5.5	9.8	3.5	6.1	10.8	8.4	8.4	21.6
SE	1.24	1.82	1.72	0.32	2.10	3.66	1.00	2.39	2.14	2.93	2.72	6.49
n	114	204	296	61	122	112	435	101	329	109	163	57
N	1568	3290	4282	810	1706	1745	5989	1458	4800	1497	2413	890
55–64												
P	1.2	2.9	11.4	6.8	10.2	16.2	6.6	13.7	14.7	7.0	13.1	46.2
SE	0.91	1.33	2.61	4.00	4.07	5.39	1.63	4.88	3.57	3.44	3.96	16.61
n	94	192	205	50	91	64	394	86	178	76	82	20
N	1320	2791	2990	708	1305	976	5599	1501	3014	1268	1369	378

TABLE J.—Continued

	Men Smoking status						Women Smoking status					
	Never	Former	Current	Light	Moderate	Heavy	Never	Former	Current	Light	Moderate	Heavy
65–74												
P	7.5	4.5	12.0	3.3	14.2	17.5	5.1	9.1	11.5	2.6	26.4	0.0[2]
SE	3.10	1.38	4.11	2.55	6.01	10.31	1.25	3.47	4.24	2.55	9.80	0.0
n	98	232	135	39	60	35	461	81	83	46	32	5
N	864	2232	1199	318	574	295	5487	958	952	523	362	66
25–74												
P[1]	4.6	3.4	7.9	3.8	7.6	10.5	4.5	6.9	11.0	5.9	12.9	19.5
SE[1]	1.04	0.93	1.02	1.43	1.31	2.04	0.63	1.34	1.26	1.18	1.84	3.86

NOTE: P = proportion; SE = standard error; n = number of people in sample; N = weighted population estimate, in thousands.

[1] Adjusted by direct method to reflect the age distribution of the U.S. population at the midpoint of the survey.

[2] Does not meet standards of reliability.

SOURCE: National Center for Health Statistics. Unpublished data from the first National Health Nutrition and Examination Survey (NHANES 1).

TABLE K.—Shortness of breath for adults, by sex, age, and smoking status, United States, 1971–1975

	Men Smoking status						Women Smoking status					
	Never	Former	Current	Light	Moderate	Heavy	Never	Former	Current	Light	Moderate	Heavy
25–34												
P	5.6	15.2	23.3	10.0	23.1	33.6	14.4	17.9	31.0	30.9	20.1	51.5
SE	1.99	4.97	3.20	3.81	4.01	7.21	1.92	4.94	3.17	5.65	3.56	7.48
n	168	78	327	72	160	94	399	121	367	119	164	81
N	3319	1593	6608	1383	3335	1875	6416	1873	6304	2239	2642	1393
35–44												
P	17.1	19.9	22.9	15.6	15.9	31.2	22.5	26.5	39.0	36.4	45.3	30.3
SE	4.62	4.89	3.26	7.08	4.71	5.46	2.42	5.32	4.62	5.48	7.07	7.08
n	101	117	226	33	93	100	310	107	270	103	114	51
N	2114	2384	4412	614	1769	2029	5197	1771	4563	1776	1968	799
45–54												
P	19.3	27.2	35.5	25.4	34.9	41.3	28.1	32.5	42.5	30.3	48.1	47.9
SE	4.07	3.58	2.99	6.35	4.64	5.40	2.85	6.05	3.93	5.01	4.95	7.57
n	114	204	296	61	122	112	435	101	329	109	163	57
N	1568	3290	4282	810	1706	1745	5989	1458	4800	1497	2413	890
55–64												
P	25.6	31.3	42.2	37.7	42.4	45.2	38.0	56.8	39.0	29.8	43.1	54.6
SE	5.79	3.94	4.37	9.57	6.14	6.39	2.94	6.24	4.60	6.85	6.06	16.51
n	94	192	205	50	91	64	394	86	178	76	82	20
N	1320	2791	2990	708	1305	9761	5599	1501	3014	1268	1369	378

TABLE K.—Continued

	Men Smoking status						Women Smoking status					
	Never	Former	Current	Light	Moderate	Heavy	Never	Former	Current	Light	Moderate	Heavy
65–74												
P	27.0	45.8	41.7	26.7	42.4	54.4	41.6	32.3	43.2	48.6	40.0	17.4[2]
SE	5.46	4.05	4.59	7.87	6.86	9.12	2.92	5.63	6.70	9.64	10.85	16.12
n	98	232	135	39	60	35	461	81	83	46	32	5
N	864	2232	1199	318	574	295	5487	958	952	523	362	66
25–74												
P[1]	17.1	25.2	31.4	21.5	29.9	39.2	27.0	31.8	38.2	34.1	38.2	42.4
SE[1]	1.89	2.38	1.75	2.84	2.31	2.74	1.27	2.82	2.08	2.59	2.88	5.07

NOTE: P = proportion; SE = standard error; n = number of people in sample; N = weighted population estimate, in thousands.

[1] Adjusted by direct method to reflect the age distribution of the U.S. population at the midpoint of the survey.

[2] Does not meet standards of reliability.

SOURCE: National Center for Health Statistics. Unpublished data from the first National Health Nutrition and Examination Survey (NHANES 1).

TABLE L.—Wheezy chest sounds of adults, by sex, age, and smoking status, United States, 1971–1975

	Men Smoking status						Women Smoking status					
	Never	Former	Current	Light	Moderate	Heavy	Never	Former	Current	Light	Moderate	Heavy
25–34												
P	2.7	13.0	15.0	11.5	12.6	22.0	7.6	11.6	17.5	12.9	14.8	29.5
SE	1.17	4.67	2.42	4.43	2.72	6.14	1.46	3.54	2.33	3.13	2.94	6.13
n	168	78	327	72	160	94	399	121	367	119	164	81
N	3319	1593	6608	1383	3335	1875	6416	1873	6304	2239	2642	1393
35–44												
P	14.0	5.1	18.4	13.6	12.3	25.2	7.9	7.7	16.4	9.9	21.9	17.9
SE	4.72	2.12	3.28	6.14	4.03	5.61	1.83	2.98	2.56	3.77	4.53	4.89
n	101	117	226	33	93	100	310	107	270	103	114	51
N	2114	2384	4412	614	1769	2029	5197	1771	4563	1776	1968	799
45–54												
P	4.3	12.3	18.8	10.2	23.2	18.7	8.5	5.3	22.7	12.9	24.1	35.7
SE	1.97	2.60	2.60	3.99	4.05	4.13	1.39	1.82	2.98	3.59	4.37	6.24
n	114	204	296	61	122	112	435	101	329	109	163	57
N	1568	3290	4282	810	1706	1745	5989	1458	4800	1497	2413	890
55–64												
P	12.0	13.6	25.9	29.9	26.6	22.1	12.7	22.0	27.3	19.5	31.0	40.0
SE	4.24	2.50	4.46	9.22	5.87	6.10	2.09	5.93	3.64	4.98	5.21	14.00
n	94	192	205	50	91	64	394	86	178	76	82	20
N	1320	2791	2990	708	1305	976	5599	1501	3014	1268	1369	378

TABLE L.—Continued

	Men Smoking status						Women Smoking status					
	Never	Former	Current	Light	Moderate	Heavy	Never	Former	Current	Light	Moderate	Heavy
65–74												
P	5.0	20.7	33.1	34.7	31.6	35.6	15.1	21.5	28.6	34.6	18.1	39.0[2]
SE	2.04	3.00	5.25	10.10	7.47	9.91	2.16	4.78	5.60	8.99	6.69	21.96
n	98	232	135	39	60	35	461	81	83	46	32	5
N	864	2232	1199	318	574	295	5487	958	952	523	362	66
25–74												
P[1]	7.4	12.1	20.6	17.6	19.6	23.5	9.8	12.6	21.7	16.4	21.7	31.6
SE[1]	1.33	1.83	1.42	2.68	1.98	2.69	0.82	1.68	1.49	2.01	1.88	4.80

NOTE: P = proportion; SE = standard error; n = number of people in sample; N = weighted population estimate, in thousands.

[1] Adjusted by direct method to reflect the age distribution of the U.S.

[2] Does not meet standards of reliability. population at the midpoint of the survey.

SOURCE: National Center for Health Statistics. Unpublished data from the first National Health Nutrition and Examination Survey (NHANES 1).

TABLE M.—Diminished or absent breath sounds of adults, by sex, age, and smoking status, United States, 1971–1975

	Men Smoking status						Women Smoking status					
	Never	Former	Current	Light	Moderate	Heavy	Never	Former	Current	Light	Moderate	Heavy
25–34												
P	1.8	0.0	0.3	0.4	0.0	0.7	0.1	0.0	0.6	0.3	0.0	2.2
SE	1.76	0.0	0.21	0.36	0.0	0.71	0.07	0.0	0.51	0.31	0.0	2.21
n	168	78	327	72	160	94	399	121	367	119	164	81
N	3319	1593	6608	1383	3335	1875	6416	1873	6304	2239	2642	1393
35–44												
P	0.6	0.5	0.6	0.0	0.7	0.6	0.3	0.2	2.3	0.4	3.4	3.5
SE	0.61	0.47	0.55	0.0	0.73	0.57	0.26	0.22	1.58	0.44	3.33	3.39
n	101	117	226	33	93	100	310	107	270	103	114	51
N	2114	2384	4412	614	1769	2029	5197	1771	4563	1776	1968	799
45–54												
P	0.7	1.0	5.9	0.4	9.8	4.7	0.8	2.4	1.4	1.0	1.6	1.5
SE	0.55	0.53	1.71	0.41	3.33	2.64	0.64	1.87	0.56	0.36	0.82	1.24
n	114	204	296	61	122	112	435	101	329	109	163	57
N	1568	3290	4282	810	1706	1745	5989	1458	4800	1497	2413	890
55–64												
P	2.5	5.7	12.4	8.4	13.0	14.4	0.8	4.1	3.36	2.7	3.9	3.5
SE	2.12	1.66	3.15	4.75	4.57	4.99	0.53	2.51	1.44	1.82	2.40	3.55
n	94	192	205	50	91	64	394	86	178	76	82	20
N	1320	2791	2990	708	1305	976	5599	1501	3014	1268	1369	378

TABLE M.—Continued

	Men						Women					
	Smoking status						Smoking status					
	Never	Former	Current	Light	Moderate	Heavy	Never	Former	Current	Light	Moderate	Heavy
65–74												
P	8.8	9.7	17.9	13.9	25.2	8.8	2.4	4.5	2.7	3.3	2.3	0.0[2]
SE	3.53	2.57	3.76	8.10	5.86	4.5	0.81	2.63	1.58	2.34	2.27	0.0
n	98	232	135	39	60	35	461	81	83	46	32	5
N	864	2232	1199	318	574	295	5487	958	952	523	362	66
25–74												
P[1]	2.2	2.44	5.8	3.3	7.5	5.0	0.7	1.9	1.9	1.32	2.1	2.3
SE[1]	0.72	0.46	0.95	1.33	1.47	1.06	0.20	0.71	0.46	0.49	0.88	1.16

NOTE: P = proportion; SE = standard error; n = number of people in sample; N = weighted population estimate, in thousands.

[1] Adjusted by direct method to reflect the age distribution of the U.S. population at the midpoint of the survey.

[2] Does not meet standards of reliability.

SOURCE: National Center for Health Statistics. Unpublished data from the first National Health Nutrition and Examination Survey (NHANES 1).

TABLE N.—Wheeze of adults, by sex, age, and smoking status, United States, 1971–1975

	Men Smoking status						Women Smoking status					
	Never	Former	Current	Light	Moderate	Heavy	Never	Former	Current	Light	Moderate	Heavy
25–34												
P	0.0	1.2	1.7	1.1	1.6	2.2	0.4	0.0	0.7	0.0	1.3	0.0
SE	0.0	1.24	0.77	1.06	1.25	1.28	0.29	0.0	0.37	0.0	0.79	0.0
n	168	78	327	72	160	94	399	121	367	119	164	81
N	3319	1593	6608	1383	3335	1875	6416	1873	6304	2239	2642	1393
35–44												
P	0.0	1.0	1.3	0.0	0.9	2.1	0.3	0.0	3.2	0.0	3.6	9.6
SE	0.0	0.75	0.67	0.0	0.89	1.22	0.26	0.0	1.28	0.0	1.50	4.97
n	101	117	226	33	93	100	310	107	270	103	114	51
N	2114	2384	4412	614	1769	2029	5197	1771	4563	1776	1968	799
45–54												
P	0.0	1.2	2.5	0.0	4.5	1.8	0.3	0.0	2.4	0.8	3.3	2.5
SE	0.0	1.02	0.93	0.0	2.13	1.27	0.33	0.0	0.94	0.78	1.40	1.76
n	114	204	296	61	122	112	435	101	329	109	163	57
N	1568	3290	4282	810	1706	1745	5989	1458	4800	1497	2413	890
55–64												
P	0.0	0.4	5.6	2.3	3.3	10.9	0.1	0.0	1.7	0.8	1.4	5.8
SE	0.0	0.37	1.76	1.95	1.69	4.48	0.05	0.0	0.95	0.77	1.18	5.78
n	94	192	205	50	91	64	394	86	178	76	82	20
N	1320	2791	2990	708	1305	976	5599	1501	3014	1268	1369	378

TABLE N.—Continued

	Men Smoking status						Women Smoking status					
	Never	Former	Current	Light	Moderate	Heavy	Never	Former	Current	Light	Moderate	Heavy
65–74												
P	0.0	2.5	10.0	0.0	11.4	18.4	1.0	1.9	3.6	2.7	1.6	20.9[2]
SE	0.0	1.11	3.75	0.0	5.27	10.98	0.56	1.85	2.14	2.66	1.64	18.53
n	98	232	135	39	60	35	461	81	83	46	32	5
N	864	2232	1199	318	574	295	5487	958	952	523	362	66
25–74												
P[1]	0.0	1.2	3.4	0.7	3.5	5.5	0.4	0.2	2.1	0.7	2.3	6.3
SE[1]	0.0	0.46	0.71	0.46	0.92	1.65	0.14	0.25	0.45	0.41	0.48	2.79

NOTE: P = proportion; SE = standard error; n = number of people in sample; N = weighted population estimate, in thousands.

[1] Adjusted by direct method to reflect the age distribution of the U.S. population at the midpoint of the survey.

[2] Does not meet standards of reliability.

SOURCE: National Center for Health Statistics. Unpublished data from the first National Health Nutrition and Examination Survey (NHANES 1).

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CHAPTER 3. MORTALITY FROM CHRONIC OBSTRUCTIVE LUNG DISEASE DUE TO CIGARETTE SMOKING

CONTENTS

Introduction

The chronic obstructive lung diseases (COLD) that are causally related to cigarette smoking are chronic bronchitis, emphysema, and chronic obstructive pulmonary disease and allied conditions without mention of asthma, bronchitis, or emphysema. The last classification was introduced by the National Center for Health Statistics in response to the changes that occurred in the late 1960s in patterns of reporting causes of death on death certificates. During this period, physicians increasingly recorded deaths as due to "chronic obstructive lung disease" rather than the more specific categories of "emphysema" or "chronic bronchitis" (NCHS 1982). Because of this shift in patterns of reporting, and in recognition of the difficulty of clinically separating these categories from one another as a cause of death, the discussion in this chapter combines all of these categories for analysis, where possible, which should result in a more complete description of death rates from COLD.

COLD Mortality Patterns in the United States

The three chronic obstructive lung diseases related to smoking may account for almost 62,000 deaths in 1983, compared with 56,920 deaths in 1982, according to provisional mortality data recently published by the National Center for Health Statistics. This data is based on a 10 percent sample of all death certificates for the 12-month period ending in November (NCHS 1984). This is a dramatic increase from 1970, when slightly over 33,000 deaths were attributed to COLD.

Complete mortality data are available through 1980, and Table 1 presents the numbers of male and female deaths from COLD for 1970, 1975, and 1980. In addition to the relatively rapid rise in COLD deaths during these years, there was also a shift in the male to female ratio of these deaths. In 1970 male deaths outnumbered female deaths by a ratio of 4.3 to 1. By 1980 this ratio had declined to 2.36.

The age-adjusted death rates for COLD during the years 1960 through 1980 are presented in Figure 1 for white men, white women, and men and women of other races. As described in the previous chapter, however, COLD is a slowly progressive disease, and death from COLD usually occurs only after extensive damage has developed in the diseased lungs. Many individuals with COLD will die with their disease rather than because of it, and even those who do die of COLD are usually symptomatic for an extended period of time prior to death.

Therefore, death rate data may not accurately reflect the true prevalence or incidence of COLD in the U.S. population. In addition, COLD is often not recorded as a cause of death in hospital records

TABLE 1.—Number of and ratio of male to female chronic obstructive lung disease (COLD) deaths for three time periods, United States

Cause of death	1970		1975		1980	
	Men	Women	Men	Women	Men	Women
Chronic bronchitis	4,282	1,564	3,260	1,452	2,380	1,348
Emphysema	18,901	3,820	14,849	3,946	10,133	3,744
COLD and allied conditions	3,601	848	13,411	4,182	24,820	10,734
Total COLD deaths	26,784	6,227	31,520	9,580	37,333	15,826
M:F ratio	4.30		3.29		2.36	

SOURCE: National Center for Health Statistics (1982, and unpublished mortality data).

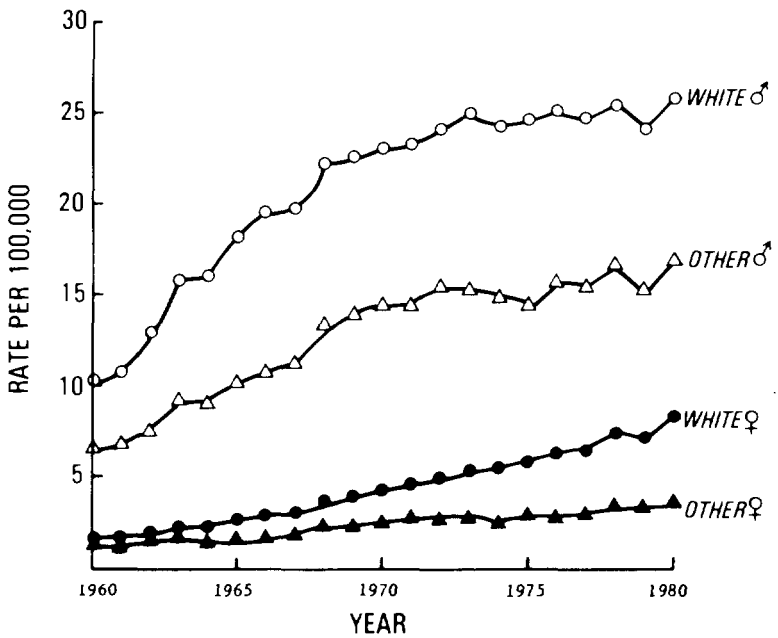

FIGURE 1.—Age-adjusted COLD mortality rates for whites and nonwhites in the United States, 1960–1980

SOURCE: National Center for Health Statistics (1982, and unpublished data).

(Moriyama et al. 1966) or on death certificates (Mitchell et al. 1968), even though it may have played an important role in a person's death. In a recent prospective study, nearly half of the excess mortality associated with significantly lowered FEV_1 was attributed to other causes (Peto et al. 1983). Relatively advanced lung disease (as judged by pathologic examination) may also exist without clinical

recognition because of the lung's large ventilatory reserve (Mitchell et al. 1968; Hepper et al. 1969). A joint committee of the American College of Chest Physicians and the American Thoracic Society (ACCP–ATS 1975) has developed standardized definitions of these conditions that may improve the accuracy of mortality reporting in the future.

As discussed in the chapter on morbidity in this Report, COLD in an individual is usually a combination of mucus hypersecretion, airway narrowing, and emphysema. The extent of damage represented by each of these three processes can vary substantially from individual to individual, both in the absolute magnitude of the damage and in the proportional contribution of each of these three components. The majority of those with smoking-induced lung damage do not have enough damage to result in clinically significant disease, and only some of those with clinically significant disease have damage to the lung that results in death from COLD. The progressive loss of FEV_1 in smokers described in the preceding chapter is one measure of the extent and progression of lung damage, and individuals with a markedly reduced FEV_1 are far more likely to die of COLD (Peto et al. 1983). These deaths commonly occur secondary to the failure of these severely damaged lungs to carry out the gas exchange required for survival.

Because death from COLD is the end result of lung damage accumulated over many years, these deaths would be expected to occur disproportionately in the older age groups; therefore, the presentation of a single age-adjusted death rate might not reflect a true picture of the changes in this disease with time. Figure 2 presents the age-specific death rates in 1977 for COLD in the different sexes and racial groups. Death rates increase rapidly over the age of 45, and this increase is particularly dramatic over the age of 65. In addition, the bulk of the difference between white men and men of other races, evident in Figure 2, occurs in those over age 65. Indeed, the COLD death rates for nonwhite men are actually higher than that for white men under age 55.

The examination of age-specific death rates over time also presents a somewhat different picture from that presented by the age-adjusted numbers in Figure 1. The age-adjusted rates for white men in Figure 1 seem to have changed only slightly between 1968 and 1980. However, when the age-specific rates for the years 1968 and 1977 are examined (Figure 3), this apparent stability can be seen to be a product of counterbalancing trends in those under and over 65 years of age. The death rates from COLD declined in white men under age 65 between 1968 and 1977, but COLD death rates increased in white men over age 65 during the same years; this increase was particularly dramatic in those over age 75.

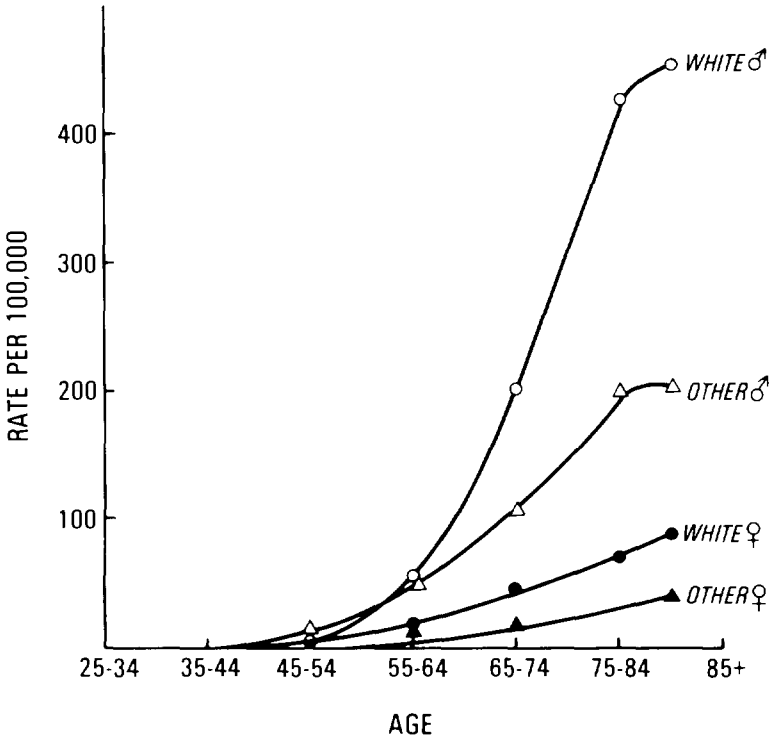

FIGURE 2.—Age-specific COLD mortality rates for whites and nonwhites in the United States, 1977

SOURCE: National Center for Health Statistics (1982).

Figure 4 presents the age-specific COLD mortality rates for white women in 1960, 1968, and 1977. As with the male rates, the female COLD death rates rise rapidly with age, but they are substantially lower than the male rates. In contrast with the male rates, however, the white female death rates increased steadily with time from 1960 through 1977 both above and below age 65. In each of the age groups over the age of 45, where significant numbers of COLD deaths would be expected, there was a steady increase in rates from 1960 to 1968 and from 1968 to 1977. As is discussed later in this chapter, these differences between men and women over time are consistent with their differences in smoking behavior.

The effect of the normal aging process on the lung is small, rarely limits maximal exercise, and never results in ventilatory failure. Therefore, death from chronic obstructive lung disease is never a natural part of the aging process; it is the result of an infectious or other disease process or of the cumulative damage of environmental respiratory toxins. The most important of these toxins in the United States is cigarette smoke.

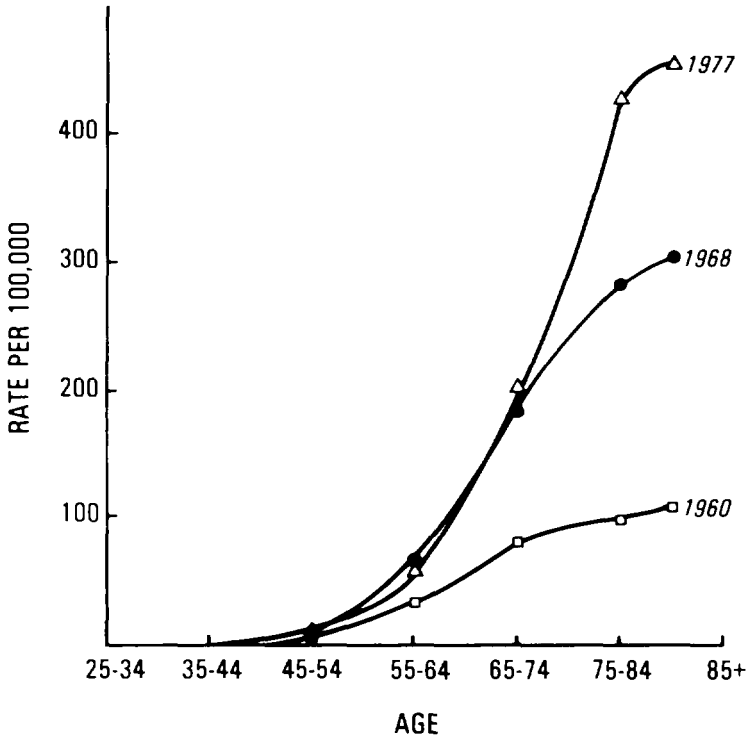

FIGURE 3.—Age-specific COLD mortality rates for white men in the United States, 1960, 1968, and 1977

SOURCE: National Center for Health Statistics (1982).

In spite of the large ventilatory reserve possessed by the lung, death from COLD is a major cause of U.S. mortality. This mortality is closely linked to cigarette smoking and has been examined extensively. Figure 5 shows the differences in COLD death rates for smokers and nonsmokers at different ages. From the rarity of COLD death in nonsmokers and the magnitude of the increased risk associated with smoking, it is clear that the overwhelming importance of cigarette smoking as a determinant of abnormal lung function demonstrated in the previous chapter is matched by the importance of cigarette smoking as a determinant of death from COLD. Examination of the death rates from COLD in smokers and nonsmokers suggests that from 85 to 90 percent of the COLD deaths in the United States can be attributed to cigarette smoking.

Prospective Studies

The relationship between smoking and death from COLD has been evaluated in a large number of prospective mortality studies. There are eight major prospective studies of the disease consequences of smoking. They involve large numbers of smokers and nonsmokers

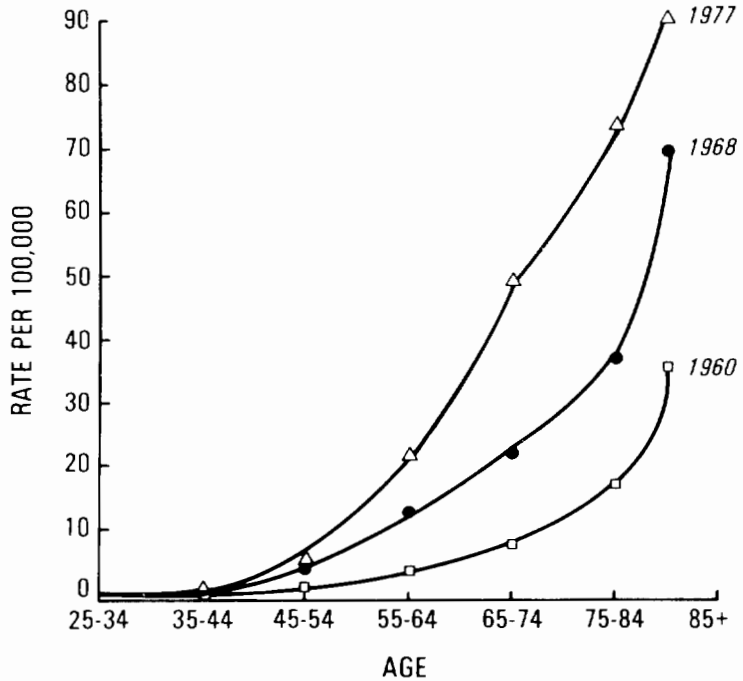

FIGURE 4.—Age-specific COLD mortality rates for white women in the United States, 1960, 1968, and 1977

SOURCE: National Center for Health Statistics (1982).

and have examined the death rates from COLD in both groups. These studies cumulatively represent more than 17 million person-years of observation and over 330,000 deaths. The size of the populations studied allows a detailed examination of the relationship between smoking and death rates. The characteristics of the populations studied are summarized in Table 2 and are briefly reviewed here.

The British Doctors Study

The British doctors study (Doll and Hill 1954, 1956, 1964a, 1964b, 1966; Doll and Peto 1976, 1977; Doll and Pike 1972; Doll et al. 1980) of 40,000 male and female physicians in Britain was the first prospective study and is the longest running. Deaths from chronic bronchitis and emphysema were combined. Deaths from cor pulmonale (i.e., heart failure secondary to lung disease) were separately analyzed by smoking category and probably include some deaths from chronic bronchitis and emphysema.

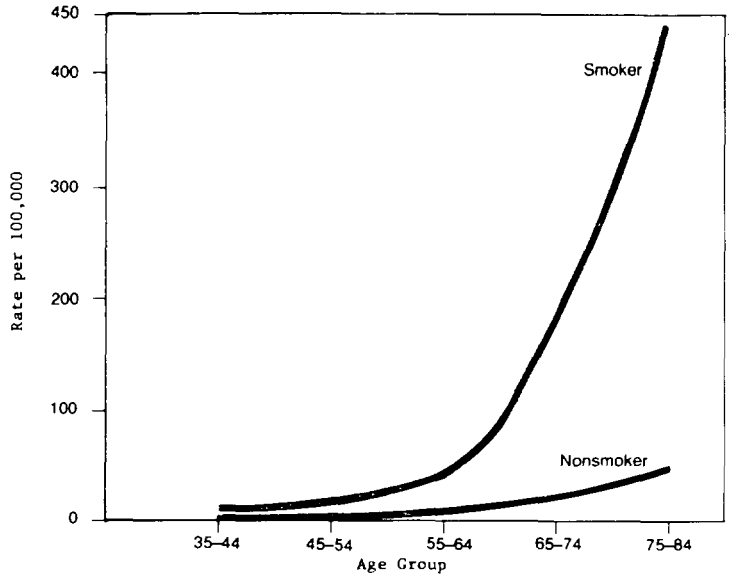

FIGURE 5.—Death rate for bronchitis, emphysema, or both, per 100,000 population, by age and smoking status[1], U.S. veterans study, 16-year followup

[1] Smoker is defined as all people who smoke cigarettes and those who have ever smoked other tobacco products.
SOURCE: Adapted from Rogot and Murray (1980).

The American Cancer Society 25-State Study

The American Cancer Society 25-State study (Hammond 1965, 1966; Hammond and Garfinkel 1969; Hammond et al. 1976; Lee and Garfinkel 1981) represents the largest investigation. Deaths from emphysema were separately analyzed by smoking habit; deaths from cor pulmonale were also separately recorded.

The U.S. Veterans Study

The mortality experience of approximately 294,000 U.S. veterans who held U.S. Government life insurance policies in December 1953 was examined in the U.S. veterans study (Dorn 1959; Kahn 1966; Rogot 1974a, b; Rogot and Murray 1980). Deaths from COLD were recorded as "bronchitis and/or emphysema"; "bronchitis, underlying or contributory"; and "emphysema without bronchitis."

The Canadian Veterans Study

Initiated in 1955 by the Canadian Department of National Health and Welfare, the Canadian veterans study (Best 1966; Best et al. 1961) included 78,000 men and 14,000 women. Over the next 6 years of followup, there were 9,491 male and 1,794 female deaths. The cause of death in most of these cases was confirmed by autopsy.

TABLE 2.—Outline of eight major prospective studies

Authors	Doll Hill Peto Pike	Hammond	Dorn Kahn Rogot	Hirayama	Best Josie Walker	Hammond Horn	Weir Dunn Linden Breslow	Cederlof Friberg Hrubec Lorich
Subjects	British doctors	Males and females in 25 States	U.S. veterans	Total population of 29 health districts in Japan	Canadian pensioners	White males in nine States	California males in various occupations	Probability sample of the Swedish population
Population size Females	40,000 6,000	1,000,000 562,671	290,000 <1%	265,000 142,857	92,000 14,000	187,000	68,000	55,000 27,700
Age range	20–85+	35–84	35–84	40 and up	30–90	50–69	33–64	18–69
Year of enrollment	1951	1960	1954 1957	1966	1955	1952	1954	1963
Years of followup reported	20–22 years	12 years	16 years	13 years	6 years	4 years	5–8 years	10 years
Number of deaths	11,166	150,000	107,500	39,100	11,000	12,000	4,700	4,500
Person years of experience	800,000	8,000,000	3,500,000	3,000,000	500,000	670,000	480,000	550,000

The American Cancer Society 9-State Study

In the American Cancer Society 9-State study (Hammond and Horn 1958a, b), 187,783 white men were followed for an average of 44 months by 22,000 American Cancer Society volunteers. All deaths from pulmonary disease (except pulmonary neoplasms) were considered as one group and included deaths from pneumonia, asthma, tuberculosis, lung abscess, pneumoconiosis, bronchiectasis, and emphysema.

California Men in Various Occupations

The study of California men in various occupations (Dunn et al 1960; Weir and Dunn 1970) examined the mortality experience of 68,153 men, aged 35 to 64, drawn from labor union rolls in specified occupations. Deaths from emphysema were separately categorized.

The Swedish Study

The study of a probability sample of 55,000 Swedish men and women (Cederlof et al. 1975), aged 18 to 69, represents a detailed analysis of mortality by smoking status over a period of 10 years. The cause of death was ascertained by death certificates collected by the Central Bureau of Statistics for all of Sweden.

The Japanese Study of 29 Health Districts

In the fall of 1965, a total of 265,118 men and women in 29 health districts in Japan were enrolled in a prospective study (Hirayama 1967, 1970, 1972, 1975a, 1975b, 1977, 1981). Mortality data regarding deaths from asthma and emphysema have recently been reported.

Cigarette Smoking and Overall COLD Mortality

The data from the major prospective studies relating smoking to mortality from COLD in men and women are presented in Table 3. These data demonstrate a uniform increase in death rates from COLD among male and female smokers when compared with nonsmokers of either sex. The mortality ratios for smokers compared with nonsmokers vary markedly, however, from 2.2 in the Japanese study to 24.7 in the study of British doctors. Some of this variability can be attributed to different patterns of certification of cause of death in different countries, but a number of other factors are also important. Perhaps the most important other factor is the age range of the population studied. As described earlier in this chapter, death rates from COLD rise steeply with age, particularly over the age of 65. Studies of populations under age 65 may significantly underestimate the impact of cigarette smoking on COLD because of the long duration of smoking required to damage enough lung to result in

death from COLD. The population under 65 contains large numbers of individuals who have significant airflow obstruction and who will die of COLD, but who have not done so prior to age 65. This effect is demonstrated in the American Cancer Society 25-State study, in which the COLD mortality ratio for male smokers aged 45 to 64 was 6.55, but increased to 11.41 in male smokers aged 65 to 79.

A second reason for differences in mortality ratios is the selection of study populations who are currently employed, particularly if the duration of followup is relatively short. The incremental nature of the lung injury in COLD often results in a prolonged period of disability prior to resulting in death. This disability is usually incompatible with full-time work, particularly in those occupations requiring substantial exertion. Therefore, the study of a working population excludes those with significant existing disability from COLD and underestimates the COLD death rates in the general population. Unless the followup period is long enough to observe the progression of COLD from its asymptomatic stages through the development of disability and finally death, the impact of cigarette smoking on COLD death rates will be underestimated. This effect is particularly important because cigarette smoking is overwhelmingly the major determinant of COLD risk, and therefore an underestimation of the true COLD prevalence leads to an underestimation of the relative risk of smoking. As the followup period is extended for a duration sufficient to allow the full time course of COLD to be observed, the impact of cigarette smoking on COLD death rates also emerges from the small background rate of COLD death certification in nonsmokers (which includes those classified in error and those with disease induced by agents that results in a more rapid progression to death).

This "healthy worker" effect is present to varying extents in all of the prospective studies and is one of the reasons the studies with the longest followup periods also tend to have the largest COLD mortality ratios. This is particularly evident in the study with the longest followup. The British doctors study, with a followup of 20 years, revealed a mortality ratio for male smokers of 24.7.

A final reason for the differences in mortality ratios is the differences in the smoking habits of the various populations. As was discussed in the previous chapter, the extent of lung injury is influenced by both the number of cigarettes smoked per day and the duration of the smoking habit. As is shown in Table 4, some of the variability in mortality ratios among the studies disappears when the mortality ratios are reported by number of cigarettes smoked per day. However, there are also substantial differences in the pattern of cigarette use in different countries, particularly in the use of the milder types of tobacco cigarettes that are more likely to be inhaled and are smoked in the United States. For example, these cigarettes

TABLE 3.—COLD mortality ratios by disease category, eight prospective studies

Study	Size of population	Nonsmoker	Emphysema		Bronchitis	Both	Other	Comments
British physicians								
Men	34,000	1.00				24.7		Ratio for women by amount smoked only; see Table 4
Women	6,195	1.00						
California men in various occupations	68,000	1.00	12.33					
Canadian veterans								
Men	78,000	1.00	5.85		11.42			
American Cancer Society 25-State			45–64 [1]	65–79 [1]				[1] Age range
Men	440,500	1.00	6.55	11.41				
Women	562,700	1.00	4.89	7.50				
U.S. veterans								
Men	290,000	1.00	14.82		5.11	12.07		
American Cancer Society 9-State								
Men	188,000	1.00					2.85	All pulmonary diseases other than cancer (pneumonia, influenza, TB, asthma, bronchitis, lung abscess, etc.)

TABLE 3.—Continued

Study	Size of population	Nonsmoker	Emphysema	Bronchitis	Both	Other	Comments
Swedish							
Men	27,000	1.00				•	• Number of deaths too small for statistical analysis; includes deaths due to asthma
Women	28,000	1.00				2.20	
Japanese							
Men	122,000	1.00					Data by amount smoked only; see Table 4
Women	143,000	1.00					

were not introduced into Japan in large numbers until after the Second World War. The chronicity of tobacco use, particularly of those forms of tobacco that are commonly inhaled, is probably more important than age per se in producing COLD death. The chronicity of tobacco use differs in different countries and between men and women in the same country; these differences would be expected to result in different COLD mortality ratios.

In several of these prospective mortality studies, the mortality ratio for COLD deaths in smokers compared with nonsmokers was even larger than that found for lung cancer. This is consistent with the data in the previous chapter showing that cigarette smoking is the major predictor of decline in lung function and is also consistent with the clinical observation that clinically significant airflow obstruction is rare in the absence of a history of smoking.

Retrospective Studies

The relationship between smoking and mortality from COLD was also examined in several large retrospective studies. Wicken (1966) conducted a study of 1,189 men living in Ireland who died from chronic bronchitis. Smoking habits were determined through personal interviews with relatives of the decedents. The relative risk for mortality from COLD was increased in smokers as compared with nonsmokers. Smokers of as few as 1 to 10 cigarettes per day had a 2.95-fold higher risk for mortality from COLD as compared with nonsmokers.

Dean and associates conducted two retrospective studies of the relationship between changes in smoking patterns and changes in mortality from bronchitis among a sample of the population in urban areas and in rural areas of northeast England. The periods of observation in the two studies were 1952 to 1962 (Wicken and Buck 1964; Wicken 1966) and 1963 to 1972 (Dean et al. 1977, 1978), respectively. Smoking status classifications in the two studies were similar, and were based upon questions relevant to the last 2 years before death or interview. In both studies, the relative risk for mortality from chronic bronchitis was substantially increased for smokers as compared with nonsmokers.

In summary, data from both the prospective and the retrospective studies consistently demonstrate an increase in mortality from COLD for smokers as compared with nonsmokers. These studies include populations of widely different ages, social and ethnic groups, geographic locations, and occupations; nevertheless, they strongly support a causal relationship between smoking and COLD.

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TABLE 4.—COLD mortality rates for men and women, by number of cigarettes smoked per day, prospective studies

Study	Men		Women		COLD disease classification
	Cigarettes per day	Mortality ratios	Cigarettes per day	Mortality ratios	
British physicians	Nonsmoker	1.00	Nonsmoker	1.00	Chronic bronchitis, emphysema, or both
	1–14	17.00	1–14	10.50	
	15–24	26.00	15–24	28.50	
	25+	38.00	25+	32.00	
U.S. veterans	Nonsmoker	1.00			Chronic bronchitis
	1–9	3.63			
	10–20	4.51			
	21–39	4.57			
	40+	8.31			
	Nonsmoker	1.00			Emphysema
	1–9	5.33			
	10–19	14.04			
	21–39	17.04			
	40+	25.34			
	Nonsmoker	1.00			Chronic bronchitis and emphysema
	1–9	4.84			
	10–19	11.23			
	21–39	17.45			
	40+	21.98			
Canadian veterans	Nonsmoker	1.00			Chronic bronchitis
	1–9	7.02			
	10–20	13.65			
	21+	14.63			
	Nonsmoker	1.00			Emphysema
	1–9	4.81			
	10–20	6.12			
	21+	6.93			
Japanese	Nonsmoker	1.00	Nonsmoker	1.00	Emphysema
	<100,000[1]	0.51	<100,000	2.28	
	<200,000	2.57	<200,000	3.14	
	>300,000	1.93	>300,000	10.93	
California men in various occupations	Nonsmoker[2]	1.00			Emphysema
	About ½ pk	8.18			
	About 1 pk	11.80			
	About 1½ pk	20.86			
American Cancer Society 9-State	Nonsmoker	1.00			All pulmonary diseases other than cancer[3]
	1–9	1.67			
	10–20	3.00			
	20+	3.64			

[1] Data for the Japanese study are for lifetime exposure by > total number of cigarettes consumed.
[2] Nonsmoker in the California occupations study also includes > smokers of pipes and cigars.
[3] Pneumonia, influenza, TB, asthma, bronchitis, lung abscess, etc.

Male and Female Differences in COLD Mortality

Mortality data presented by the National Center for Health Statistics indicate that in 1980 the number of deaths from COLD was 2.36 times higher among men than among women (9th ICDA nos. 490, 491, 492, and 494–496). In the prospective studies reviewed above, it is also apparent that the relative risk for death from COLD was greater for male smokers than for female smokers, although both male and female smokers exhibited a greater risk than nonsmokers for death from COLD. These differences are most likely a consequence of differences in male and female smoking patterns. The women in these studies tended to smoke fewer cigarettes, inhale less deeply, and begin smoking later in life than the men. They more frequently smoked filtered and low tar and nicotine cigarettes and had less occupational exposure to pulmonary irritants than men. These differences in mortality from COLD are narrowing because of a more rapid rise in female mortality from COLD (see Table 1).

Figures 6 and 7 help to explain the male–female differences in COLD mortality ratios in the prospective mortality studies and in U.S. COLD death rates. The figures are descriptions of the prevalence of cigarette smoking in successive 10-year birth cohorts of men and women as those cohorts progressed through the years 1900–1980 (Harris 1983). Examination of these figures revealed several important findings. Relatively few women took up smoking prior to 1930. The heaviest smoking cohorts of men have a prevalence of over 70 percent compared with 45 percent of women, and the male cohorts with these peak prevalences are older than the female cohorts. However, as discussed earlier, the incremental and progressive nature of cigarette-induced lung injury results in both prevalence and duration of cigarette smoking having an impact on COLD death rates. Therefore, in examining Figures 6 and 7 it is important to consider the span of years of a given prevalence of smoking maintained by a given birth cohort as well as the peak prevalence achieved by that cohort. The COLD death rates should then be proportional to the area under the prevalence curve described by each cohort, rather than to the peak of that curve.

A careful examination of Figure 6 reveals that the area under the prevalence curve for the cohort born between 1921 and 1930 is less than the area under the curve for the cohort born between 1911 and 1920, in spite of their similar peak prevalences. This difference is due to the more rapid decline in prevalence with age in the 1921 to 1930 cohort. Similarly, the cohort born between 1901 and 1910 partially compensates for a peak prevalence that is lower than the 1911 to 1920 cohort by having a somewhat a broader base. Each of the cohorts born prior to 1900 have substantially smaller areas under their curves than those born during the first three decades of this century. These differences in prevalence are reflected in the changes

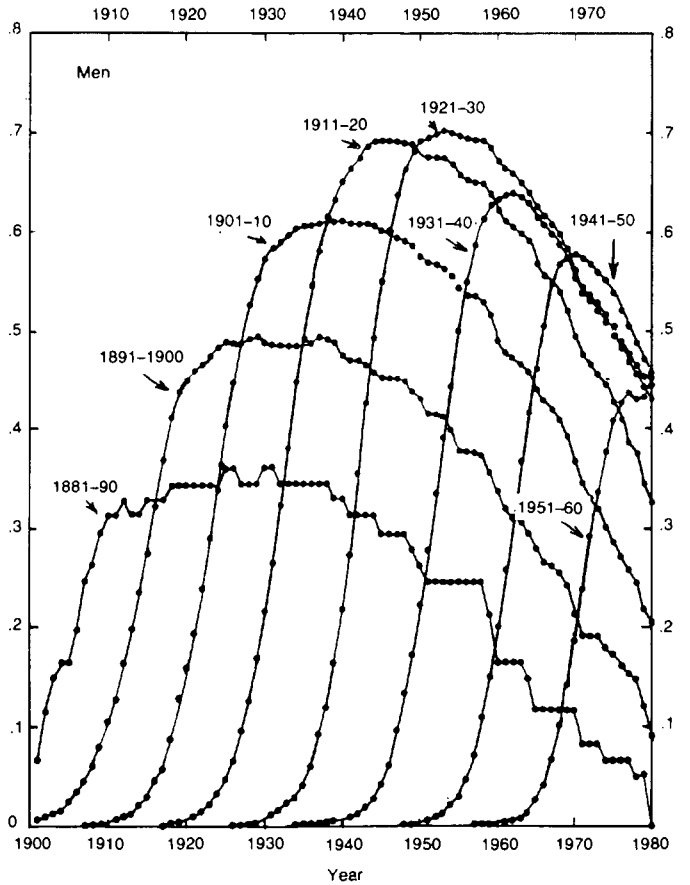

FIGURE 6.—Prevalence of cigarette smoking among successive birth cohorts of men, 1900–1980, derived from smoking histories in the National Health Interview Survey (HIS)

SOURCE: Harris 1983.

in age-specific death rates portrayed in Figure 8 and Table 5. The oldest age group (75–84) continues to show a rapid rise in COLD death rates as those birth cohorts with increasing prevalence and duration of smoking move into this age range. In the age range 65–74 the rates rose rapidly from 1960 through the mid 1970s, but seem to be leveling off, consistent with the fact that this age group is now made up entirely of men born after 1900. In the age range 55–64 the rates suggest a slight downturn beginning in the mid 1970s, coincident with the entry of the 1921 to 1930 birth cohort into this age group. The numbers for the age range 45–54 are too small to

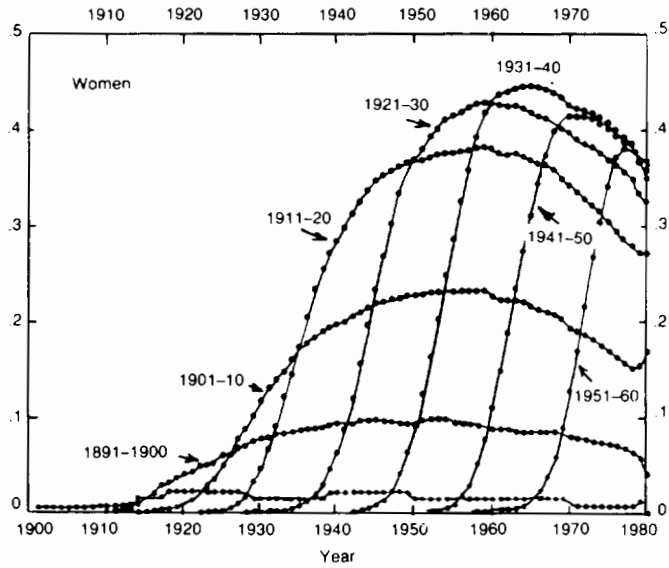

FIGURE 7.—Prevalence of cigarette smoking among successive birth cohorts of women, 1900–1980, derived from smoking histories in the National Health Interview Survey (HIS)

SOURCE: Harris 1983.

permit firm conclusions, but also suggest that a downturn in rates occurred in this group in the late 1960s.

A close examination of Figures 6 and 7 also offers an explanation of the differences in mortality ratios for men and women observed in the prospective studies. COLD is a slow, progressive disease, and death from COLD usually results only after extensive lung damage has occurred. The fact that death from COLD is unusual prior to age 45 reflects, in part, the 30 or more years required for cigarette smoke to damage enough lung to result in death. The substantial ventilatory reserve of the lung allows a significant amount of damage to exist in a person without symptomatic limitation or risk of death from COLD. The prospective mortality studies were conducted in the 1950s and 1960s, a point in time approximately 30 years after the beginning of the rise in smoking prevalence among women demonstrated in Figure 7. Even the older cohorts, where significant mortality might be expected, had begun smoking largely after 1930, and therefore had a shorter duration of smoke exposure than the men born in the same years. This shorter duration of the smoking habit, together with the previously described tendency of women to

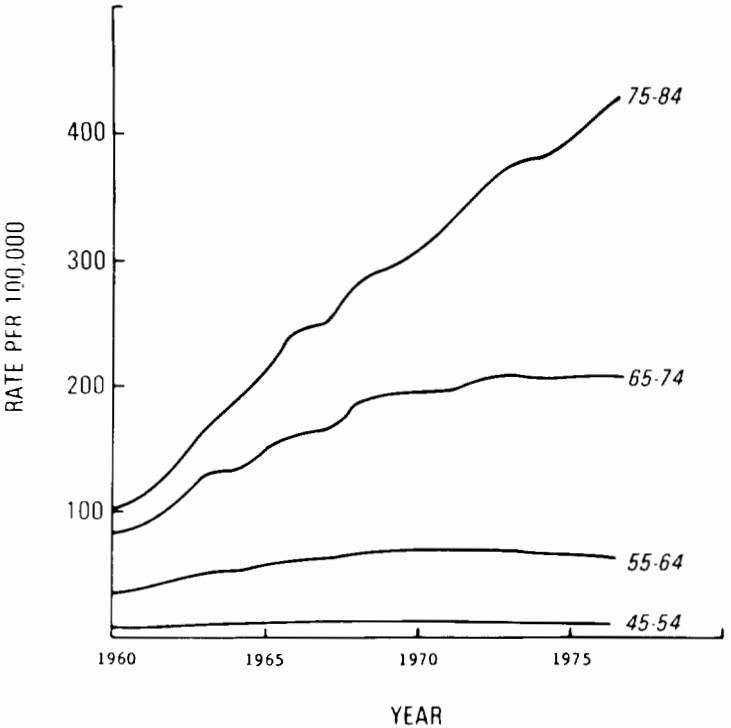

FIGURE 8.—Age-specific COLD mortality rates for white men in the United States, 1960–1977

NOTE: ICDA Nos. 490–492 and 519.3.
SOURCE: National Center for Health Statistics (1982).

smoke fewer cigarettes per day and to inhale less deeply, would be expected to result in less cumulative lung damage at any given age. This difference in extent of lung damage could explain the difference in COLD mortality ratios between men and women observed in the prospective mortality studies.

The British doctors study examined the risk of COLD death for male and female physicians who smoked similar numbers of cigarettes per day (Table 4), and the mortality ratios were similar for similar numbers of cigarettes smoked per day.

In summary, data from the prospective studies indicate that the relative risk of death from COLD is greater for male smokers than for female smokers. These differences are most likely a consequence of differences in female smoking patterns. Women tend to smoke fewer cigarettes, inhale less deeply, and begin to smoke later in life than men. These differences in mortality from COLD are narrowing because of a more rapid rise in female mortality from COLD than in male COLD mortality. This reflects the narrowing in differences between male and female smoking patterns and the rising prevalence of female smokers in successive cohorts born between 1920 and

TABLE 5.—Age-specific COLD death rates per 100,000 population

Year	Age			
	45–54	55–65	65–74	75–84
1960	8.6	36.1	82.9	101.8
1961	7.6	38.7	87.9	111.8
1962	9.6	44.2	107.2	136.7
1963	11.7	52.3	131.2	169.6
1964	12.1	51.8	131.6	181.9
1965	12.4	57.8	153.6	216.6
1966	12.4	61.9	161.9	244.8
1967	12.4	61.2	164.8	248.6
1968	13.1	67.4	186.7	286.5
1969	13.9	67.5	189.5	294.3
1970	13.6	68.1	196.5	311.5
1971	13.5	67.4	195.6	327.4
1972	13.0	67.7	204.8	351.4
1973	12.7	69.9	210.1	378.4
1974	12.8	64.8	204.8	380.4
1975	11.9	64.7	207.6	399.7
1976	12.2	64.0	210.7	419.7
1977	11.4	60.1	206.1	431.5

SOURCE: National Center for Health Statistics (1982).

1950. These data are ominous for women, portending a rising mortality from COLD over the next decades.

Amount Smoked and Mortality From COLD

Six of the major prospective studies evaluated the influence of different smoking levels on mortality from COLD. These studies employed a variety of measures of tobacco exposure, including number of cigarettes smoked per day, grams of tobacco smoked, and total number of cigarettes smoked in a lifetime. The data, presented in Table 4, show a gradient in risk for mortality from COLD as the number of cigarettes smoked per day increases and as the cumulative number of lifetime cigarettes smoked increases. In the U.S. veterans study, smokers of two packs or more per day had 22 times the risk of COLD death of nonsmokers. Furthermore, mortality ratios between the two followup periods for bronchitis and emphysema actually increased overall and by the amount smoked (Figure 9). The authors noted that this was the only major disease of those associated with cigarette smoking that showed such an increase, suggesting that mortality ratios have been increasing over time at all levels of smoking. In the British and Japanese studies, women smokers at the highest levels exhibited a 32- and an 11-fold higher risk for death from COLD (respectively) than their nonsmoking counterparts. The variability in COLD mortality ratios noted in

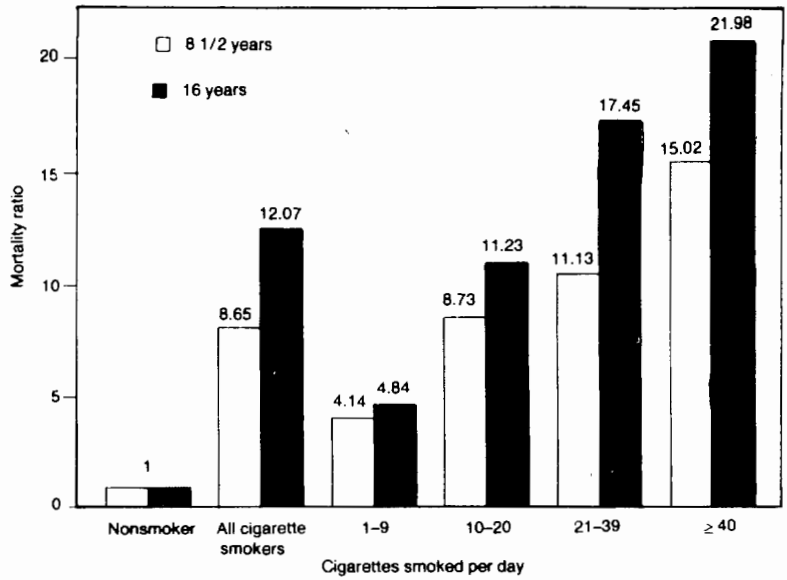

FIGURE 9.—Bronchitis and emphysema for male smokers number of cigarettes smoked per day, U.S. veterans study, 8½-year and 16-year followup

Table 3 is much less evident when the mortality ratios are presented by amount smoked.

In summary, the degree of tobacco exposure strongly affects the risk for death from COLD in men and in women. This clearcut dose–response relationship enhances the strength of the causal relationship between smoking and COLD.

Inhalational Practice and Mortality From COLD

The inhalation of tobacco smoke is the major mechanism whereby bronchial and alveolar tissues are exposed to the potentially damaging effects of tobacco smoke. In the British doctors study, subjects who acknowledged inhaling exhibited a 1.53-fold higher risk for COLD death as compared with those who stated they did not inhale (see Table 6). However, all smokers, regardless of their inhalational practice, exhibited higher risk for COLD mortality than did nonsmokers.

In the retrospective study from northeast England (Dean et al. 1977, 1978), the risk among men for mortality from chronic bronchitis steadily declined with a decrease in the depth of inhalation (Table 7). Among women, the risk for mortality from chronic bronchitis was lower for all other groups than for those who stated they "inhaled a lot."

TABLE 6.—COLD mortality by inhalation practice, British doctors study, men

Cause of death	Number of deaths	Annualized death rate per 100,000 men responding to question: do you inhale?		Risk in inhalers compared with unity in noninhalers
		Yes	No	
Chronic bronchitis and emphysema and pulmonary heart disease	71	89	58	1.53

Table 7.—Relative risk for mortality by depth of inhalation, 1963–1972, second retrospective mortality study in northeast England

Depth of inhalation	Relative risk for chronic bronchitis	
	Men	Women
A lot (base)	1.00	1.00
A fair amount	0.98	0.54
A little	0.62	0.41
None	0.58	0.58

SOURCE: Dean et al. (1977, 1978).

Results from prospective mortality studies comparing COLD death rates by inhalation are identical to those observed in the morbidity studies, which have consistently shown that COLD is more prevalent among inhalers than noninhalers (Ferris et al. 1972; Comstock et al. 1970; Rimington 1974).

These data suggest that inhalational practice affects the risk of mortality from COLD. People who inhale deeply experience a higher risk for mortality from COLD than people who do not inhale. Regardless of their inhalational practice, however, smokers still experience higher rates of death from COLD than nonsmokers.

Age of Initiation and COLD Mortality

Another indicator of exposure to tobacco smoke that may influence risk for mortality from COLD is the age of initiation of smoking. If their smoking habits are otherwise similar, people who take up smoking at a younger age have a greater total exposure to tobacco smoke than those who take up smoking later in life, and might be expected to experience greater adverse consequences from smoking. In the Japanese prospective study (Hirayama 1981), men who began to smoke before the age of 19 exhibited slightly higher mortality ratios for emphysema than did men who began to smoke after the

TABLE 8.—Number of deaths from chronic bronchitis, emphysema, and pulmonary heart disease in ex-cigarette smokers, by years of cessation, versus number of deaths in lifelong nonsmokers, British doctors study

	Number of deaths in ex-smokers, divided by number expected in lifelong smokers					Number of deaths in nonsmokers
Years of cessation	0*	<5	5–9	10–14	>14	
	35.6	34.2	47.7	7.3	8.1	2

* Current smokers.

age of 20. In the retrospective study from northeast England (Dean et al. 1977, 1978), the relative risk for death from chronic bronchitis among men who began to smoke after the age of 25 was 60 percent of that of men who began to smoke between the ages of 15 and 19. Among women in the same study who began to smoke between the ages of 15 and 19, the relative risk for death from chronic bronchitis was 1.28-fold higher than for women who began to smoke after age 25; however, the number of deaths was small.

Smoking Cessation and COLD Mortality

The effects of smoking cessation on mortality from COLD were examined in the British doctors study and the U.S. veterans study. In the British doctors study, men who quit smoking experienced no change in mortality from COLD in the first 4 years and a rise in the next 5 years; presumably, this is related to the presence of many people in this group who quit smoking for health reasons (Table 8). Thereafter, ex-smokers experienced lower death rates from COLD, although their rates were still higher than those of the nonsmokers. Female ex-smokers also experienced lower mortality rates than current smokers, but the rates in ex-smokers were still higher than those in nonsmokers.

In the U.S. veterans study, ex-smokers who had quit for reasons other than ill health experienced lower mortality rates for COLD than did current smokers. However, the benefit of cessation upon risk for mortality was heavily dependent upon the prior level of smoking and the length of time of cessation. These data are presented in Table 9. Ex-smokers who had smoked less than 10 cigarettes per day had a 1.64-fold higher risk for mortality from COLD than nonsmokers; in contrast, ex-smokers who smoked more than 39 cigarettes per day had a 9.91-fold higher rate of death from COLD than nonsmokers. For any given number of cigarettes smoked

TABLE 9.—Mortality ratios for bronchitis and emphysema in nonsmokers and in ex-smokers and current smokers by number of cigarettes smoked daily and number of years of cessation, U.S. veterans study

	Cigarettes/day				
Smoking status	0	<10	10–20	21–39	>39
Nonsmoker	1.00	—	—	—	—
Ex-smoker	—	1.64	5.35	7.68	9.91
Current smoker	—	4.84	11.23	17.45	21.98

		Years of cessation				
Nonsmoker	Current smoker	<5	5–9	10–14	15–20	>20
1.00	12.07	11.66	14.35	10.19	5.66	2.64

per day, however, ex-smokers had a lower risk than current smokers. As in the British study, mortality ratios initially increased over the first 9 years of cessation. After the first 9 years, mortality ratios for ex-smokers fell, but never reached the level of the nonsmoker.

Two studies have evaluated mortality rates from COLD among physicians, a group among whom many quit smoking to protect their health. Fletcher and Horn (1970) assessed the mortality rates from bronchitis among physicians in England and Wales. Among doctors aged 35 to 64, there was a 24 percent reduction in bronchitis mortality between 1953–1957 and 1961–1965, as compared with a reduction of only 4 percent in the national bronchitis mortality rates for men of the same age in England and Wales. Enstrom (1983) assessed mortality trends from COLD in a cohort of 10,130 physicians in California. The standardized mortality ratio for bronchitis, emphysema, and asthma among male California physicians relative to American white men declined from 62 during the period 1950 to 1959 to 35 during the period 1970 to 1979.

In summary, cessation of smoking leads to a decreased risk for mortality from COLD as compared with that of current smokers. The residual risk of death for the ex-smoker is determined by the person's prior smoking status and the number of years of cessation. However, the residual risk remains larger than that of the nonsmoker, presumably because of the presence of irreversible lung damage acquired during prior smoking.

Pipe and Cigar Smoking Mortality From COLD

Several of the prospective epidemiological studies examined the relationship between pipe and cigar smoking and mortality from COLD. The data from these studies indicate that pipe smokers and

TABLE 10.—COLD mortality ratios in male pipe and cigar smokers, prospective studies

Study	Category	Non-smoker	Type of smoking: Cigar only	Pipe only	Total pipe and cigar	Cigarette only	Mixed
American Cancer Society 9-State	COLD total	1.00	1.29	1.77		2.85	
	Emphysema						
	Bronchitis						
British doctors	COLD total	1.00			9.33	24.67	11.33
	Emphysema						
	Bronchitis	1.00			4.00	7.00	6.67
Canadian veterans	COLD total						
	Emphysema	1.00	3.33	.75		5.85	
	Bronchitis	1.00	3.57	2.11		11.42	
American Cancer Society 25-State	COLD total						
	Emphysema	1.00			1.37	6.55[1]	
	Bronchitis						
U.S. veterans (8.5-year followup)	COLD total	1.00	.79	2.36	.99	10.08	
	Emphysema	1.00	1.24	2.13	1.31	14.17	
	Bronchitis	1.00	1.17	1.28	1.17	4.49	
U.S. veterans (16-year followup)	COLD total	1.00	0.84[2]	1.44[3]		4.75[4]	
	Bronchitis, emphysema	1.00		2.53[3]		13.13[4]	

[1] Mortality ratios for ages 55 to 64 only are presented.
[2] Pure cigar.
[3] Pure pipe.
[4] Pure cigarette.

cigar smokers also experience higher mortality from COLD as compared with nonsmokers. However, the risk of dying from COLD is less than that of current cigarette smokers (Table 10).

International Comparison of COLD Death Rates and Smoking Habits: The Emigrant Studies

Reid (1971) reported that age-adjusted mortality rates from chronic nonspecific lung disease among British citizens varied with migration patterns. British men living in the United Kingdom had a chronic, nonspecific lung disease death rate of 125 per 100,000, whereas migrants to the United States experienced a mortality rate of only 24 per 100,000, which is similar to the rate found in the U.S. population. Differences in cigarette smoking and air pollution were identified as the major factors contributing to the real excess in bronchitis morbidity experienced by the British in the United Kingdom. Rogot (1978) conducted a study of British and Norwegian emigrants to the United States. The mortality rate from chronic nonspecific lung disease (CNSLD) in Great Britain is about fivefold

that in the United States, whereas the mortality rate from CNSLD in Norway is slightly lower than that in the United States. In contrast, the British migrant rates were about equal to those of native-born Americans and the Norwegian migrant rates were the lowest. Mortality rates for CNSLD were higher for smokers than for nonsmokers in all groups. These data suggest that ethnic origin plays a minor role, if any, in determining COLD risk. Regardless of country of origin, these studies indicate that tobacco smokers experience higher mortality rates for COLD than do nonsmokers.

COLD Mortality Among Populations With Low Smoking Rates

Numerous studies have reported that certain population groups who traditionally abstain from cigarette smoking for religious or other reasons have lower mortality rates from those diseases traditionally related to tobacco use. The 1982 and 1983 Reports of the Surgeon General, *The Health Consequences of Smoking* (USDHHS 1982, 1983), extensively reviewed this phenomenon as it relates to cancer and cardiovascular diseases among Mormons, Seventh Day Adventists, and others. Because Amish are seen as strict and fundamentalist in outlook, it is assumed that their use of tobacco is severely restricted. While cigarettes are largely considered taboo, pipe and cigar smoking and tobacco chewing are widespread (Hostetler 1968). Hamman et al. (1981) examined the major causes of death in Old Order Amish people in three settlements in Indiana, Ohio, and Pennsylvania to determine if their lifestyle altered their mortality risk compared with neighboring non-Amish. Mortality ratios from all respiratory diseases were significantly lower by over 80 percent in Amish men 40 to 69 years old, and by 50 percent in those 70 and older. In the chronic pulmonary disease categories including emphysema, bronchitis, and asthma, only one Amish male death occurred, whereas approximately 23 were expected. The pattern of mortality from chronic respiratory diseases was similar for Amish women.

Summary and Conclusions

1. Data from both prospective and retrospective studies consistently demonstrate a uniform increase in mortality from COLD for cigarette smokers compared with nonsmokers. Cigarette smoking is the major cause of COLD mortality for both men and women in the United States.
2. The death rate from COLD is greater for men than for women, most likely reflecting the differences in lifetime smoking patterns, such as a smaller percentage of women smoking in

past decades, and their smoking fewer cigarettes, inhaling less deeply, and beginning to smoke later in life.

3. Differences in lifetime smoking behavior are less marked for younger age cohorts of smokers. The ratio of male to female mortality from COLD is decreasing because of a more rapid rise in mortality from COLD among women.
4. The dose of tobacco exposure as measured by number of cigarettes or duration of habit strongly affects the risk for death from COLD in both men and women. Similarly, people who inhale deeply experience an even higher risk for mortality from COLD than those who do not inhale.
5. Cessation of smoking eventually leads to a decreased risk of mortality from COLD compared with that of continuing smokers. The residual excess risk of death for the ex-smoker is directly proportional to the overall lifetime exposure to cigarette smoke and to the total number of years since one quit smoking. However, the risk of COLD mortality among former smokers does not decline to equal that of the never smoker even after 20 years of cessation.
6. Several prospective epidemiologic studies examined the relationship between pipe and cigar smoking and mortality from COLD. Pipe smokers and cigar smokers also experience higher mortality from COLD compared with nonsmokers; however, the risk is less than that for cigarette smokers.
7. There are substantial worldwide differences in mortality from COLD. Some of these differences are due to variations in terminology and in death certification in various countries. Emigrant studies suggest that ethnic background is not the major determinant for mortality risk due to COLD.

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CHAPTER 4. PATHOLOGY OF LUNG DISEASE RELATED TO SMOKING

CONTENTS

Introduction

It is usual to think of chronic airflow obstruction as being caused by airway narrowing or loss of airflow driving pressure—the elastic recoil of the lung (Macklem 1971)—or both. Lesions of the airways are often divided into those of the "large airways" and those of the "small airways." The reasons for this division are both historical and conceptual. Hogg et al. (1968) showed that in patients with chronic obstructive lung disease (COLD) the major site of airway obstruction lay in airways that were peripheral to the wedged catheter that the researchers used to partition airway resistance. The catheter was wedged in airways 2 or 3 mm in diameter, and thus the airways peripheral to the catheter included the smallest bronchi (airways with cartilage in their walls) and bronchioles (conducting airways without cartilage in their walls). Since both bronchi and bronchioles were involved, Hogg and associates used the term "small airways" to describe them, which has since become a popular term. Conceptually, lesions of airways may consist of an intraluminal component (mucus) or a mural component. Most of the mucus in the airways is thought to be secreted by the tracheobronchial submucosal glands (Reid 1960); these are mainly confined to airways more than 2 or 3 mm in diameter, or large airways. Because of the documented association between chronic productive cough and airflow obstruction (Fletcher et al. 1959), for a long time it was thought by many that intraluminal mucus was a major source of chronic airflow obstruction. Thus, the notion developed, without proper substantiation, that central airways obstruction was due to intraluminal mucus and peripheral airway obstruction was due to inflammation and narrowing. It is also true that many have equated emphysema with loss of elastic recoil, but when this has been examined in vivo (Park et al. 1970; Boushy et al. 1970; Gelb et al. 1973; Berend et al. 1979; Pare et al. 1982) or in excised lungs (Berend et al. 1980; Silvers et al. 1980), the association has not been close, with some notable exceptions (Niewoehner et al. 1975; Greaves and Colebatch 1980). Thurlbeck (1983) reviewed the evidence and argued that loss of recoil in emphysematous lungs may not be due to the lesions of emphysema per se but to defects in apparently morphologically normal intervening lung tissue.

The classical approach to considering the different sites of flow obstruction is used in this chapter to analyze the relationship between smoking and the morphologic lesions associated with chronic airflow obstruction in humans. Lesions of the large airways (bronchi) are discussed first, followed by small airways, and then by alveolated structures. It has very recently become apparent that it is important to include respiratory bronchiolitis as well as emphysema in the last category (Wright et al., in press); this issue is discussed in the paragraphs on peripheral (small) airways. Definitions and a brief

review of the diseases involved are provided. This chapter attempts to present the morphologic changes associated with chronic obstructive lung disease. The detailed epidemiologic and experimental evidence relating cigarette smoking and COLD are presented elsewhere in this Report.

Lesions Associated With Chronic Airflow Obstruction

Central Airways

Mucus

It is convenient to discuss intraluminal mucus and increased tracheobronchial mucus gland size together, because they are thought to be related (Reid 1960). Chronic bronchitis is defined as "the condition of subjects with chronic or recurrent excess mucus secretion into the bronchial tree" (Ciba Foundation Guest Symposium 1959). Because there is no way to accurately measure the amount of mucus secreted into the bronchi, the empirical approach was taken that production of any sputum was abnormal. Chronic was defined as "occurring on most days for at least 3 months of the year for at least 2 successive years" (Ciba Foundation Guest Symposium 1959). A further qualification was that such sputum production should not be on the basis of specific diseases such as tuberculosis, bronchiectasis, or lung cancer.

The initial step was to correlate chronic bronchitis, as defined above, with lesions in the central airways. This was first done by Reid (1960), who assessed gland size by comparing the thickness of the submucosal bronchial mucus glands in histologic sections to the thickness of the bronchial wall. The latter was defined as the distance from the basement membrane of the epithelium to the inner periochondrium. This measurement is now known as the Reid Index. This increase has been confirmed by several observers (Thurlbeck et al. 1963; Thurlbeck and Angus 1964; Mitchell et al. 1966; MacKenzie et al. 1969; Scott 1973), but not by all (Bath and Yates 1968; Karpick et al. 1970). An important observation was that there was a distinct overlap in the value of the Reid Index between bronchitics and nonbronchitics (Thurlbeck and Angus 1964) as opposed to Reid's 1960 finding that there were two completely separate groups. In practical terms, this meant that the Reid Index had limitations in predicting the presence or absence of chronic bronchitis. More important, it suggested a broad border between health (nonbronchitis) and disease (bronchitis). For a variety of technical reasons (Jamal et al., in press), the Reid Index is a difficult measurement to use; thus, other measurements of mucus gland size were developed. The most popular was the volume density of mucus glands, i.e., the ratio of area of mucus glands to area of the entire bronchial wall as seen on histologic slides (Hale et al. 1968; Dunnill

et al. 1969; Takizawa and Thurlbeck 1971; Oberholzer et al. 1978). Other methods included absolute gland size (Restrepo and Heard 1963; Bedrossian et al. 1971) and a radial intercept method (Alli 1975). The size of the acini (tubules) of mucus glands, the number per unit area, and the ratio of mucus to serous tubules have also been used (Reid 1960).

The Reid Index, the volume density of mucus glands, and the ratio of mucus to serous acini have been examined in smokers and nonsmokers; the results are shown in Table 1. When one considers the overwhelming association between smoking and chronic bronchitis in living subjects, differences in mucus gland size are insignificant. For example, three laboratories (Reid 1960; Thurlbeck et al. 1963; Thurlbeck and Angus 1964; Scott 1973) have found a difference in Reid Index between smokers and nonsmokers; two have not (Bath and Yates 1968; Hayes 1969). The results from volume density of mucus glands are clearer—Ryder et al. (1971) found a higher volume density of mucus glands in both male and female subjects. In populations of mixed sex, Cosio et al. (1980) and Pratt et al. (1980) found a higher volume density of glands, but Sobonya and Kleinerman (1972) and Scott (1973) did not. When observers have expressed their morphologic findings as either "normal" or "abnormal" (using different criteria), the smokers have been significantly abnormal in all the studies (Field et al. 1966; Megahed et al. 1967; Petty et al. 1967; Vargha 1969). The balance of the evidence is that there is an increase in mucus gland size in smokers. The discrepancy between the clinical and the morphologic findings may reflect several factors: the wide variation in mucus gland size in normal subjects, the difficulties in measuring the Reid Index and volume density of mucus glands, the different ways in which the cases have been collected, and the errors inherent in assessing smoking histories from analysis of charts; also, the fact that mucus glands can enlarge terminally (Helgason et al. 1970) might obscure true differences between the two groups. In addition, submucosal gland enlargement is a nonspecific change that can also occur in pneumoconiosis and cystic fibrosis.

Mucus is also secreted by goblet cells, most of which are in the major airways. Pratt et al. (1980) showed that goblet cells constituted 10.7 percent of the cells in the central airways of nonsmoking nontextile workers and 20.4 percent in smoking nontextile workers. Interestingly, they found an 18 percent frequency of goblet cells in nonsmoking textile workers; the frequency was about the same in smokers, whether or not they were textile workers.

Other Abnormalities of Central Airways

A variety of other changes have been described in the central airways in patients with chronic airflow obstruction, including

TABLE 1.—Comparison of mucus gland size in smokers and nonsmokers

Assessment of mucus gland enlargement	Author	Findings in smoking category			
		Non-smokers	Smokers	Light and moderate smokers	Heavy smokers
Reid index	Reid (1960)			0.46	0.43
	Thurlbeck et al. (1963)	0.43	0.50	0.45	0.53
	Thurlbeck and Angus (1964)	0.44	0.49		
	Bath and Yates (1968)	0.45	0.49		
	Hayes (1969)	0.32	0.33		
	Scott (1973)	0.41	0.46		
Mucus gland proportion	Ryder et al. (1971) (men)	14.5%	17.8%		
	Ryder et al. (1971) (women)	14.5%	17.1%		
	Sobonya and Kleinerman (1972)	11.2%	10.7%		
	Scott (1973)	14.1%	14.4%		
	Cosio et al. (1980)		Increased		
	Pratt et al. (1980)	9.3%	12.6%		
Frequency of cases with MGH[1] expressed as a percentage of cases in the group	Field et al. (1966) (men)	12%	37%		
	Field et al. (1966) (women)	18%	26%		
	Megahed et al. (1967)	14%	61%		
	Petty et al. (1967)	8.8%	37%		
	Vargha (1969)	18%	44%		

[1] MGH = Mucus gland hypertrophy.

inflammation and edema of the wall (Reid 1954), increase in bronchial smooth muscle (Hossain and Heard 1970; Takizawa and Thurlbeck 1971), and diminished cartilage, which is related more to emphysema than to chronic bronchitis (Thurlbeck et al. 1974a).

Peripheral (Small) Airways

General Review

As indicated, it was as recent as 1968 that the obstruction in patients with chronic airflow obstruction was conclusively shown to be due mainly to lesions in airways less than 2 or 3 mm in diameter. However, abnormalities in these airways had long been recognized. Indeed, Laennec (1962) pointed out in 1826 that air remained trapped in emphysematous lungs even when the major bronchi had been opened, and he reasoned that the source of the air-trapping was obstruction in the airways peripheral to the opened ones. Since then, numerous descriptions have been made of the peripheral airways in severe chronic airflow obstruction (see Table 2). Smokers were not compared with nonsmokers in any of these series. The probable reason is that for a long time it was thought that bronchiolitis was an infective complication of chronic bronchitis. Only very recently, and from studies in patients with mild chronic airflow obstruction,

has the link between smoking and peripheral airway lesions become established.

Hogg et al. (1968) not only found that the peripheral airways were the site of airflow obstruction in patients with severe disease, but also observed that peripheral airways contributed only about 15 percent of resistance to flow in normal lungs. It followed that considerable disease could be present in these peripheral airways without airway resistance being measurably increased. It was reasoned also that standard tests of expiratory function, such as the FEV_1 and the FEF_{25-75}, might not be abnormal in the presence of significant disease. Thus a variety of "tests of small airway function" were devised; these evolved to the single breath nitrogen washout test and to flow volume studies, in some instances comparing the effect of breathing helium mixtures with the effect of breathing room air. It soon became apparent that these tests could be abnormal when the FEV_1 was greater than the 80 percent predicted and that tests of small airway function could return to normal after cessation of smoking (Buist et al. 1976, 1979; Beck et al. 1981; Bouse et al. 1981). The term "small airways disease" was and is often applied to these abnormalities. It then became of interest to determine what the lesions in the airways were. Long before this, Reid (1955) had studied nine lungs resected from patients with chronic bronchitis and two lungs from chronic bronchitics obtained at autopsy. She found excess intraluminal mucus and narrowing and obliteration of airways, as assessed subjectively. Because the surgical patients also had lung cancer, most likely they were chronic smokers. Matsuba and Thurlbeck (1973) compared the airways of chronic bronchitics to those of nonbronchitics in nonemphysematous lungs. All the bronchitics were smokers and two nonbronchitics were smokers. Morphometrically, they found obvious narrowing of airways less than 2 mm in diameter, which also contained excess mucus.

The important study by Cosio et al. (1978), using surgically resected lungs, showed for the first time that abnormal tests of small airway function were related to abnormal morphology. There were 34 smokers and 2 nonsmokers in their group. A variety of abnormalities were observed, including inflammation, squamous cell metaplasia, ulceration, fibrosis, pigmentation, and increased muscle. They developed a score that summed the observed lesions (the total pathology score), and divided their patients into four groups on the basis of this score. They showed that as the total pathology score increased, tests of small airway function (single breath nitrogen test and flows on air and helium mixtures) deteriorated, as did standard tests of pulmonary function such as the FEV_1 and FEF_{25-75}. The data concerning smoking are hard to interpret, but the smoking index (number of cigarettes smoked per day times number of years smoked) increased from groups I to III and was similar in groups III

TABLE 2.—Occurrence of lesions of peripheral airways in patients with severe chronic airflow obstruction

Authors	Disease investigated	Abnormalities found
Laennec (1962)	Emphysema	Obstruction to flow in peripheral airways
Spain and Kaufman (1953)	Emphysema	Mural inflammation and fibrosis of bronchioles
Reid (1954)	Chronic bronchitis	Bronchiolitis, bronchiolar obliteration, and mucus plugging
Leopold and Gough (1957)	Centrilobular emphysema	Inflammation, fibrosis with narrowing of 60% of bronchioles supplying centrilobular space
McLean (1958)	Emphysema	Inflammation of proximal respiratory bronchioles, mucus plugging, and loss of bronchioles
Anderson and Foraker (1962)	Emphysema	Collapse of bronchioles due to loss of alveolar attachments
Pratt et al. (1965)	Centrilobular emphysema	Loss or distortion of the radial support of bronchioles
Anderson and Foraker (1967)	Emphysema	Loss of bronchioles in patients under age 70
Hogg et al. (1968)	Emphysema with severe chronic airflow obstruction	Inflammation and fibrosis of bronchi and bronchioles and mucus plugging
Mitchell et al. (1968)	Chronic airflow obstruction and severe emphysema	Inflammation, atrophy, goblet cell metaplasia, squamous metaplasia, and mucus plugs in bronchioles
Bignon et al. (1969, 1970)	Cor pulmonale and centrilobular emphysema	Inflammatory narrowing and fibrosis, loss of bronchioles, and mucus plugging
Karpick et al. (1970)	Respiratory failure	Goblet cell metaplasia
Linhartova et al. (1971)	Emphysema	Plugging of bronchioles with inflammatory cells and mucus
Matsuba and Thurlbeck (1972)	Severe emphysema and chronic airflow limitation	Loss of lumen of airways less than 2 mm in diameter due primarily to narrowing and mucus plugs
Linhartova et al. (1973, 1974, 1977)	Emphysema	Distortion, tortuosity, and irregular narrowing of bronchioles
Scott and Steiner (1975)	Cor pulmonale	Lack of filling bronchioles of less than 1 mm
Scott (1976)	Chronic airflow obstruction	Loss of airway lumen
Mitchell et al. (1976)	Chronic airflow obstruction obstruction	Chronic inflammation ($r=0.48$), narrowing (0.29), fibrosis (0.27), goblet cell metaplasia (0.24), and fewer small airways (–0.18)

and IV. The lesions that were different in group II from lesions in group I were squamous cell metaplasia, inflammation, and fibrosis. Fibrosis and squamous cell metaplasia increased steadily from groups I to III. Increased muscle and goblet cell metaplasia occurred only in group IV. One extrapolation of these data is that inflammation in the peripheral airways is the initial event produced in response to cigarette smoke. This inflammation leads to, or is associated with, squamous metaplasia and mural fibrosis. Goblet cell metaplasia and increase in muscle subsequently occur and are associated with decrements of function.

Berend et al. (1979) did a similar study on 21 smokers and 1 nonsmoker, and added the important information that airway narrowing occurred and was associated with abnormalities of the single breath nitrogen washout test and the FEF_{25-75}. The data were reanalyzed subsequently (Berend et al. 1981b) and showed that inflammation was the lesion associated with the most abnormalities in tests of expiratory function. Airway inflammation was significantly related to abnormalities of the FEV_1, FEF_{25-75}, slope of phase III of the single breath nitrogen test, and closing volume expressed as a percentage of vital capacity. The authors also noted that as the total pathology score got worse, the airways diminished in caliber in surgically derived lungs, but not in autopsy lungs. They noted that airway caliber was larger in autopsy lungs than surgical lungs, and suggested that this represented functional narrowing due to increased muscle tone, which was caused by release of mediators affecting the muscle directly or reflexly.

Studies of lungs at autopsy have shown correlations between airway lesions and abnormal tests of function. Petty et al. (1980, 1982) have shown that correlations exist between inflammation, and increased muscle and elevations in the closing capacity; that occlusion of airways by cells and mucus, inflammation, and increased airway muscle are related to abnormalities of the slope of phase III of the nitrogen washout; that airway narrowing is closely related to the FEV_1, FEF_{25-75}, and slightly less well related to closing capacity. Similarly, Berend et al. (1981a) showed an association between post-mortem closing capacity and both peripheral airways inflammation and a total pathology score. Decrease in maximum flow at a transpulmonary pressure of 5 cm H_2O was related to inflammation and the total pathology score, but not as well related to airway narrowing (Berend and Thurlbeck 1982). Morphologic abnormalities similar to those found in autopsy lungs have been found in surgically excised lungs derived almost entirely from smokers, and these in turn have been related to abnormal tests of small airway function.

Smoking and Lesions of Peripheral (Small) Airways

An increase in goblet cells was the first abnormality of peripheral airways noted in smokers. The observation was made in bituminous coal workers. In nonsmokers, about 0.66 percent of peripheral airway cells were found to be goblet cells; in smokers, this rose to about 1.0 percent (Naeye et al 1971).

The critical observation, both factually and conceptually, was that of Niewoehner et al. (1974). In an autopsy study of men under the age of 40 who died suddenly elsewhere than in the hospital, they compared lesions of bronchioles and respiratory bronchioles (airways with both nonrespiratory epithelium and alveoli in their walls) in smokers and nonsmokers. Emphysematous lungs were excluded, and the smoking history was obtained by personal interview with close relatives, using a standard questionnaire. The researchers found that intraluminal mucus, mural edema, peribronchiolar pigment, peribronchiolar fibrosis, denuded epithelium, mural inflammatory cells, and respiratory bronchiolitis were more severe in the smokers. The last three were significantly different statistically. They emphasized the importance of respiratory bronchiolitis, which consisted of aggregates of brown macrophages in and around the first and second order respiratory bronchioles and was associated with edema, fibrosis, and epithelial hyperplasia in adjacent bronchioles and alveolar walls. Bronchiolitis was found in all of the smokers, but in only 5 of the 20 nonsmokers, and it was the lesion that showed the greatest difference between smokers and nonsmokers. Since respiratory bronchiolitis was found in precisely the same regions where centrilobular emphysema is found in subjects 20 years older, the researchers suggested that this lesion might evolve into emphysema. This observation fits well the proteolytic–antiproteolytic hypothesis of the pathogenesis of emphysema.

Ebert and Terracio (1975) compared the peripheral airways in resected lungs of 22 smokers and 3 nonsmokers and found that the number of Clara cells (the tall nonciliated airway cells thought to be secretory, although the nature of their secretion is not completely certain) was diminished, as assessed subjectively, and the number of goblet cells was increased, as assessed quantitatively.

Two laboratories have concentrated on the association between smoking and lesions of vessels as well as of airways. One has used autopsy-derived lungs (Cosio et al. 1980; Hale et al 1980); the other, surgically excised lungs (Wright et al. 1983a, b, in press). The first material has the advantage that the entire lung can be examined, but has the disadvantage that agonal changes may affect the airway; the second has the advantage that agonal changes are absent and structure–functional studies can be done, but has the serious disadvantage that usually only a part of the lung is examined. Because of the wide variation in severity of emphysema from lobe to

lobe, emphysema in the whole lung cannot be assessed from a single lobe. Also, airway inflammation may not be evenly distributed through the airways (Berend 1981; Hale et al. 1980).

Cosio et al. (1980) studied 14 nonsmokers with an average age of 71.6 years and 25 long-term smokers with an average age of 58.4 years. The total pathology score was significantly higher in the smokers; in them, but not in the nonsmokers, the total pathology score was significantly related to age. Respiratory bronchiolitis was more common in the smokers, and of the components of the total pathology score, goblet cell metaplasia ($p < 0.001$), inflammation of the bronchiolar wall ($p < 0.01$), and smooth muscle hypertrophy ($p < 0.05$) were significantly more abnormal in the smokers. Smokers had an excess of airways less than 400 μ in diameter, also related to the total pathology score. Because goblet cell metaplasia and increased smooth muscle were not significantly increased in the researchers' previous study of young smokers (Niewoehner et al. 1974), they concluded that these lesions were a late complication of cigarette smoking. They noted that there was a considerable similarity of all lesions of both smokers and nonsmokers, and felt that this indicated the existence of other causes of small airway lesions. They also made the interesting suggestion that the relationship between the total pathology score and the proportion of airways less than 400 μ in diameter might indicate a predisposition of subjects with small airways to develop peripheral airway lesions.

Wright et al. (1983b) studied 9 nonsmokers, 51 current smokers, 18 ex-smokers who had quit less than 2 years, and 19 ex-smokers who had quit more than 2 years. The only lesion of the bronchioles that distinguished the nonsmokers from the smokers and the long-term ex-smokers was goblet cell metaplasia, although there were obvious differences in pulmonary function among these groups. The significance of goblet cell metaplasia may be related to mucus production in airways not usually lined by mucus. There is evidence that they are lined by surfactant. If this is displaced by mucus with a higher surface tension it will produce narrowing difficult to detect by standard morphological methods. Respiratory bronchiolitis was more severe in the smokers and ex-smokers than in the nonsmokers. No differences were noted between the ex-smokers and smokers. This study has recently been extended (Wright et al., in press), and correlations between both bronchiolar inflammation and respiratory bronchiolitis and the FEV_1 were evident. When the FEV_1 was greater than the 80 percent predicted, the most important determinant of abnormalities of tests of small airway function was respiratory bronchiolitis. Thus, respiratory bronchiolitis may not only represent a stage in the pathogenesis of centrilobular emphysema, but also result in abnormalities of the single breath nitrogen test and other tests of small airway function.

It is not certain why cessation of smoking results in improvement of lung function. The most likely reversible parameter is inflammation; the lack of difference between nonsmokers and the other groups in the study by Wright et al. (1983b) is very surprising in view of the observations of Niewohner et al. (1974) and Cosio et al. (1980), but may be due to the very small number of nonsmokers studied and the fact that the nonsmokers had lung lesions for which resection was performed. An additional factor is the use of lobes in the study, which in the small group of normals may produce distortions in the data because of lobar variations in the total pathology score.

Vascular Lesions Related to Smoking

At first sight it may appear surprising that vascular lesions are detectable in asymptomatic smokers or those with only mild or moderate chronic airflow obstruction. On reflection, this could be anticipated. Severe chronic airflow obstruction, usually related to smoking, is often accompanied by pulmonary artery hypertension; mild chronic airflow obstruction might be associated with mild pulmonary artery hypertension and vascular lesions. The first study (Hale et al. 1980) involved the same cases reported by Cosio et al. (1980). They found that the smokers had an increased number of arteries less than 200 μ in diameter and also an increased medial and intimal thickness of the pulmonary arteries. The intimal thickness was increased more in those vessels of less than 200 μ in diameter. Both intimal and medial thickness were directly related to the total pathology score. Wright et al. (1983a) found an increase in the vessel area from an average of 0.12 mm^2 in nonsmokers to approximately 0.3 mm^2 in smokers. Intimal area expressed as a proportion of vessel area increased; there was an absolute increase of the medial area, but no proportional change. The adventitial area also increased in absolute terms, but the adventitial proportional area was decreased and was related to the pulmonary wedge pressure. Pulmonary artery pressures were normal at rest, but abnormal and reversible by oxygen on exercise in the smokers with the worst airway inflammation and emphysema.

Emphysema

Of the lesions associated with chronic airflow obstruction, emphysema has been the one most clearly associated with tobacco smoking. There are several different types of emphysema, however, and cigarette smoking has not been clearly linked to, or examined in, all forms of the disorder. Therefore, the definition and classification of emphysema are reviewed before discussing the association between smoking and emphysema.

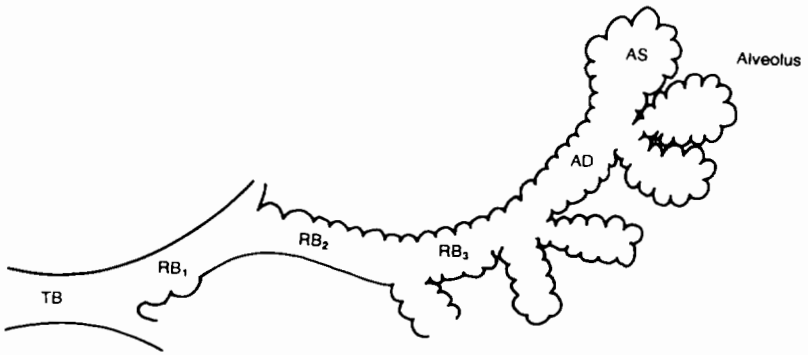

FIGURE 1.—Components of the acinus

NOTE: TB: terminal bronchiole; RB_1, RB_2, RB_3: the three orders of respiratory bronchioles; AD: alveolar duct; AS: alveolar sac.

SOURCE: Thurlbeck (1976).

Definition

Emphysema is defined as an abnormal enlargement of the air spaces of the lung accompanied by destruction of alveolar walls (World Health Organization 1961; American Thoracic Society 1962). Thus, emphysema is a disorder of anatomy, and one must know the appropriate normal anatomy in order to understand the pathology of emphysema. The structure involved is the acinus, the unit gas-exchanging structure of that part of the lung containing alveoli. The last purely conducting airway is the terminal bronchiole; structures distal to it constitute the acinus. The acinus is a complex unit, but a simplified model will suffice (Figure 1). The structures immediately before the terminal bronchiole are the respiratory bronchioles, which, as indicated previously, have both alveoli and nonalveolated epithelium forming their walls; thus, respiratory bronchioles both conduct and exchange gas. Proceeding distally, progressively more alveoli appear in the walls of respiratory bronchioles, of which there are three orders in the usual model of the acinus. Alveolar ducts succeed respiratory bronchioles, and their walls are entirely alveolated. Alveolar ducts lead into alveolar sacs, the terminal respiratory structures, which are likewise completely alveolated.

Classification

Emphysema is classified by the way it involves the acinus, and four forms of emphysema are usually recognized (Thurlbeck 1976): (1) proximal acinar emphysema, (2) panacinar (panlobular) emphyse-

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ma, (3) distal (paraseptal) acinar emphysema, and (4) irregular emphysema.

Proximal Acinar Emphysema

In *proximal acinar emphysema,* the respiratory bronchioles are selectively or dominantly involved. Emphysema involving the proximal part of the acinus is found in two different circumstances—centrilobular emphysema and focal emphysema.

Proximal acinar emphysema is the common form of nonindustrial emphysema and is associated with inflammation of the distal airways (Leopold and Gough 1957) and of the walls of emphysematous spaces. This form of emphysema is usually referred to as centrilobular emphysema (Figure 2) because the lesions lie close to the center of the secondary lobules. The emphysematous spaces are found more frequently in the upper zones of the lungs, and centrilobular emphysema is usually more severe there (Thurlbeck 1963a). Involvement of the lung is characteristically quite uneven; some respiratory bronchioles are spared or slightly involved, whereas others close by may be severely affected, producing large emphysematous spaces. Centrilobular emphysema is frequently associated with chronic bronchitis, and is the form of emphysema most commonly encountered in patients with symptomatic chronic airflow obstruction.

Focal emphysema, or simple pneumoconiosis of coalworkers, also involves the proximal part of the acinus. It can be distinguished from centrilobular emphysema in that there is always a heavy deposit of coal around the emphysematous spaces, the enlargement of respiratory bronchioles is usually moderate, and the process is more uniform through the lung. Simple pneumoconiosis is usually associated with only mild impairment of function, producing only minor abnormalities of gas exchange (Morgan and Seaton 1975).

Panacinar (Panlobular) Emphysema

In *panacinar* or *panlobular emphysema,* there is more or less uniform involvement of the acinus (Figure 3). Controversy exists concerning the distinction between centrilobular and panacinar emphysema; some believe them to be different conditions (Anderson and Foraker 1973), but others believe them to have the same clinical and functional associations (Mitchell et al. 1970). The reason for this disagreement is discussed below. Four different associations of panacinar emphysema are described (Thurlbeck 1976), each with its specific clinicopathologic associations. This view is not shared by all, however.

The classical association of panacinar emphysema is with α_1-antitrypsin deficiency (Eriksson 1965), most commonly with the PiZ

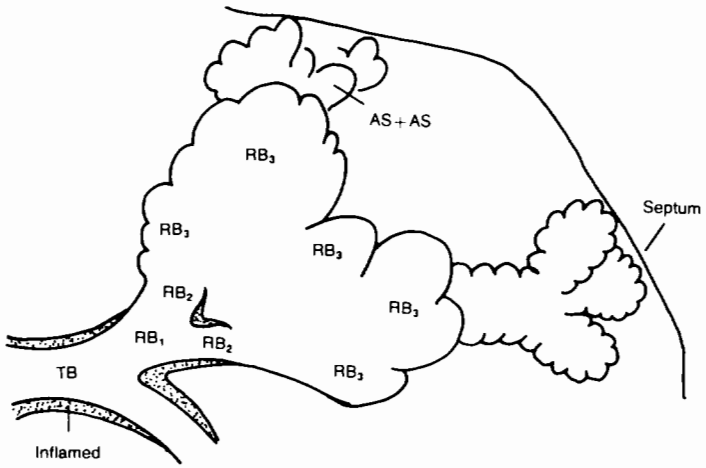

FIGURE 2.—Centrilobular emphysema
NOTE: See footnote to Figure 1 for definitions.
SOURCE: Thurlbeck (1976).

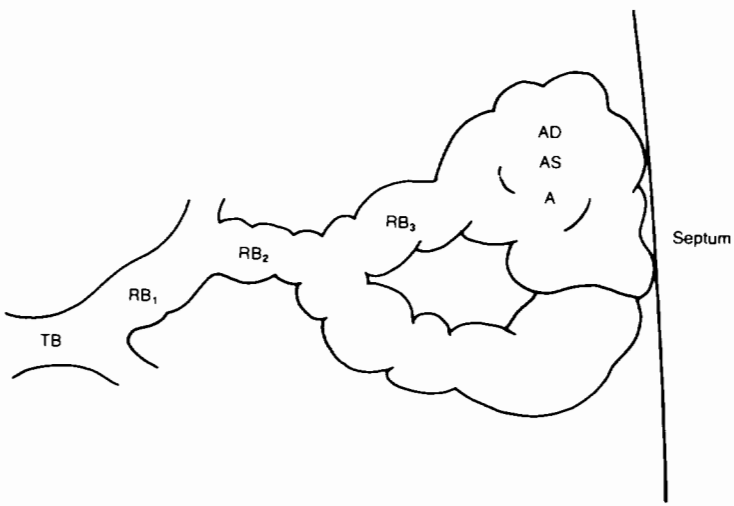

FIGURE 3.—Panlobular emphysema
NOTE: See footnote to Figure 1 for definitions.
SOURCE: Thurlbeck (1976).

phenotype. It is probable that other forms of Pi-associated emphysema, such as PiSZ, are also panacinar in type. Familial emphysema unassociated with α_1-antiprotease deficiency has been shown to be panacinar (Martelli et al. 1974). Familial emphysema is characteristically worse in the lower zones of the lung. Severe, pure panacinar emphysema is uncommon.

Localized panacinar emphysema is found fairly frequently at autopsy (Thurlbeck 1963a). It is found more commonly in older people and is usually not associated with clinical evidence of chronic airflow obstruction. Under these circumstances, it is more frequent in the lower and anterior parts of the lung. It may represent a focal exaggeration of the aging process in the lung, which includes a well documented set of changes (Thurlbeck 1976), including changes in the shape of the lung with an increase in anteroposterior diameter, loss of volume density of alveolar walls, increase in the distance between alveolar walls, decrease of alveolar surface area, increase in volume density of alveolar ducts, and decrease of volume density of alveoli. The reason for referring to these changes with age as the "aging lung" rather than "senile emphysema" is that it is a normal change, affecting virtually all people. The definition of emphysema requires that the enlargment and destruction of respiratory tissue be abnormal; therefore, it is probably inappropriate to categorize these changes as emphysema.

Bronchial and bronchiolar obliteration may be associated with panacinar emphysema. Most commonly it is associated with Swyer-James (1953) or MacLeod's (1954) syndrome of unilateral pulmonary hyperlucency, in which one lung or a major portion of the lung is unduly transradiant. The involved region or regions of the lung characteristically trap air on expiration so that the mediastinum then moves to the unaffected side. The syndrome is usually due to severe acute bronchitis and bronchiolitis in childhood, resulting in obliteration of airways. A detailed study of the lung parenchyma in cases of unilateral pulmonary transradiancy has never been reported, but it seems likely that emphysema may not be present in the affected lung tissue. However, when emphysema is present, it is panacinar in type.

Panacinar emphysema may be found in the lower zones of the lung in patients with upper zonal centrilobular emphysema. The combination of the two forms of emphysema is probably the classical finding in patients with severe chronic airflow obstruction, and it is also one reason for the controversy concerning similarities or differences between centrilobular and panacinar emphysema. Transitions, real or imagined, may be apparent between the upper zonal centrilobular emphysematous spaces and lower zonal panacinar emphysema in this situation. Some believe the transitions are real, and maintain that centrilobular emphysema has progressed to

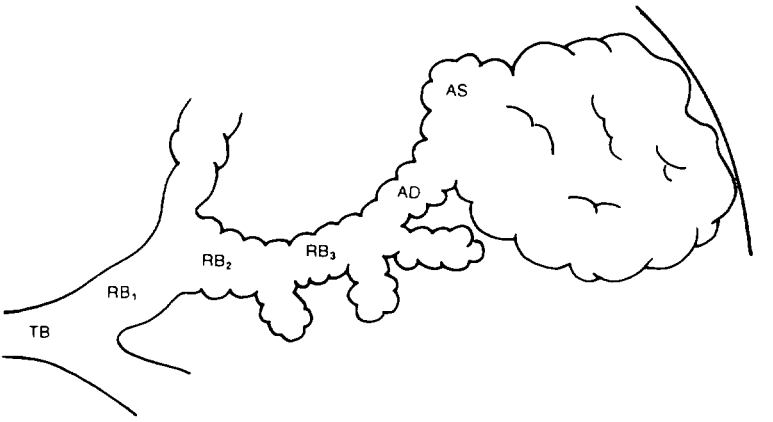

FIGURE 4.—Distal or paraseptal acinar emphysema
NOTE: See footnote to Figure 1 for definitions.
SOURCE: Thurlbeck (1976).

panacinar emphysema and that these lungs should be classified as examples of centrilobular emphysema. Others feel that it is panacinar emphysema, and thus the same lung may be classified differently.

Distal (Paraseptal) Acinar Emphysema

Distal (paraseptal) acinar emphysema is the third generally recognized form of emphysema. In this form, the alveolar ducts and sacs are predominantly involved, and there may be substantial associated fibrosis (Figure 4). Since the distal acinus abuts on pleura, vessels, airways, and lobular septa, the emphysema is worse in these regions. The occurrence of distal acinar emphysema along the lobular septa had led to the term "paraseptal emphysema." A characteristic clinical association of distal acinar emphysema is spontaneous pneumothorax of young adults (Edge et al. 1966).

Irregular Emphysema

In *irregular emphysema,* the acinus is irregularly enlarged (Figure 5). It is nearly always associated with scarring. It may be the most common form of emphysema, because nearly all lungs on close examination will disclose a scar associated with emphysema. The majority of these examples of irregular emphysema are unassociated with symptoms.

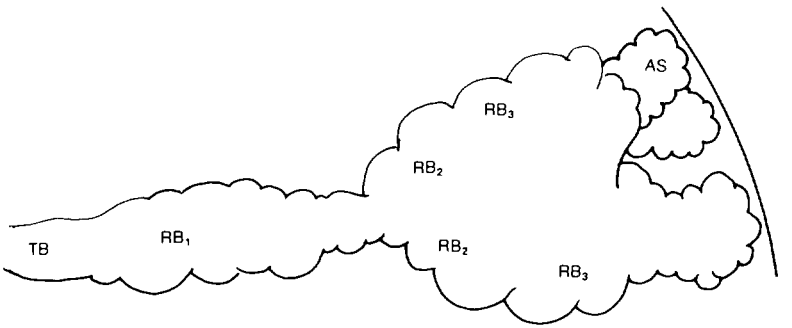

FIGURE 5.—Irregular emphysema
NOTE: See footnote to Figure 1 for definitions.
SOURCE: Thurlbeck (1976).

Tobacco Smoking and Emphysema

The apparently neat and orderly classification described above and the classical examples of emphysema illustrated in original articles and monographs should not obscure the lack of agreement between expert observers in the classification of severely emphysematous lungs (Thurlbeck et al. 1968, Mitchell et al. 1970). Severe emphysema is usually atypical in morphology, and often more than one type of emphysema is present. It might be more rational to speak of "end stage emphysema" when describing an extensively damaged lung, rather than attempting to fit all of the damage under one classification.

These differences in classification may lead to differing assessments of degrees of association between smoking and individual forms of emphysema. For example, Anderson and Foraker (1973) found that all of their 21 patients with centrilobular emphysema were cigarette smokers, whereas 8 of the 17 patients with panacinar emphysema were cigarette smokers. Contrarily, Mitchell et al. (1970) found that 20 of their 21 patients with centrilobular emphysema were cigarette smokers and all 6 of their patients with panacinar emphysema were cigarette smokers.

Including all of the different abnormalities described above under the single term "emphysema" may lead to confusion about the relationship between smoking and emphysema. Each of the different forms of emphysema may have different etiologies; while cigarette smoking is clearly implicated in the etiology of centrilobular emphysema (Mitchell et al. 1970, Anderson and Foraker 1973), it may not play a role in irregular or distal acinar emphysema and is

clearly not implicated in the etiology of unilateral pulmonary transradiancy.

Another problem is the sensitivity with which emphysema is recognized. Thurlbeck (1976) reviewed the incidence of emphysema found at autopsy in 28 series. An extremely wide variation has been recorded, including three series with an incidence of 100 percent. The variation in incidence probably represents the care with which the lung is examined and the threshold for defining emphysema being present as much as a true difference in incidence.

It is not relevant to the present discussion whether rare or unusual disease processes can cause abnormal enlargement of the air spaces or whether, after careful and exhaustive search, all lungs demonstrate minute areas of focal enlargement. The lung has substantial ventilatory reserve; therefore, what is significant is not the presence or absence of any emphysema, but rather the extent or severity of the emphysematous change in the lung. What is both clear and relevant to the present discussion is that the relationship between smoking and emphysema represents an association between smoking and the severity of emphysema, and that the relationship is between smoking and those forms of emphysema commonly found in patients with COLD.

In 1963, clinicopathologic findings (Thurlbeck 1963b) in a group of patients dying at the Massachusetts General Hospital showed that 18 of 38 patients without emphysema were cigarette smokers, whereas all of the 19 patients with severe emphysema were cigarette smokers. A formal study of the relationship between emphysema and smoking was first made by Anderson et al. (1964), who showed that one-third of patients without emphysema, 19 of 37 patients with mild emphysema, 19 of 23 patients with moderate emphysema, and all 6 patients with severe emphysema were smokers. In 1966, an extended study (Anderson et al. 1966) found in the four groups, respectively, that 12 of 33 patients, 58 of 84 patients, 30 of 33 patients, and 14 of 15 patients were smokers. Mitchell et al. (1964) found 62 smokers among 85 patients with no or mild emphysema and 39 smokers among 40 patients with moderate or severe emphysema. These researchers also extended their series (Petty et al. 1967) and found 6 nonsmokers among 57 patients with moderate emphysema and 1 nonsmoker among 61 patients with severe emphysema. A very dramatic difference was shown between smokers and nonsmokers by Ryder et al. (1971). Figures 6 and 7 indicate very graphically the rarity of emphysema of even moderate severity in nonsmokers and the high incidence of emphysema in smokers over 50 years of age. Of the 21 patients in their series whose lungs had a more than 25 percent involvement by emphysema, only 1 was a nonsmoker.

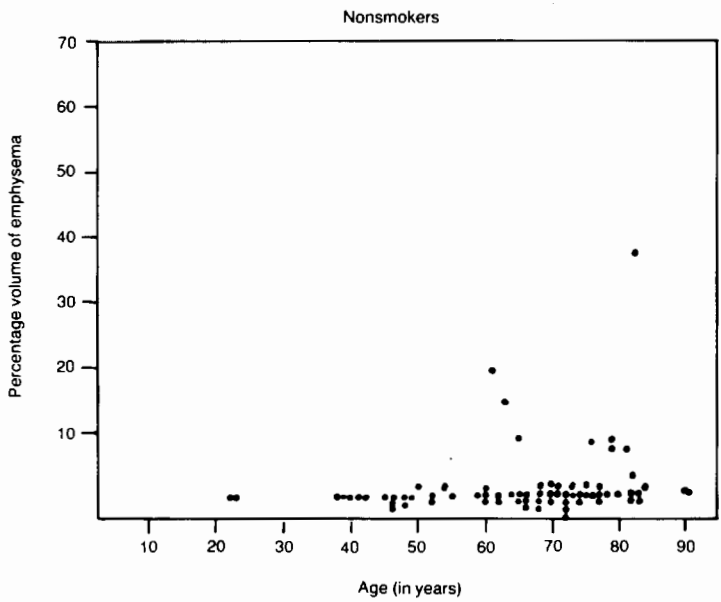

FIGURE 6.—Percentage of lung occupied by emphysema in nonsmokers

SOURCE: Ryder et al. (1971).

Only a small effect of smoking was noted in coal miners by Naeye et al. (1971), an increase from 24.3 percent of the lung involved in nonsmokers to 30 percent in smokers. A much greater effect of smoking was noted by Auerbach et al. (1972), who studied lungs from 2,613 autopsies and were able to obtain smoking histories in 1,831 of the patients. They found that 10 percent of male patients who had not smoked had emphysema; this percentage rose to 53.5 percent for pipe smokers and cigar smokers, 86.9 percent for smokers of less than a pack per day, and 99.7 percent for smokers of more than a pack per day. Of the 130 patients with severe emphysema, 126 smoked more than a pack a day, 2 smoked less than a pack, 2 were pipe or cigar smokers, and none were nonsmokers. Their findings were subsequently extended and confirmed by histologic examination of these lungs (Auerbach et al. 1974). Findings in women were similar. Spain et al. (1973) studied lungs from 134 persons who died suddenly and unexpectedly and who had no previous known pulmonary disease. In men, they found an incidence of emphysema of more than grade 20 (mild emphysema) of 10 percent in nonsmokers, 36 percent in smokers of less than a pack per day, and 39 percent

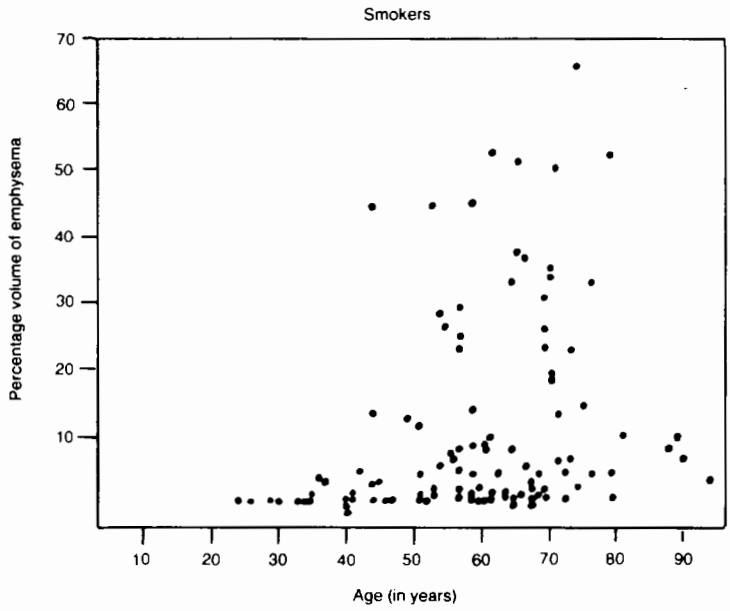

FIGURE 7.—Percentage of lung occupied by emphysema in smokers

SOURCE: Ryder et al. (1971).

in smokers of more than a pack. In women the incidences in the same categories were 0, 17, and 23 percent, respectively. Bonfiglio and Schenk (1974) found that the diagnosis of emphysema was made in 40 percent of autopsy protocols from smokers and in 12 percent from nonsmokers.

Using the autopsy populations of teaching hospitals in three separate cities, Thurlbeck et al. (1974b) reported the average emphysema score per decade for male and female nonsmokers (Figure 8) and for male and female smokers combined with ex-smokers (Figure 9). The severity of emphysema is expressed using the panel grading method (Thurlbeck et al. 1970). With this method, a score of up to 25 is "mild emphysema." As Figure 8 indicates, in nonsmokers there is an increasing average severity of emphysema with age, starting in the fifth decade, reaching an average score in the eighth and ninth decades of 10 to 15 in men and 4 to 6 in women. There is a dramatic difference in male heavy smokers and ex-smokers, for whom the average score of 25 to 30 in the seventh decade is maintained for the next two decades. The number of heavy smoking and ex-smoking women is very small, and the effects in

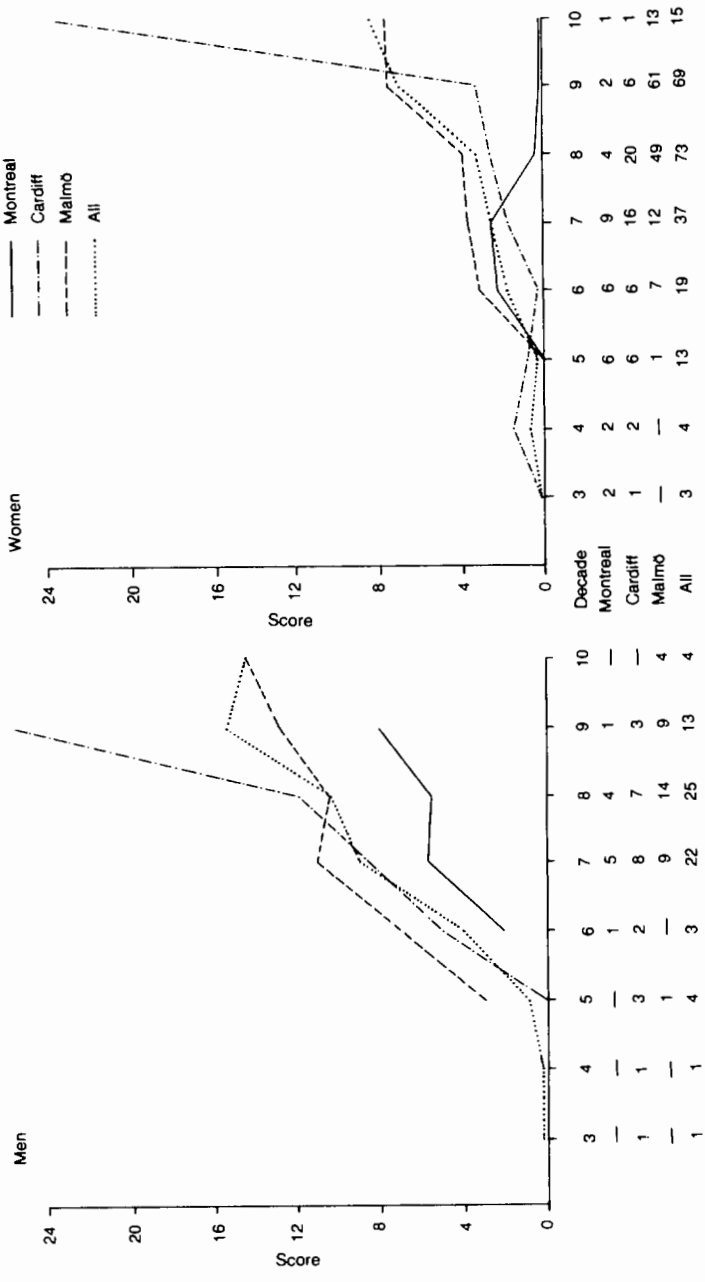

FIGURE 8.—Average emphysema score in male and female nonsmokers in Montreal, Cardiff, and Malmö, by decade

NOTE: All: The average for the three cities.
SOURCE: Thurlbeck et al. (1974b).

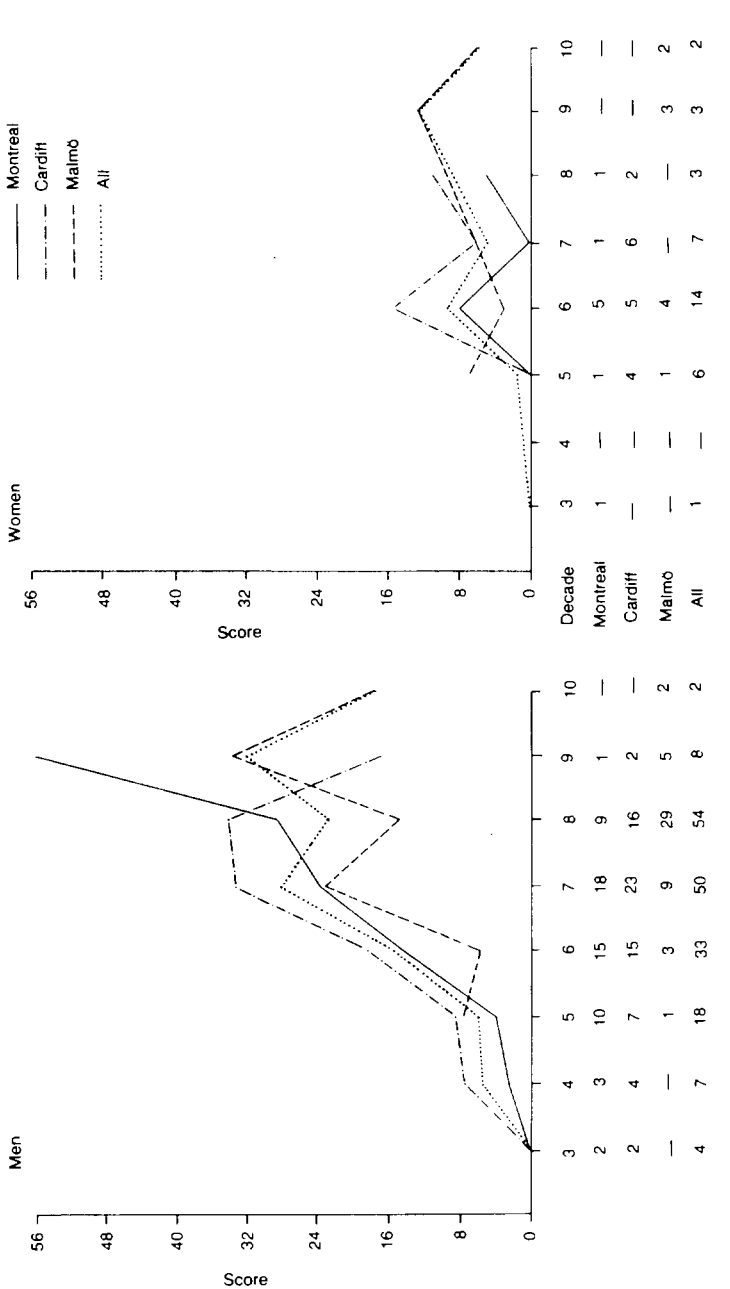

FIGURE 9.—Average emphysema score in male and female heavy cigarette smokers (>pack per day) and ex-smokers, by decade

NOTE: All: The average for the three cities.
SOURCE: Thurlbeck et al. (1974b).

women are more modest, with an average emphysema score of 8 to 12 from the sixth to the ninth decade.

Pratt et al. (1980) studied the effect of smoking on cotton textile workers and on workers not exposed to cotton. They found that the incidence of centrilobular emphysema was 6.7 percent in nonsmoking non-cotton-textile workers, 6.9 percent in nonsmoking cotton-textile workers, 26.5 percent in smoking non-cotton-textile workers, and 26.2 percent in smoking cotton-textile workers. The variation in the incidence of centrilobular emphysema involving more than 25 percent of the lung was even more dramatic—1.1, 0.4, 11.0, and 12.6 percent for the respective categories.

Thus, despite the limitations in interpretation of the types of emphysema and in recognition of the presence of emphysema, the association between smoking and emphysema—particularly severe emphysema—is overwhelming. In the various series referred to, of the 227 patients with severe emphysema, only 3 were nonsmokers.

Summary and Conclusions

1. Smoking induces changes in multiple areas of the lung, and the effects in the different areas may be independent of each other. In the bronchi (the large airways), smoking results in a modest increase in size of the tracheobronchial glands, associated with an increase in secretion of mucus, and in an increased number of goblet cells.
2. In the small airways (conducting airways 2 or 3 mm or less in diameter consisting of the smallest bronchi and bronchioles) a number of lesions are apparent. The initial response to smoking is probably inflammation, with associated ulceration and squamous metaplasia. Fibrosis, increased muscle mass, narrowing of the airways, and an increase in the number of goblet cells follow.
3. Inflammation appears to be the major determinant of small airways dysfunction and may be reversible after cessation of smoking.
4. The most obvious difference between smokers and nonsmokers is respiratory bronchiolitis. This lesion may be an important cause of abnormalities in tests of small airways function, and may be involved in the pathogenesis of centrilobular emphysema. The severity of emphysema is clearly associated with smoking, and severe emphysema is confined largely to smokers.

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CHAPTER 5. MECHANISMS BY WHICH CIGARETTE SMOKE ALTERS THE STRUCTURE AND FUNCTION OF THE LUNG

CONTENTS

EFFECT OF CIGARETTE SMOKING ON INFLAMMATORY AND IMMUNE PROCESSES IN THE LUNG

EFFECTS OF CIGARETTE SMOKE ON AIRWAY MUCOCILIARY FUNCTION

EFFECT OF CIGARETTE SMOKING ON INFLAMMATORY AND IMMUNE PROCESSES IN THE LUNG

Cigarette smoke is a complex mixture of several thousand different constituents that may produce physiologic and pathologic changes. This discussion focuses on the cellular and immune responses of the lung to cigarette smoke, the mechanism by which smoking can cause emphysema, and the impact of smoking on mucociliary clearance. The last 20 years have witnessed dramatically increased understanding of cigarette-induced lung injury, particularly emphysema, thus enhancing our understanding of the process by which cigarette smoking can lead to emphysema.

Introduction

Inhalation of cigarette smoke markedly alters the inflammatory and immune processes in the lung, leading to increases in the total number of inflammatory cells and to changes in cell type and function. These effects of cigarette smoke on lung inflammatory cells may play a role in decreased pulmonary host defenses against various microorganisms and the development of lung cancer, chronic bronchitis, and pulmonary emphysema (USPHS 1971, 1972, 1973, 1974, 1975; USDHHS 1981).

Effect of Smoking on Numbers and Types of Inflammatory Cells

One of the most consistently observed effects of cigarette smoking on the lung is a marked increase in the numbers of inflammatory cells, especially at sites of disease. Increased numbers of inflammatory cells have been seen in pathological studies of the lungs of cigarette smokers, as well as in lungs of animals exposed to cigarette smoke. In addition, increased numbers of inflammatory cells occur in bronchoalveolar lavage fluid of cigarette smokers and in lavage fluid of animals exposed to cigarette smoke.

Spain and Kaufman (1953) noted inflammatory changes in the lung bronchi of cigarette smokers. Later, Anderson and Foraker (1961) described the presence of an alveolitis, and McLean (1959) described the presence of a bronchiolitis in these patients. In an autopsy study of patients with early emphysema (McLaughlin and Tueller 1971), numerous abnormal, brownish-pigmented alveolar macrophages were found in adjacent, otherwise intact parenchyma, but none were found in normal lungs. Identical pigmented macrophages were found in the sputum of patients obtained from apparently healthy cigarette smokers. The frequency of occurrence of these macrophages in the tissue appeared to be related to the

number of cigarettes consumed. Niewoehner et al. (1974) evaluated the lungs of young smokers and controls of comparable age from a population that had experienced sudden nonhospital deaths. In smokers, a characteristic lesion occurred in the form of respiratory bronchiolitis associated with clusters of pigmented alveolar macrophages. This lesion was present in the lungs of all smokers studied, but was rarely seen in nonsmokers. Lungs of smokers also showed small, but significant, increases in mural inflammatory cells and denuded epithelium in the membranous bronchioles as compared with controls. The researchers suggested that this respiratory bronchiolitis may be a precursor of emphysema and may be responsible for the subtle functional abnormalities that are observed in young smokers. Mitchell et al. (1976) also noted the presence of significant amounts of inflammation in the small airways of cigarette smoker lungs, and Cosio et al. (1978) suggested that the primary lesion in the small airways was a progressive inflammatory reaction, leading to fibrosis with connective tissue deposition in the airway walls. These lesions were closely correlated with abnormalities in pulmonary function.

As noted above, most early investigators concentrated on the role of the increased numbers of pigmented alveolar macrophages present at disease sites in cigarette smokers. These pigmented macrophages, because of their numbers and prominent coloration on histologic sections, were initially the sole focus of research on the inflammatory response in these patients. More recently, however, Ludwig et al. (1983) evaluated the relationship between cigarette smoking and the accumulation of neutrophils in the lungs of smoking and nonsmoking humans. Human lungs were obtained from autopsies of 10 cigarette smokers and 5 nonsmokers who experienced nonhospital death. These studies indicated a marked increase in neutrophil infiltration in the lungs of cigarette smokers compared with nonsmokers, and identified the site of the accumulation as the alveolar septa. Neutrophils were found in the alveolar walls of smokers both with and without emphysema. The researchers concluded that a marked neutrophil accumulation occurs in the lungs of cigarette smokers, that it precedes the development of emphysema, and that it continues once emphysema is established. They further suggested that the neutrophils may play a role in the destruction of the alveolar septa of the lungs in cigarette smokers. The presence of increased numbers of neutrophils in cigarette smokers' lungs has also been documented by extracting inflammatory cells from open lung biopsies of smokers and nonsmokers (Hunninghake and Crystal 1983). A higher percentage of these inflammatory cells were neutrophils in smokers compared with nonsmokers. Finally, the association between cigarette smoking and increased numbers of inflammatory cells, including neutrophils, at disease sites has also

been confirmed in numerous animal studies (Frasca et al. 1971; Dahlgren et al. 1972; Rylander 1974; Park et al. 1977).

Increased numbers of inflammatory cells in the lungs of smokers, as compared with nonsmokers, have also been observed by all investigators performing bronchoalveolar lavage studies (Davis et al. 1976; Demarest et al. 1979; Harris et al. 1970, 1975; Hunninghake et al. 1979a, 1980a; Hunninghake and Crystal 1983; Hunninghake and Gadek 1981-1982; Hunninghake and Moseley, in press; Reynolds et al. 1977; Reynolds and Newball 1974, 1976; Rodriquez et al. 1977; Warr et al. 1976, 1977; Warr and Martin 1974, 1978). Such increases have been detected additionally in lavage fluid of animals chronically exposed to cigarette smoke (Davies et al. 1977; Flint et al. 1971; Holt et al. 1973). The majority of these studies have demonstrated increases in both the number of macrophages and the number of neutrophils, although Hoidal and Niewoehner (1982) found increases only in the former.

The presence of neutrophils in the lungs of cigarette smokers is of interest because these cells contain elastase, an enzyme believed to be important in the pathogenesis of emphysema (Lieberman 1976; Karlinsky and Snider 1978; Kuhn and Senior 1978; Carp and Janoff 1978; Snider and Korthy 1978; Schuyler et al 1978; Janoff et al. 1977; Hunninghake et al. 1979a; Hunninghake and Crystal 1983; Hunninghake and Gadek 1981-1982; Hunninghake and Mosley 1984; Laurell and Eriksson 1963). Alveolar macrophages have also been implicated as a source of an elastase-like metalloprotease (Harris et al. 1975; Rodriguez et al. 1977). This enzyme is not inhibited by alpha$_1$-antitrypsin (α_1AT) (Banda and Werb 1981), the major anti-elastase in the lower respiratory tract (Gadek et al. 1981). Although macrophages are clearly present in large numbers in the alveolar structures of smokers (Niewoehner et al. 1974; Harris et al. 1975), several lines of evidence suggest that neutrophils may play a significant and perhaps more important role in increasing the elastase burden of the lungs.

First, neutrophils store and release significantly more elastase than do alveolar macrophages (Barrett 1977; Rodriguez et al. 1977; Levine et al. 1976). Comparative estimates of elastase production by human neutrophils and alveolar macrophages suggest that neutrophils are at least 1,000 times more potent elastase producers (Janoff et al. 1979).

Second, although alveolar macrophages of cigarette smokers have been shown to release elastase in vitro (Rodriguez et al. 1977), it is not clear whether the elastase was produced by these cells or was secreted by other types of cells, such as neutrophils, and subsequently ingested by the macrophages (Janoff et al. 1977). In this regard, recent studies by Campbell et al. (1979) and McGowan et al. (1983) have shown that alveolar macrophages are capable of phagocytosing

neutrophil elastase via a receptor-mediated mechanism; some of the elastase remains enzymatically active for up to 48 hours. These findings suggest that alveolar macrophages may, in fact, be capable of both decreasing and increasing the protease burden of the lung.

Third, once a neutrophil has left its vascular space, its lifespan is only a few hours; when the neutrophil dies, it may release at least a portion of its preformed enzymes, including elastase. Thus, when a neutrophil is present within a tissue, it is possible that the tissue will be exposed not only to the elastase secreted by the neutrophil while it is functional, but also to the elastase stored by the neutrophil and released when the neutrophil disintegrates. In this context, the finding that neutrophils represent only a small percentage of all inflammatory and immune effector cells in the smoker's lungs would not preclude the smoker's exposure to a large chronic burden of neutrophil elastase. In contrast, the alveolar macrophage has a half-life of months to years (Thomas et al. 1976), and it stores little, if any, elastase (Rodriguez et al. 1977; Levine et al. 1976).

Macrophages may also play an important role in this process by secreting a potent chemotactic factor for neutrophils (Hunninghake and Crystal 1983). This hypothesis is supported by the following observation: alveolar macrophages of cigarette smokers spontaneously release a chemotactic factor for neutrophils, whereas alveolar macrophages of nonsmokers do not. In addition, in vitro exposure to cigarette smoke particulates results in the release of a chemotactic factor from the alveolar macrophages of nonsmokers. The migration of neutrophils to the lung in response to the chemotactic factor may be augmented by factors in cigarette smoke. In this regard, McCusker et al. (1983) have shown that nicotine is a potent chemokinetic factor for neutrophils, enhancing the migration of these cells to other chemotactic factors. Once neutrophils are present in the lung, they may release elastase, because both cigarette smoke (Blue and Janoff 1978) and the macrophage-derived chemotactic factor stimulate these cells to release the enzyme (Gadek et al. 1979a, b).

The postulated release of elastase by neutrophils could also partly explain how the number of macrophages are increased in this disorder. Fragments of elastin (which are probably generated by the release of neutrophil elastase at sites of disease activity) are potent chemoattractants for blood monocytes, the precursors of alveolar macrophages (Senior et al. 1980; Hunninghake et al. 1981). These fragments of elastin possess no chemotactic activity for neutrophils.

Effect of Smoking on the Morphology and Function of Inflammatory Cells

No size differences have been observed between alveolar macrophages from smokers and those from nonsmokers when the cells are

fixed in suspension immediately after bronchoalveolar lavage (Table 1). Harris and coworkers (1970) observed a mean size of 23.3 μm (range, 10 to 47 μm) for nonsmokers and 26.4 μm (range, 12 to 53 μm) for smokers. Reynolds and Newball (1974), using similar methods, did not find any size differences between smoker and nonsmoker alveolar macrophages.

The morphology of smoker macrophages clearly differs, however, from that of nonsmokers (Table 1). Macrophages of smokers show increased numbers of large lysosomes, phagolysosomes, endoplasmic reticulum, ribosomes, and Golgi vesicles (Golde 1977; McLemore et al. 1977; Martin 1973; Warr and Martin 1978; Rasp et al. 1978; Pratt et al. 1971; Brody and Craighead 1975). These findings are generally associated with activated mononuclear phagocytes, and these macrophages have probably become activated by the ingestion of the particulates present in cigarette smoke. Smoker macrophages have pigmented inclusions that appear to have platelike or needlelike configurations when seen by electronmicroscopy (Golde 1977; Warr and Martin 1978; Pratt et al. 1971; Brody and Craighead 1975). Studies of the nature of these inclusions by X-ray analysis suggest they may be, at least in part, particulates of aluminum silicate (Brody and Craighead 1975). Together with in vitro studies showing that alveolar macrophages are activated following phagocytosis of particulates (Hunninghake et al. 1980a), these findings are compatible with the notion that macrophages of smokers are activated in vivo.

Alveolar macrophages from cigarette smokers have an increased ability to generate superoxide anion (Hoidal et al. 1979a, 1980, 1981), the functional effects of which include an increased capacity to kill lung fibroblasts. These observations suggest that alveolar macrophages from cigarette smokers are increasingly able to injure lung parenchymal cells, and that they may contribute to the observed loss of lung cells in the alveoli of patients with pulmonary emphysema.

A variety of other effector functions of smokers' alveolar macrophages have also been evaluated (Table 1). Alveolar macrophages from cigarette smokers appear to have a normal or increased ability to migrate in response to chemotactic factors (Demarest et al. 1979; Warr and Martin 1974). They differ, however, from normal alveolar macrophages in several other respects: for example, increased glucose utilization has been reported in some studies (Harris et al. 1970), but was normal in others (Hoidal et al. 1979a). Oxygen consumption has been reported to be normal (Hoidal et al. 1979a), but the protein content of these cells has been increased (Harris et al. 1975; Warr and Martin 1978). Alveolar macrophages from smokers release less PGE_2 and thromboxane B_2 than normal macrophages (Laviolette et al. 1981), suggesting that cigarette smoking induces a lesion in phospholipid hydrolysis or the mecha-

TABLE 1.—Cigarette-smoking-induced abnormalities in the inflammatory and immune effector systems within human alveolar structures

Parameter	Findings in smokers
Cell types present	
Total number of cells	Increased
Percent polymorphonuclear leukocytes	Increased
Percent T lymphocytes	Increased or normal
Percent B lymphocytes	Normal
Lymphocyte function	
Response to mitogens	Decreased
Macrophage structure	
Diameter	Normal
Ruffling of cell surface	Decreased
Number and size of cytoplasmic structures	Increased
Abnormal cytoplasmic inclusions	Pigmented inclusions, particulates with plate or needle-like configuration, presence of aluminum silicate
Macrophage properties and function	
Surface receptors	
IgG-Fc	Normal
C3b	Decreased
Phagocytosis and killing of microorganisms	
Bacteria	Normal or decreased
Fungi	Normal
Effector and accessory cell function	
responsiveness to chemotactic factors	
Casein	Increased
Activated serum	Normal
Function as accessory cell to lymphocytes	Decreased
Responsiveness to MIF	Decreased
Production of neutrophil chemotactic factor	Increased
Secretion of superoxide anion	Increased
Secretion of elastase	Increased
Release of prostaglandin E_2 and thromboxane B_2	Decreased
Miscellaneous properties and function	
Glucose utilization	Increased or normal
Oxygen consumption	Normal
Protein content	Increased
Content of various enzymes	
Elastase	Increased
Acid protease	Increased
Neutral protease	Normal
Esterase	Increased
Acid phosphatase	Increased
β-glucuronidase	Increased
Lysozyme	Normal or increased
Aryl hydrocarbon hydroxylase	Increased
Angiotensin-converting enzyme	Increased
Spreading and adherence properties	Increased in presence of serum, decreased nylon adherence
Pinocytosis	Decreased
Content of α_1-antiproteinase	Increased

SOURCE: Adapted from Hunninghake et al. (1979).

nism regulating hydrolysis. Smoker macrophages also appear to have increased amounts of various enzymes, including acid protease (Harris et al. 1975), neutral protease (Harris et al. 1975), esterase (Harris et al. 1975), acid phosphatase (Martin 1973), angiotensin-converting enzyme (Hinman et al. 1979), β-glucuronidase (Martin 1973), lysozyme (Martin 1973), and arylhydrocarbon hydrolase (Cantrell et al. 1973; Harris et al. 1978; McLemore et al. 1977b, c, 1978; McLemore and Martin 1977). The functional significance of increased amounts of these enzymes is not entirely clear.

In addition to its effects on the inflammatory and immune effector cells in the lung, cigarette smoke may also affect the composition of epithelial surface fluid. For example, some investigators have found that the amount of immunoglobulin G (IgG) present in lavage fluid is increased (Reynolds and Newball 1974); others have noted normal levels (Warr et al. 1977). Interestingly, cigarette smoking appears to cause a significant decrease in the secretory component of immunoglobulin A (IgA) in the lavage fluid of some people who smoke cigarettes (Merrill et al. 1980). This effect most likely indicates a subtle injury to the epithelium of the lung that produces this factor. The only additional factors that have been reported to be abnormal in lavage fluid of cigarette smokers are an increase in the amounts of fibronectin (Villiger et al. 1981) and a decrease in the function, but not the amount, of α_1AT (Gadek et al. 1979; Janoff et al. 1979). This latter finding has been disputed by others (Stone et al. 1983).

Emphysema

A number of lines of evidence link the cellular changes described above with the development of emphysema. They include observations in populations deficient in α_1AT, in animal models of emphysema, and most important, in human cigarette smokers.

Populations Deficient in Alpha$_1$-antitrypsin

Eriksson (1965) described the characteristic features of α_1AT-deficiency-associated lung disease. Approximately 60 percent of affected individuals develop symptoms of airways obstruction by age 40, and 90 percent by age 50. Excluding the influence of cigarette smoking, there is no sexual predominance of disease. Kueppers and Black (1974) found that dyspnea occurred a decade earlier in cigarette smokers (35 years in smokers versus 44 years in nonsmokers), and estimated that 70 to 80 percent of all PiZZ persons (where Pi= protease inhibitor) will develop lung disease. Larsson (1978) has projected that nearly 60 percent of PiZZ people will ultimately die of lung-related disease.

Orell and Mazodier (1972) reviewed the morphologic features of α_1AT-deficiency-associated emphysema and found primarily the

panacinar or panlobular form. Emphysematous lesions may be distributed uniformly throughout the lungs (Orell and Mazodier 1972), but frequently show a predominant lower lobe distribution (Greenberg et al 1973).

In people genetically deficient in α_1AT, the increased numbers of inflammatory cells found in the lungs of smokers probably present an increased elastase burden to the lung and magnify the protease–antiprotease imbalance. This may explain the deleterious effects of cigarette smoke in this population. Kueppers and Black (1974) reviewed data on the impact of cigarette smoking in people severely deficient in α_1AT and concluded that, in addition to experiencing earlier onset of respiratory symptoms and pulmonary function abnormalities, cigarette smokers die at an earlier age from respiratory failure than similiarly afflicted nonsmokers. The increased prevalence of emphysema in populations deficient in α_1AT, plus the exacerbation of this lung disease by smoking, suggests that protease–antiprotease imbalance may also play a role in the development of emphysema by smokers who are not deficient in α_1AT. This suggestion has resulted in a substantial body of research that has characterized α_1AT, defined the nature of elastase-induced emphysema, and clarified and supported the protease–antiprotease hypothesis of cigarette-induced emphysematous lung injury.

Alpha$_1$-antitrypsin

The deficient constituent of α_1-globulin was initially described by Schultze et al. (1955) as α_1-3,5-glycoprotein but later renamed α_1-antitrypsin (α_1AT) when it was found to inhibit trypsin activity (Schultze et al. 1962). Subsequently, α_1AT has been shown to inhibit a variety of proteolytic enzymes including neutrophil elastase (Ohlsson 1971), neutrophil collagenase (Tokoro et al. 1972; Ohlsson 1971), cathepsin-G (Travis et al. 1978), chymotrypsin (Travis et al. 1978; Rimon et al. 1966), plasmin (Rimon et al. 1966), thrombin (Rimon et al. 1966), Hageman factor cofactor (Crawford and Ogston 1974), coagulation factor XI (Heck and Kaplan 1974), acrosin and kallikrein (Fritz et al. 1972a, b), urokinase (Crawford and Ogston 1974; Clemmensen and Christensen 1976), and renin (Scharpe et al. 1976). Although the range of proteases inhibited by α_1AT appears broad, the association rate constants of these enzymes for α_1AT differ (leukocyte elastase > chymotrypsin > cathepsin-G > trypsin > plasmin > thrombin) (Beatty et al. 1980), and the inhibitory role of α_1AT against enzymes with low association rate constants, such as trypsin, may be negligible. The names α_1-protease inhibitor or α_1-proteinase inhibitor better describe this broader range of inhibitory functions and are preferred by some authors. In deference to historical usage and in accord with the recommendations of the

Nomenclature Meeting for this substance (Cox et al. 1983), the name α_1AT has been retained in this discussion.

The inhibitor α_1AT is a polymorphic plasma protein (Fagerhol and Cox 1981; Cox and Celhoffer 1974; Cox et al. 1980; Cox 1981; Fagerhol and Braend 1965) encoded by two codominant autosomal alleles and inherited as a single Mendelian trait. The basal serum concentration is genetically determined (Eriksson 1964; Kueppers et al. 1964; Fagerhol and Gedde-Dahl 1969; Talamo et al. 1966). More than 31 allelic variants or Pi types (where Pi, or protease inhibitor, is the symbol assigned the genetic locus of the α_1AT allele) have been identified (Cox and Celhoffer 1974; Cox et al. 1980; Cox 1981). The variants are designated by capital letters, B through Z, corresponding to their approximate electrophoretic mobility, relative to the anode, in acid starch gel electrophoresis or their relative positions on polyacrylamide isoelectric focusing. New variants are named according to the conventions established by the Fifth International Workshop on Gene Mapping and the Nomenclature Meeting for α_1AT (Cox et al. 1980).

The M allele (PiM) has a gene frequency of about 0.9 and is the most common Pi type in all populations tested (Kueppers 1978). The α_1AT serum concentration in PiMM homozygotes is between 1.3 and 2.2 g/liter (depending on the method of measurement and the purity of standard) (Kueppers 1968; Jeppsson et al. 1978a) and, by convention, defines normal. Pi types with decreased circulating levels of α_1AT include (serum concentration expressed as percent normal) null 0% (Feldman et al. 1975; Talamo et al. 1973), Mmalton and Mduarte 12% (Cox 1976; Lieberman et al. 1976), Z 15% (Laurell and Eriksson 1963; Fagerhol and Laurell 1970), P 30% (Fagerhol and Hauge 1969), S 60% (Fagerhol 1969), and I 68% (Arnaud et al. 1978).

PiZ was the first variant recognized (Laurell and Eriksson 1963) and is the Pi type most frequently associated with a serum deficiency of α_1AT (Kueppers 1978). Its allele frequency varies markedly between different ethnic and racial groups. In the United States, the allele frequency is greater than 0.010 in whites but nearly zero in blacks (Kueppers 1978). Approximately 1 in 2,000 whites is homozygous for the Z gene (Laurell and Sveger 1975).

Although a decrease in hepatic synthesis is probably the major mechanism for quantitatively significant reductions in serum α_1AT, the factors that modulate such synthesis are only partially understood (Morse 1978). Impaired hepatic secretion, as evidenced by the presence of intrahepatic cytoplasmic inclusions containing accumulations of α_1AT polypeptides (Blenkensopp and Haffenden 1977), occurs in persons with the PiZ genotype. It is uncertain if these intrahepatic inclusions exert a negative feedback inhibition on the hepatocyte and thereby retard biosynthesis of α_1AT. Intrahepatic inclusions are not found with the S and null Pi types (Carrell et al.

1982), suggesting that decreased synthesis, independent of impaired secretion, is primarily responsible for the reduced serum levels of α_1AT. Catabolic studies of the PiM and PiZ proteins have identified similar half-lives in the circulation, 6 to 7 days and 5 days, respectively (Laurell et al. 1977; Jeppsson et al. 1978b). It is therefore unlikely that accelerated peripheral catabolism contributes significantly to serum deficiencies in α_1AT.

In addition to quantitative deficiencies in serum α_1AT, a reduction in serum inhibitory capacity could also result from a loss in the functional activity of α_1AT. Most genetic variants, however, are functionally equivalent to normal α_1AT (PiMM) in their capacities to inhibit both trypsin and elastin (Billingsley and Cox 1982).

The inhibitor α_1AT is a low molecular weight (51,000 daltons) (Mega et al. 1980; Carrell et al. 1981; Chan et al. 1976; Pannell et al. 1974; Jeppsson et al. 1978) protein comprised of a single polypeptide chain containing 394 amino acid residues. Three carbohydrate side chains are attached, each containing terminal sialic acid residues (Mega et al. 1980; Carrell et al. 1981). The α_1AT reacts stoichiometrically with free protease in a ratio of 1:1; one mole of α_1AT inhibits one mole of protease and yields a stable complex (Cohen 1973). An in vitro study (James and Cohen 1978) found, however, that complete inhibition of elastase requires molar ratios of α_1AT to elastase greater than 2.2:1. This phenomenon may be explained by elastase having two major sites of attack on α_1AT. Attack against one site leads to a conformational change in α_1AT and inhibition of elastase, whereas attack against the other site results in cleavage and inactivation of α_1AT. The α_1AT-protease complexes that form during protease inhibition are not reutilized by the body (Balldin et al. 1978), and the body supplies of α_1AT are replenished via de novo synthesis by the liver.

In addition to hepatic biosynthesis, α_1AT is synthesized by at least two other endogenous sources. Both human peripheral lymphocytes and rat alveolar macrophages have been shown to synthesize α_1AT. Ikuta et al. (1982) demonstrated that concanavalin A-stimulated monocytes interact with human peripheral lymphocytes, causing a threefold increase in α_1AT synthesis. White et al. (1981) cultured rat alveolar macrophages and recovered newly synthesized radio-labeled (^{35}S)α_1AT from the cell culture medium. Macrophages and lymphocytes, by virtue of their close physical proximity to the sites of connective tissue injury, may play a significant role in defense against proteolytic destruction. The physiologic significance of extrahepatic synthesis of α_1AT remains speculative, however.

While certain chemical and physiological aspects of α_1AT are clear, the exact biochemical mechanism by which it causes protease inhibition is uncertain. It is generally agreed that the reactive center of α_1AT is located on a single serine–methionine segment peptide

bond on the carboxyl-terminal end (Carrell et al. 1982; Kurachi et al. 1981).

Proteolytic Enzymes Inducing Emphysematous Change

Proteolytic enzymes have been a major focus of investigation following the demonstration by Gross et al. (1965) of papain's ability to induce emphysematous changes in rats.

Papain

Papain, a proteolytic enzyme with a broad range of substrate specificities (Bergmann and Fruton 1941; Kimmel and Smith 1953), reproducibly causes emphysema-like lesions in a variety of experimental animals following aerosolization or intracheal instillation (Gross et al. 1965; Palecek et al. 1967; Goldring et al. 1968; Caldwell 1971; Pushpakom et al. 1970; Marco et al. 1969). A number of studies have helped to clarify the critical importance of elastolysis in papain-induced emphysema.

Snider et al. (1974) tested amorphous and crystalline forms of papain and found that the emphysema-inducing properties of these preparations were directly proportional to their abilities to degrade and solubilize elastin. Heat inactivation of papain destroyed its emphysema-inducing capabilities. Similarly, intratracheal pretreatment of hamsters with human α_1AT, an inhibitor of papain elastolytic activity, ameliorates papain-induced emphysematous changes (Martorana and Share 1976). Furthermore, Blackwood et al. (1973) showed that the elastolytic activities of several microbial enzymes, rather than their nonspecific protease activities, correlate best with the enzyme's ability to induce emphysematous changes following intravenous administration to rats. Snider et al. (1977) showed that enzymes lacking elastolytic activity, such as collagenase or trypsin, do not produce emphysema in hamsters.

Whereas these studies support the notion that the early histologic changes induced by papain are a direct consequence of its elastolytic activity, they do not preclude the possibility that endogenous factors may contribute to subsequent disease progression. Snider and Sherter (1977) noted a gradual increase in static lung volumes in hamsters following a single intratracheal injection of pancreatic elastase. Stone et al. (1979) followed the fate of tritium-labeled pancreatic elastase and found that enzymatically active preparations are retained longer within the lung than inactive preparations, and that ^{14}C-guanidated elastase remains bound to lung matrix for at least 96 hours. This suggests that tissue-bound elastase may continue to digest elastin for extended periods of time. Martorana et al. (1982) found no progression in the mean linear intercept measurements or internal surface areas in the lungs of papain-treated dogs between 3

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and 6 months after treatment. However, the mean pulmonary arterial pressure and pulmonary arteriolar resistance did increase during this interval.

Papain-treated animals exhibit the expected physiologic changes of emphysema: increased RV, FRC, and TLC, decreased elastic recoil, increased static lung compliance at middle and low lung volumes, and reduced diffusing capacity ($DL_{CO}VA$ and DL_{CO}) (Caldwell 1971; Pushpakom et al. 1970; Marco et al. 1969; Giles et al. 1970; Johanson and Pierce 1973). Studies by Kobrle et al. (1982) have shown that following papain administration the elastic fibers are disrupted and that the elastin content of the lung initially decreases, but later returns to normal after a period of accelerated synthesis. The newly synthesized fibers are disordered; however (Kuhn and Senior 1978; Kuhn and Starcher 1980).

Pancreatic Elastase

The ability of porcine pancreatic elastase to rapidly hydrolyze insoluble elastin (Partridge and Davis 1955) and its commercial availability in a highly purified crystalline form have led to its extensive use as an experimental agent for inducing emphysema in animals (Karlinsky and Snider 1978). Lesions resembling human panacinar emphysema can be induced in hamsters within 2 hours of intratracheal instillation of pancreatic elastase (Kaplan et al. 1973). The severity of the lesions, as assessed by histologic or physiologic criteria, is dose related (Raub et al. 1982), with adult animals being more susceptible to pancreatic elastase than young animals (Lucey and Clark 1982). Within a few hours of intratracheal instillation in hamsters, hemorrhagic lesions develop and an influx of polymorphonuclear leukocytes is seen (Hayes et al. 1975; Kuhn and Tavassoli 1976). Digestion of elastin fibers is apparent in the pleura and in the alveolar walls by 4 hours, but is more extensive at 24 and 48 hours (Kuhn et al. 1976). By day 4, there is a diminution in the number of polymorphonuclear leukocytes (PMNs), but many macrophages remain (Morris et al. 1981). The hemorrhage and cellular infiltration resolves within 3 weeks, and the ensuing lesions resemble panacinar emphysema (Kuhn et al. 1976). Over 95 percent of the detectable urinary excretion of desmosine and isodesmosine, amino acid markers of in vivo elastolysis, appears within 2 days of elastase instillation; only small amounts can be detected by day 3 (Goldstein and Starcher 1977). Kucich et al. (1980) developed a hemagglutination inhibition assay to measure elastin-derived peptides in serum, and found that elastin-derived peptides could be detected in the serum of dogs for a period of 12 days following administration of a 25 to 50 mg dose of porcine pancreatic elastase and for 40 days following a 100 mg dose. Janoff et al. (1983b) found increases in urinary desmosine excretion during the first 48 hours following endobronchi-

al instillation of pancreatic elastase to sheep; increases in mean linear intercepts and decreases in lung ventilation and perfusion were found after 4 weeks. All changes correlated positively with the elastase dose. Studies have shown a decrease in the lung elastin content within the first 24 hours of intratracheal injection of elastase (Kuhn et al. 1976; Ip et al. 1980; Goldstein and Starcher 1977). Physiologic studies (Snider and Sherter 1977; Snider et al. 1977) of experimental animals after pancreatic elastase administration have shown increases in the lung compliances and in the volume of air within the lungs at specified transpulmonary pressures (25 and –20 cm H^{20}). These physiologic alterations appear to progress in severity for about 26 weeks following exposure to elastase (Snider and Sherter 1977).

In spite of substantial experimental verification of ability of pancreatic elastase to induce emphysematous changes in animals following intratracheal instillation, there is little evidence implicating endogenous pancreatic elastase in the pathogenesis of pulmonary emphysema in humans. A serine endopeptidase of pancreatic origin (elastase 2) has been shown to circulate in human blood (Geokas et al. 1977). However, the enzyme is rapidly bound to serum inhibitors α_1AT and α_2-macroglobulin (α_2M) and inactivated (Gustavsson et al. 1980). Although α_2M-elastase complexes retain enzymatic activity against low molecular weight synthetic elastin substrates (N-succinyl-L-alanyl-L-alanyl-L-alanine-4-nitroanilide) (Twumasi and Liener 1977; Barrett and Starkey 1973); high molecular weight proteins such as elastin are prevented from reaching the enzyme and are not hydrolyzed (Barrett and Starkey 1973).

Attempts to induce emphysematous changes via the intravenous injection of elastase have met with limited success. Hamsters injected intravenously with nonfatal doses of pancreatic elastase fail to show histologic changes characteristic of emphysema (Schuyler et al. 1978) and do not manifest detectable reductions in lung elastin (Ip et al. 1980). However, elastic recoil is lost at low lung volumes (Schuyler et al. 1978). Fierer et al. (1976) has noted enlargements in the airspaces of rats treated intravenously with large doses (330 U) of pancreatic elastase. They also found increases in the mean linear intercepts and rarefication of the amorphous components of elastin within the lungs. It is doubtful, however, if proportionally similar intravenous levels of pancreatic elastase occur in humans with pulmonary emphysema.

Polymorphonuclear Leukocyte Elastase

Polymorphonuclear leukocytes (PMN) appear to be a more plausible source of endogenous elastase in the human lung than the pancreas, and are more likely to be incriminated in the pathogenesis of naturally occurring pulmonary emphysema. PMNs contain elasto-

lytic enzymes (Janoff 1973; Ohlsson and Ohlsson 1974; Rindler-Ludwig et al. 1974) that can be released in active form within the lung. Experimental studies have clearly demonstrated the ability of PMN elastase to degrade lung elastin and to induce emphysematous lesions in animals.

Marco et al. (1971) and Mass et al. (1972) induced experimental emphysema in dogs by the administration of aerosolized crude leukocyte homogenates. Using purified human leukocyte elastase, Janoff et al. (1977) demonstrated the ability of the enzyme to digest dog lung elastin in vitro and to cause significant dilation of terminal respiratory structures when instilled into isolated perfused dog lungs. The in vivo intratracheal instillation of human leukocyte elastase in dogs produces foci of alveolar destruction within 90 minutes of administration (Janoff et al. 1977). Senior et al. (1977) studied the effects of intratracheally injected human leukocyte elastase on hamsters and found a reduction in lung elastin in treated animals, as well as mild patchy airspace dilation. Sloan et al. (1981) were able to show that purified dog leukocyte elastase could also produce emphysematous lesions in dogs when instilled endobronchially.

Guenter et al. (1981) developed a dog model of experimentally induced emphysema that avoided the necessity of intratracheal instillation of enzymes. They repetitively injected *E. coli* endotoxin intravenously, thereby inducing extensive leukocyte sequestration within the lungs of the dogs. A previous study had shown that the sequestered cells degranulate and disintegrate within the vascular bed (Coalson et al. 1970). Histologic studies of these dogs revealed mild airspace destruction and prominent intra-alveolar fenestrations.

Alveolar Macrophage Elastase

In a widely cited article (Mass et al. 1972), dog alveolar macrophage homogenates (obtained by the method of Brain 1970), administered to two mongrel dogs produced "some dilatation and nonuniformity in the size of the airspaces accompanied by some alveolar wall destruction" in one of the dogs. The other dog showed no evidence of emphysema.

In spite of the paucity of animal data, the pulmonary alveolar macrophage (PAM) has been the focus of much investigation. Both experimental and clinical evidence is available that implicates this cell in the pathogenesis of pulmonary emphysema.

Two possible mechanisms by which macrophages may mediate tissue injury are being actively studied. One mechanism involves the release of elastolytic enzymes followed by unrestrained proteolysis. The second mechanism involves either a direct or an indirect injury

following the release of toxic forms of partially reduced oxygen such as superoxide anions, hydroxyl radicals, and hydrogen peroxide.

The ability of human alveolar macrophages to synthesize and secrete an elastolytic enzyme distinct from PMN elastase is the subject of controversy. Although human alveolar macrophages have been shown to synthesize a metalloprotease distinct from the serine protease (elastase) of the PMNs (DeCremoux et al. 1978), its hydrolytic activity against insoluble elastin substrate has not been conclusively demonstrated (Hinman et al. 1980; Levine et al. 1976). Interpretation of the observation that human alveolar macrophages raised in cell culture systems secrete an enzyme with true elastolytic activity against insoluble elastin (Rodriguez et al. 1977; DeCremoux et al. 1978) is complicated by the fact that alveolar macrophages bind and internalize PMN elastase (Campbell and Greco 1982; White et al. 1982; Campbell and Wald 1983). Hinman et al. (1980) detected a calcium-dependent metalloprotease in the culture medium and in the cell lysates of human alveolar macrophages and initially demonstrated elastolytic activity against synthetic elastin substrate and soluble elastin by both the culture medium fluid and the cell lysates. However, after 3 and 5 days of culture, no detectable activity against insoluble elastin was evident. The authors calculated that the initial elastolytic activity observed could be quantitatively explained by PMN contamination. The recognition that human alveolar macrophages internalize human PMN elastase (Campbell and Greco 1982; White et al. 1982; Campbell et al. 1979; Campbell and Wald 1983) and that the internalized PMN elastase retains enzymatic activity for at least 48 hours (McGowan et al. 1983) suggests an alternative explanation.

Green et al. (1979) subcultured human alveolar macrophages for 3 months and found measurable elastase activity against solubilized elastin during the entire period. They concluded that the elastase activity appeared to be synthesized continuously rather than being internalized from external sources.

In summary, human alveolar macrophages release elastolytic enzymes capable of digesting connective tissue. Whether the elastase released by these cells represents an enzyme synthesized de novo or a previously internalized PMN elastase is uncertain and requires further study.

Human alveolar macrophages, especially from cigarette smokers, secrete highly reactive oxygen species (Hoidal et al. 1979a) that are capable of directly injuring endothelial cells (Sacks et al. 1978) and fibroblasts (Hoidal et al. 1981) and of inactivating α_1AT (Carp and Janoff 1979, Janoff 1979a).

Whole cigarette smoke inhibits PMN chemotaxis in vitro in a dose-dependent manner (Bridges et al. 1977). However, when alveolar macrophages are exposed to cigarette smoke either in vitro or in

vivo, they release a PMN chemotaxic factor (Hunninghake et al. 1980c) (see above).

Protease–Antiprotease Hypothesis

The protease–antiprotease hypothesis proposes that enzymatic digestion of lung parenchyma occurs as a direct consequence of a genetic or acquired imbalance of the protease–antiprotease system and that the subsequent repair of connective tissue is unable to return the structures to normal. This hypothesis derives principally from two observations: (1) people genetically deficient in α_1AT (Laurell and Eriksson 1963), the major antielastase of the lower respiratory tract of humans (Gadek et al. 1981a), are at greatly increased risk of developing pulmonary emphysema, and (2) proteolytic enzymes produce physiologic and anatomic lesions resembling emphysema when administered to experimental animals (Gross et al. 1965). Attempts to integrate the clearly established relationship of cigarette smoking and pulmonary emphysema with the protease–antiprotease hypothesis have led investigators to search for ways in which smoking perturbs this balance.

Increased Elastase Owing to the Cellular Response to Smoke

At least five variables, aside from the genetically determined level of antiprotease activity, could influence the elastase burden of the lungs. These variables include (1) an increase in the number of elastase-containing cells within the lung, (2) an increase in the quantity of prepackaged or newly synthesized elastase per cell, (3) the quantity of elastase released from the cells, (4) the proximity of the elastase to suitable substrate, and (5) the extracellular milieu (i.e., pH, ionic strength, and factors such as platelet factor 4).

Number of Cells

As discussed earlier, the human cigarette smoker has increased numbers of alveolar macrophages in the bronchoalveolar lavages compared with nonsmokers (Rodriguez et al. 1977; Harris et al. 1975; Reynolds and Newball 1974; Hoidal and Niewoehner 1982). Holt and Keast (1973b) found sustained elevations of pulmonary macrophages in mice exposed to cigarette smoke. Cigarette smoke has been shown to recruit PMNs into the airways (Kilburn and McKenzie 1975; Rylander 1974) and to induce alveolar macrophages to release a chemotactic factor for PMNs (Hunninghake et al. 1980c). The circulating PMNs are reported to be increased in cigarette smokers (Corre et al. 1971; Galdston et al. 1977). Hunninghake et al. (1980c) and Reynolds and Newball (1974) found increased numbers of PMNs in the lavage fluid of smokers, but Hoidal and Niewoehner (1982) reported similar numbers of PMNs in the lavages of cigarette

smokers and nonsmokers. Hunninghake and Crystal (1983) obtained isolated cell suspensions from the bronchoalveolar lavage fluids and from open lung biopsies of nonsmokers and cigarette smokers with both normal lung parenchyma and sarcoidosis. They found a significantly increased number of neutrophils and macrophages in the lavage fluid and in the biopsy specimens from cigarette smokers as compared with nonsmokers, both in patients with normal lung parenchyma and in those with sarcoidosis.

Elastase Content

Harris et al. (1975) found an increase in the elastase-like esterase and protease activity of macrophages obtained from smokers as compared with nonsmokers. Galdston et al. (1977) found the PMN elastase levels of circulating PMNs to be elevated in patients with chronic obstructive lung disease and suggested that the intracellular elastase levels may be genetically determined (Galdston et al. 1973). Other investigators (Lam et al. 1979; Rodriquez et al. 1979) reported similar findings, but Kramps et al. (1980) failed to find any correlation between the PMN elastase levels and obstructive lung disease in PiZZ patients, although they did note a difference in PiMM patients. Lonky et al. (1980) demonstrated that dogs infected with Type 3 pneumococcus had increased PMN elastase-like esterase activity within their cells, suggesting an acute phase reaction.

Release

A variety of mechanisms may lead to the extracellular release of lysosomal contents. These include cell lysis, regurgitation during phagocytosis, reverse endocytosis, humoral mediation, and cytochalasin B treatment of cells (Klebanoff and Clark 1978). Wright and Gallin (1979) showed that migration of PMNs is associated with the leakage of various enzymes. Sandhaus (1983) found that migrating human neutrophils degrade elastin in vitro in the presence or absence of human α_1AT. A similar mechanism may occur during neutrophil migration in vivo. Hutchison et al. (1980) found that the soluble fraction of cigarette smoke suppressed the release of lysosomal enzymes (acid phosphatase and acid ribonuclease) from PMNs obtained from healthy persons, but not from the PMNs of emphysematous patients. Blue and Janoff (1978) demonstrated that the water-insoluble fraction of cigarette smoke has a cytotoxic effect on PMNs in vitro and causes them to release their lysosomal contents, including beta-glucuronidase, acid phosphatase, and elastase. Eliraz et al. (1977) found that canine alveolar macrophages and PMNs, when stimulated with the water-soluble fraction of cigarette smoke, secrete elastase. Abboud et al. (1983), however, compared the release of elastase and β-glucoaminodase from PMNs obtained from ciga-

rette smokers and with that from nonsmokers and found no differences. In vitro stimulation of these cells by either phagocytosis or chemotactic polypeptides did not alter the results. These researchers concluded that chronic smoking does not affect neutrophil elastase release in vitro and that among smokers there is no significant relationship between in vitro neutrophil elastase release and abnormalities in lung function. They speculated that some of the differences between studies may be related to experimental conditions, such as the concentrations of cigarette smoke.

Because the mechanisms involved in the release of intracellular contents are complex and the representativeness of in vitro conditions to in vivo events is uncertain, definite conclusions await further studies.

Proximity

Elastolytic activity is conditioned by the absorption of elastase onto elastin substrate (Robert and Robert 1970); the adsorption, in turn, results from the electrostatic attraction between negatively charged carboxylate groups of elastin and positively charged groups of elastase (Hall and Czerkowski 1961; Gertler 1971). Campbell et al. (1982) found that α_1AT has less inhibitory activity against PMN elastase derived from cells in contact with substrate than against PMN elastase free in solution. They reasoned that the partial exclusion of protease inhibitors from the PMN-connective tissue interface may account for this phenomena and may be an important factor in elastase-mediated injury. Focusing more on the macroenvironment within the lung, Janoff et al. (1983c) found that the bronchoalveolar lavage fluids of young asymptomatic cigarette smokers contain significantly more elastase activity than the lavage fluids from nonsmokers. Kucich et al. (1983) found that the serum lung elastin-derived peptides were elevated in some smokers and most patients with COLD, suggesting that elastolysis may be taking place in smokers and COLD patients.

Milieu

A number of in vitro experiments have examined the chemical and physical conditions that modify neutrophil elastase kinetics. Lestienne and Bieth (1980) demonstrated that human leukocyte elastase activity is activated in the presence of substrate excess, hydrophobic solvents, and increasing ionic strength. The adsorption of sodium dodecyl sulfate (SDS), a hydrophobic, anionic ligand, onto the surface of elastin enhances the elastolytic activity of pancreatic elastase (Kagan et al. 1972). Lonky et al. (1978) showed that platelet factor 4 (PF_4) in physiologic concentrations is capable of in vitro stimulation of human neutrophil elastase (HLE) against lung elastin. Low doses

of HLE instilled intratracheally in hamsters failed to induce physiologic, morphologic, or biochemical changes, but following the addition of PF_4, a significant injury was evident, and the elastin content of the lung was lowered by 20 percent (Lonky et al. 1978). Boudier et al. (1981) demonstrated that human leukocyte cathepsin-G, an enzyme in the azurophilic granules that possesses little intrinsic elastolytic activity, stimulates the rate of solubilization of human lung elastin by HLE. The elastolytic activity increased by more than five times the HLE rate when the HLE-cathepsin-G mixture was present in equimolar concentrations. The relevance of these findings to the physiologic conditions that prevail in vivo requires further study.

Laurent et al. (1983) recently discovered that the water-soluble components of filtered cigarette smoke suppress, in a dose-dependent manner, the lysyl oxidase-catalyzed oxidation of the epsilon-amino groups of lysine residues in tropoelastin. This step is essential for the formation of covalent cross-links between neighboring elastin polypeptide chains that, in turn, are necessary for normal elastic strength within the lung.

Decreased Antiprotease Owing to Oxidation

A comprehensive review of the role of oxidative processes in emphysema has recently been published by Janoff et al. (1983a). In vitro studies have revealed that oxidants such as chloramine T (Abrams et al. 1981) or ozone (Johnson 1980) cause a loss in the inhibitory capacity of α_1AT for neutrophil elastase. The mechanism of inactivation has been identified as the oxidation of methionine and tyrosine residues (Johnson and Travis 1979; Cohen 1979; Carp and Janoff 1978) within the α_1AT molecule. Chloramine T, when administered differentially to dogs, reduces EIC > TIC of serum and also results in emphysema (Abrams et al. 1981). Cigarette smoke is also known to contain oxidants (Stedman 1968; Pryor et al. 1983). Aqueous solutions of cigarette smoke reduce the elastase inhibitory capacity of human serum (Carp and Janoff 1978) and result in less binding of elastase to α_1AT in vitro (Carp and Janoff 1978). Some investigators have found that the α_1AT activity is reduced in the lavage fluids (BALF) obtained from human cigarette smokers and from rats exposed to cigarette smoke (Gadek et al. 1979; Carp et al. 1982; Janoff et al. 1979a). Stone et al. (1983) reported similar levels of functional α_1-antitrypsin in the bronchoalveolar lavage fluids of human smokers and nonsmokers. Janoff and Chan (1984) have suggested that this difference in results may reflect the timing of the lavage in these studies, as rats chronically exposed to cigarette smoke had rapid inactivation of α_1-antitrypsin following smoke exposure, but also had a more rapid recovery of α_1-antitrypsin activity than did rats acutely exposed to smoke. Stone et al. also

recognized that their study may not have detected a reduction in alpha$_1$-antitrypsin activity if it was accompanied by a rapid recovery to normal levels. Methionine sulfoxide peptide reductase, an enzyme present in human PMNs, can reactivate α_1AT oxidized by chloramine T or by the myeloperoxidase system, but α_1AT exposed to cigarette smoke plus peroxide (Carp et al. 1983) has been shown to be either resistant to reactivation by the myeloperoxidase system (Carp et al. 1983) or incompletely reactivated (James et al. 1984).

Human ceruloplasmin has been shown to prevent myeloperoxidase mediated oxidation of α_1AT under specified conditions of pH and solvency (Taylor and Oey 1982), although the role played by ceruloplasmin in limiting oxidation by phagocytes in vivo is unclear. Taylor et al. (1983) examined plasma and leukocyte lysosomal samples from a group of COLD patients and measured the ability of these samples to inhibit lipid peroxidation. While they reasoned that inhibitors of peroxidation could protect α_1AT from inactivation by neutralizing lipid free radicals, they found that inhibition required factors from both plasma and lysosomal extracts and that the factor was not ceruloplasmin. Two of ten emphysematous patients had reduced plasma factor activity, and one of these patients also had reduced lysosomal factor. Controls had normal values for both of these factors.

Galdston et al. (1984) examined serum ceruloplasmin concentrations and antioxidant activity in male and female smokers. Smokers of both sexes had higher serum ceruloplasmin concentrations than did nonsmokers; women in both smoking categories had higher concentrations than their male counterparts. Serum antioxidant activity showed a significant positive correlation with serum ceruloplasmin levels; however, for comparable ceruloplasmin concentrations, serum antioxidant activity was significantly lower in smokers than in nonsmokers of both sexes. The researchers suggest that cigarette smoking may cause partial inactivation of serum antioxidant activity that is accompanied by an insufficient increase in ceruloplasmin concentration.

Endogenous phagocytes are also capable of generating oxidants (Babior 1978; Klebanoff and Clark 1978). The phagocytic enzyme myeloperoxidase, in the presence of hydrogen peroxide and halide ions, oxidatively inactivates α_1AT (Matheson et al. 1979, 1981). Smoking, as described above, elevates the oxidative metabolism in lung macrophages (Hoidal and Niewoehner 1982; Fox et al. 1979; 1980; 1981).

Thus, it is clear that the oxidants present in cigarette smoke and the lung macrophages of smokers can inactivate α_1AT. This inactivation, coupled with the increased elastase burden that may result from the inflammatory cell response of the lung to smoke, could tip

the balance of the protease–antiprotease system in the direction of elastin degradation.

Explanation for Upper Lobe Distribution

In accord with the protease–antiprotease hypothesis, emphysematous lesions result from the unrestrained proteolytic digestion of connective tissue elements. The regional distribution of lesions within the lung is thought to be conditioned by both biochemical and physiological variables.

The predilection of lower lobe involvement in persons with α_1AT deficiency is hypothesized to result from an increased number of elastase-containing cells because of the higher vascular perfusion to this area in erect man. This excess could occur because of the deposition of senescent leukocytes in these areas of higher blood flow (Guenter et al. 1981). In addition, inhaled particulates preferentially deposit in the lower lobes (Milic-Emili et al. 1966; Dollfuss et al. 1967), and the leukocytes release their enzyme extracellularly during the ingestion of these particulates. Because of the genetic deficiency of α_1AT, the proteolytic activity is unopposed and destruction occurs.

The predominance of upper lobe lesions in cigarette smokers with normal systemic levels of α_1AT is again thought to result from variations of ventilation and perfusion within the lung (Cockcroft and Horne 1982). However, in normal individuals the proteolytic activity due to the excess particulate deposition in the bases is inhibited by α_1AT that is replenished by the increased vascular perfusion also occurring in the bases. The upper lobes, although less well ventilated than the lower lobes, nevertheless have higher ventilation:perfusion ratios because of the proportionately greater fall in perfusion. The oxidative inactivation of α_1AT by cigarette smoke in the upper lobes therefore may not be compensated by vascular repletion of the inactivated α_1AT, and an imbalance of protease–antiprotease may occur. The upper lobe injury may then be magnified by mechanical stresses caused secondary to the negative intrapleural pressures generated by gravitational forces in erect man (West 1971).

Animal Models of Emphysema

Spontaneous Emphysema

Emphysema occurs spontaneously in animals in forms resembling the types seen in human disease (Karlinsky and Snider 1978). However, the low incidence and unpredictable occurrence of disease in animals greatly limit their utility as experimental models.

Experimentally Induced Emphysema

A number of insults, including oxides of nitrogen, cadmium salts, whole cigarette smoke, ozone exposure, and proteolytic enzymes, have been used to induce or augment emphysematous lesions in a variety of experimental animals. The reader interested in a comprehensive review of this topic is referred to the well-documented article by Karlinsky and Snider (1978). The evidence for each of these insults, as they pertain to cigarette smoke, is reviewed below.

Oxides of Nitrogen

Oxides of nitrogen, present in the gas phase of smoke, appear to induce or potentiate emphysema-like lesions in some animals (Karlinsky and Snider 1978).

Nitrogen dioxide (NO_2) exposure causes airway narrowing and an increase in the proteolytic burden within the lungs of experimental animals. Airway narrowing is postulated as a contributing factor in the pathogenesis of pulmonary emphysema (Juhos et al. 1980). Following exposure to NO_2, rats develop bronchiolar stenosis. The nitrogen dioxide exposure also induces an influx of alveolar macrophages (AM) and polymorphonuclear leukocytes (PMNs) (cells known to contain proteolytic enzymes) into the lungs (Juhos et al. 1980). Kleinerman et al. (1982) demonstrated an increased number of alveolar macrophages and PMNs in lung lavages from hamsters exposed to NO_2. Although there is no detectable increase in the elastolytic activity from lung lavages of NO_2-exposed animals, the cell-free culture medium from macrophage cultures of NO_2-exposed animals does show a twofold to fivefold increase in elastolytic activity during the first 2 weeks of exposure (Kleinerman et al. 1982).

Nitrogen dioxide exposure has not been shown to cause alveolar septal disruption, an essential feature of centrilobular emphysema, but it does result in a significant reduction in the internal surface area in the lungs of hamsters exposed for 12 to 14 months (Kleinerman and Niewoehner 1973).

Cadmium Salts

Animals exposed to cadmium, a constituent found in the particulate phase of cigarette smoke, develop a number of histologic and biochemical changes that may lead to emphysematous lesions.

Exposed animals develop pulmonary edema, vascular congestion, intraparenchymal hemorrhages, and a loss of Type I pneumocytes (Palmer et al. 1975; Strauss et al. 1976), and PMNs and mononuclear cells influx into the lungs (Snider et al. 1973). The animals develop acute peribronchial damage followed by the accumulation of granulation tissue near the respiratory bronchioles, thickened alveolar

septa, and distortion and distention of neighboring alveoli (Snider et al. 1973). These histologic changes are more suggestive of the scar or paracicatricial form of emphysema than the centrilobular form reported in some industrial workers exposed to $CdCl_2$ (Princi 1947). This disparity in response to $CdCl_2$ could be related to species differences or the interaction of $CdCl_2$ with other factors.

When hamsters are exposed to $CdCl_2$ plus beta-amino proprionitrile (β-APN), an inhibitor of lysyl oxidase, they develop thin-walled subpleural bullae and airspace enlargements resembling panlobular emphysema (Niewoehner and Hoidal 1982). The mean linear distance between alveolar intercepts is significantly increased; pressure–volume studies show overinflation and increased compliance of the lungs (Niewoehner and Hoidal 1982). This study suggests that $CdCl_2$, perhaps in conjunction with some other as yet undetermined agent, may be important in the pathogenesis of pulmonary emphysema. The fact that $CdCl_2$ is a constituent of cigarette smoke (Randi et al. 1969) lends support to this hypothesis.

Cigarette Smoke

Cigarette smoking has been clearly identified as a major causal factor in the development of pulmonary emphysema in humans (Auerbach et al. 1972; 1974; Petty et al. 1967; Andersen et al. 1967; Niewoehner et al. 1974; USDHEW 1979). However, an animal model for the development of emphysema using the inhalation of cigarette smoke alone has not been convincingly demonstrated. Parenchymal disruption resembling human emphysema has been reported in some dogs following prolonged cigarette exposure, but this histologic pattern is not uniformly present (Hernandez et al. 1966; Auerbach et al. 1967a; Zwicker et al. 1978).

This difficulty in developing an animal model for cigarette-induced emphysema may relate to the reluctance of animals to inhale smoke and the relatively long duration of exposure required to produce emphysema in humans. However, it may also result from the need for a combination or sequence of effects to induce emphysematous change. That is, an increased elastase burden might be necessary (secondary to the cellular response to smoke) before the oxidant damage of smoke to α_1AT, or to repair mechanisms, results in emphysema. Hoidal and Niewoehner (1983) examined this question in hamsters exposed to low doses of smoke and elastase. Neither exposure alone resulted in significant emphysematous change, but the combined exposure did cause change. This suggests that an increased elastase burden may be a precondition for smoking-induced emphysematous lung injury, and may also explain the long exposure period required in humans prior to the demonstration of an increased prevalence of emphysema in smokers.

Experimental studies have shown that cigarette smoke can induce a number of cellular, biochemical, and metabolic changes within the lungs that may be causally related to the development of emphysema. Macrophages and leukocytes, cells known to contain proteolytic enzymes, are recruited to the lungs of hamsters (Kilburn and McKenzie 1975) and guinea pigs (Flint et al. 1971) following exposure to cigarette smoke, thereby increasing the proteolytic burden of the lungs. Conversely, the α_1AT activity decreases in rats after inhalation of cigarette smoke (Janoff et al. 1979a). The increased proteolytic burden within the lungs coupled with the concomitant diminution in inhibitory capacity tends to create a protease–antiprotease imbalance and a situation whereby unrestrained connective tissue destruction may occur.

The Effects of Smoking on Cellular and Immune Defense Mechanisms

There are important functional differences between macrophages from smokers and those from nonsmokers (Table 1). For example, Warr and Martin (1977) demonstrated that receptors for the third component of complement (C3b) are decreased in number or function on the surface of smokers' alveolar macrophages. The receptors for the Fc portion of IgG, however, are normal on these cells (Warr and Martin 1977). An important function of the C3b receptor is to augment the attachment and phagocytosis of microorganisms and particulates by the macrophages. It is not clear whether this subtle defect in cell function results in a significant alteration in phagocytosis or clearance of particulates or microorganisms by these cells. In this regard, the phagocytosis and killing of a variety of microorganisms by smokers' alveolar macrophages have been shown to be normal by Harris et al. (1970) and Cohen and Cline (1977). One report by Martin and Warr (1977), however, suggests that the capacity of alveolar macrophages to kill bacteria is decreased in smokers.

The observation that human alveolar macrophages from cigarette smokers function normally to kill microorganisms appears to differ, at first glance, from a number of animal studies demonstrating that the capacity of alveolar macrophages to phagocytose and kill bacteria is impaired following exposure to cigarette smoke (Holt and Keast 1973; Rylander 1971, 1973). In these animal studies, there was an initial decrease in the numbers of alveolar macrophages and a decrease in their bactericidal function following exposure to cigarette smoke. With prolonged exposure, however, the number of macrophages increased and their ability to kill microorganisms returned to normal (Rylander 1973, 1974). These observations suggest that cigarette smoke, initially, is toxic to alveolar macro-

phages. However, it is likely that the macrophages, with time, adapt to the presence of cigarette smoke. In addition, a subpopulation of macrophages that are more resistant to cigarette smoke may increase in number in the lung. The macrophages isolated from the lungs of smokers resemble those isolated from animals following prolonged exposure to cigarette smoke. The acute effects of cigarette smoking on the number and functions of alveolar macrophages in man has not been systematically evaluated.

Alveolar macrophages of cigarette smokers appear to interact in an abnormal fashion with lymphocytes (Table 1). In this regard, the alveolar macrophages from cigarette smokers function poorly as accessory cells in presenting antigen to autologous lymphocytes (Laughter et al. 1977). This latter defect may be further magnified by the observation that lymphocytes from cigarette smokers also respond poorly to mitogens (Neher 1974; Daniele et al. 1977). Additional evidence for an abnormal interaction of macrophages and lymphocytes in lungs of cigarette smokers is a decreased response of alveolar macrophages to the lymphokine, macrophage migration inhibitory factor (Warr 1979). These observations suggest that cigarette smoking may have broad effects on the ability of the lung to generate a cellular immune response.

In Vitro Effects of Cigarette Smoke on Inflammatory and Immune Effector Cells

The most readily demonstrable effect of cigarette smoke, in vitro; is a decrease in cell viability (Holt et al. 1974; Holt and Keast 1973; Nulsen et al. 1974; Weissbecker et al. 1969). At relatively low concentrations, cigarette smoke and its constituents rapidly kill alveolar and peritoneal macrophages in vitro. Lymphocytes and polymorphonuclear leukocytes are also very susceptible to these agents (Holt et al. 1974; Blue and Janoff 1978).

When sublethal amounts of cigarette smoke are employed, a number of metabolic and functional changes occur in macrophages. Phagocytosis is depressed, as is the function of a number of macrophage enzymes (Vassallo et al. 1973; Green 1968a, b, c, 1969, 1970; Green and Carolin 1966, 1967; Green et al. 1977; Powell and Green 1971; Hurst and Coffin 1971). In addition; protein synthesis is also depressed (Yeager 1969; Low 1974), and stimulatory effects have been noted. While cigarette smoke depresses phagocytosis and intracellular killing, nitrogen dioxide increases the metabolic activity of macrophages (Vassallo et al. 1973). Similar effects have been observed under some conditions with cigarette smoke (Holt and Keast 1973; Leuchtenberger and Leuchtenberger 1971). Results from a number of investigators suggest that the balance between stimulation and inhibition of macrophage activity is determined by dosage, with stimulation occurring at low exposure levels and inhibition at

higher concentrations (Holt and Keast 1973; Lentz and DiLuzio 1974; York et al. 1973). The most potent stimulation occurs after prolonged exposure to low levels of the agent.

These in vitro effects of cigarette smoke are also seen acutely in vivo following exposure to smoke. The immediate effect of exposure to cigarette smoke, and to agents present in the smoke, is a decrease in viability of the pulmonary alveolar macrophages (Holt and Keast 1973a, b; Rylander 1971, 1973; Coffin et al. 1968; Dowell et al. 1970; Holt and Nulsen 1975; Gardner et al. 1969). Although not well studied, it is also likely that cigarette smoke is toxic to polymorphonuclear leukocytes (Blue and Janoff 1978). In support of these observations are studies demonstrating that acute exposure of experimental animals to tobacco smoke, or to components of cigarette smoke, also lowers their resistance to bacterial infection (Rylander 1969, 1971; Acton and Myrick 1972; Gardner et al. 1969; Goldstein et al. 1971; Huber and LaForce 1971; Huber et al. 1971). Short-term exposure to components of cigarette smoke, particularly nitrogen oxide, has also reduced resistance to viral infection, probably by inhibiting interferon production by macrophages (Valand et al. 1970). As noted above, these in vitro and acute in vivo effects of cigarette smoke are not seen following long-term in vivo exposure in animals; very little work has been done on the effects of cigarette smoke in vitro, using human cells. However, several studies have shown that cigarette smoking and nicotine, at levels comparable to those encountered in the circulation of smokers, produce a slight but significant depression of PHA-stimulated DNA synthesis in human peripheral blood lymphocytes (Neher 1974; Silverman et al. 1975; Vos-Brat and Rumke 1969).

The Effect of Cigarette Smoke on Antibody Production

The available data on antibody production in human smokers suggest that cigarette smoking may depress these responses. The production of antibodies was investigated in a large study involving influenza vaccination. Smokers in the population exhibited increased susceptibility to infection during an influenza outbreak (Finklea et al. 1969, 1971). Prior to immunization with influenza vaccine, smokers exhibited significantly lower titers of specific antibodies than did nonsmokers. Immediately following vaccination of both groups, the smokers developed levels of antibodies comparable to those of nonsmokers. However, the antibody titer in the smokers fell below their nonsmoking counterparts within a few weeks, and by a year after vaccination the smokers exhibited markedly depressed levels of circulating antibodies.

The capacity of cigarette smoking to alter antibody production was also studied by evaluating the capacity of a fetus to stimulate lymphocytotoxic antibodies against HLA antigens in the mother

(Nyman 1974). Sera from a large number of pregnant women were tested for the presence of lymphocytotoxic antibodies against a 48-donor panel. The smokers exhibited a significantly lower incidence of these antibodies than did nonsmokers, and the divergence between groups increased with the number of deliveries. Infections during pregnancy were observed significantly more often in the smokers in this trial.

In several animal models, acute exposure to whole cigarette smoke or components of cigarette smoke depressed the numbers of antibody-forming cells in the spleen and the serum levels of antibodies in animals exposed to a variety of antigens (Miller and Zarkower 1974; Zarkower and Marges 1972; Zarkower et al. 1970). The depression was greatest when the antigen was administered by an aerosol (rather than by systemic inoculation), indicating that smoke appears to exert an effect close to the point of entry. Prolonged exposure ultimately resulted in severe depression both in local and in systemic antibody responses (Esber et al. 1973; Holt et al. 1976; Thomas et al. 1973, 1974a, 1974b, 1975).

Although it is tempting to relate these abnormalities in immune response to the known association between cigarette smoking and increased incidence of upper respiratory infection, it is not clear whether the subtle defects in immune functions can entirely account for the infections present in cigarette smokers. Clearance of bacteria from the respiratory tract is a complex process that involves interplay between a variety of different mechanisms, only some of which include the function of alveolar macrophages and the capacity of the lung to mount cellular and humoral immune responses. Other abnormalities present in cigarette smokers that could account for this increased incidence of infection include a markedly abnormal tracheal bronchial clearance of particulates and an increased adherence of bacteria to airway epithelium (reviewed in USPHS 1971, 1973, 1974).

EFFECTS OF CIGARETTE SMOKE ON AIRWAY MUCOCILIARY FUNCTION

Introduction

There is extensive literature on the effects of cigarette smoke on mucociliary clearance in the airways, with the majority of the reports appearing between 1965 and 1975. Different experimental approaches have been used, including in vivo measurement of mucociliary function in animal models and in human subjects. The results of some of these studies have been contradictory, presumably because of differences in experimental technique or the influence on mucociliary function of factors other than cigarette smoking. For example, tracheal mucociliary transport appears to decline with age in normal subjects (Goodman et al. 1978), an important phenomenon to consider when assessing the effects of long-term cigarette smoking. Another complicating factor is the clearly demonstrated impairment of mucociliary function produced by chronic bronchitis even in nonsmokers, such as in patients with cystic fibrosis (Wood et al. 1975) or immunoglobin deficiency (Mossberg et al. 1982). Therefore, it is difficult to separate the direct effects of cigarette smoke on mucociliary function from those of smoking-associated chronic bronchitis. Finally, in vitro bioassays for ciliotoxicity may not reliably reflect the effects of cigarette smoke on the mucociliary apparatus in the intact airways. Thus, Dalhamn et al. (1967) found that smoke produced by cigarettes containing a high concentration of hydrogen cyanide was more ciliotoxic in vitro than that produced by cigarettes containing a low concentration of hydrogen cyanide, and the two types of cigarettes caused a comparable reduction of mucus transport in vivo.

This review is divided into three parts. The first part summarizes the normal structure and function of the mucociliary system in the airways. The second part deals with the direct effects of short-term and long-term cigarette smoke exposure on mucociliary function, and the third part discusses mucociliary function in chronic bronchitis.

Normal Mucociliary Function

The principal function of the airway mucociliary system is its contribution to host defenses. This is accomplished by physical removal of inhaled foreign material from the ciliated airways by mucous transport and by biochemical and immunological processes that protect against invasion of the mucosa by infectious agents. Normal mucociliary clearance depends upon an optimal interaction between cilia and mucus.

Cilia

The respiratory mucosa from the proximal trachea to the terminal bronchioles consists of a pseudostratified epithelium with cilia protruding from the luminal surface of columnar cells (Figure 1). The larynx contains a mucus-secreting squamous epithelium over most of its surface, and cilia are present only in the posterior commissure (Wanner 1977). The major cell types in the respiratory mucosa are basal cells, intermediate cells, nonciliated columnar cells, ciliated columnar cells, and goblet cells. In the larger airways, the major part of the epithelial surface is ciliated. The ratio of ciliated columnar cells to goblet cells is approximately 5:1 in the trachea, with a relative decrease in the number of both cell types toward the peripheral airways. The surface of each ciliated columnar cell contains approximately 200 cilia with an average length of 6 μm and diameter of 0.2 μm. Both ciliated and nonciliated columnar cells are characterized by microvilli on their luminal surface. These measure 0.3 μm in length and 0.1 μm in diameter. The ultrastructure of cilia in lower animals and mammals is remarkably similar. Each cilium contains longitudinal microtubules that appear to represent contractile elements. Two single microtubules form a central core, and nine microtubules with a doublet structure are arranged in a circular fashion in the periphery of the cilium. A basal body in the apex of the cell corresponds to each cilium. Circular and radial bridges have been demonstrated between the peripheral microtubules and between the peripheral and central microtubules. These bridges (dynein arms, nexin links, radial spokes) appear to be crucial for ciliary bending.

Mucus

Respiratory secretions consist of mucus produced by submucosal glands and goblet cells and tissue fluid. The total volume of all mucus-producing structures has been estimated at approximately 4 ml in human lungs; submucosal glands make up most of this volume (Wanner 1977). The submucosal glands are under parasympathetic nervous control, with an estimated daily volume of respiratory secretions between 10 and 100 ml. Human respiratory secretions contain approximately 95 percent water. The rest consists of micromolecules (electrolytes and amino acids) and macromolecules (lipids, carbohydrates, nucleic acid, mucins, immunoglobulins, enzymes, and albumin). In situ, the respiratory secretions take the form of two layers, i.e., periciliary fluid (sol phase), and mucus (gel phase), as shown in Figure 1. Mucus has been clearly identified as the product of submucosal glands and goblet cells; the origin of the periciliary fluid has not been definitely established, although transepithelial water transport appears to be the most likely source. In central airways, the mucus layer is 5 to 10 μm deep and may be

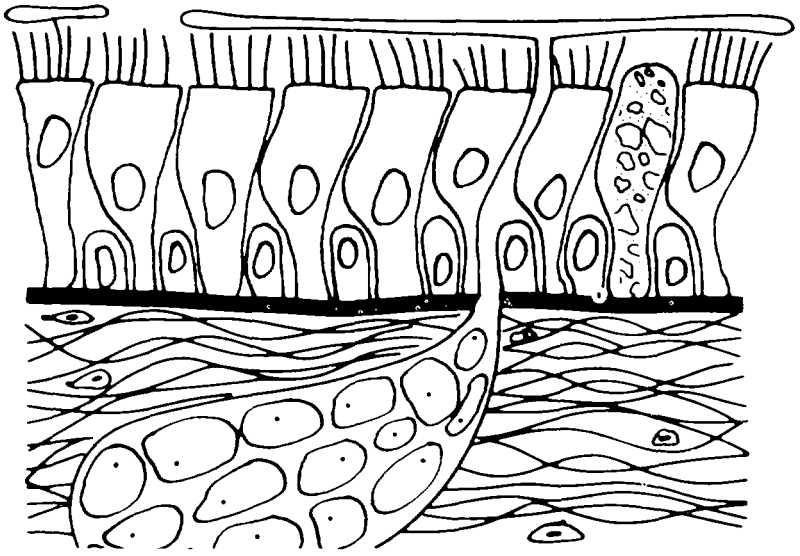

FIGURE 1.—Schematic representation of normal mucosa (central airway) with the components of the mucociliary apparatus

NOTE: From top (airway lumen) to bottom, note mucus layer, periciliary fluid layer, epithelium with a predominance of ciliated columnar cells and an interspersed goblet cell, basement membrane, and submucosal gland.

SOURCE: Wanner (1979).

discontinuous. In peripheral airways where submucosal glands are absent and goblet cells are rare, mucus is either absent or present only in small quantities. Regeneration of injured ciliated respiratory epithelium takes approximately 2 weeks in animals; the exact regeneration time of damaged human tracheobronchial ciliated epithelium is not known (Wanner 1977). It appears that regeneration does not begin until 2 to 3 days following mechanical injury.

Mucociliary Interaction

Mucociliary interaction depends on ciliary activity, the rheologic properties and depth of the mucus layer, and the depth of the periciliary fluid layer. The viscoelastic properties of mucus are determined by its biochemical characteristics (disulfide cross-linking and hydrogen bonding between glycoprotein molecules and water) (Wanner 1977). Cilia beat in one plane, with a fast effective stroke (power stroke) in the cephalad direction and a recovery stroke that is two to three times slower. Adenosine triphosphate has been identified as the energy source for ciliary bending. In mammals, the average normal ciliary beat frequency is approximately 1,000 beats per minute, with coordinated motion in adjacent cilia on an individual cell and in cilia of adjacent cells. This interciliated

TABLE 2.—Measurement of airway mucociliary function in humans

Method	Reference
Clearance of inhaled radioactive aerosols from the lungs	Morrow et al. (1967)
Transport of discrete markers	Friedman et al. (1977) Sackner et al. (1973)
Central airway clearance of inhaled boli of radioactive microspheres	Yeates et al. (1975)

pattern of motion by which adjacent cilia beat one after another to generate a wave of ciliary motion is called metachronism.

The "normal" thickness of the periciliary fluid layer is less than, or at best equal to, the length of the ciliar shafts, which measure approximately 6 μm in the central airways. The luminal surface of the mucus layer appears smooth, whereas the surface in contact with the cilia is irregular, and the mucus penetrates between the ciliary shafts. This penetration and the claw-like projections at the cilia tips may further facilitate the mechanical interaction between cilia and mucus. In the trachea, the "normal" surface mucus transport velocity is between 5 and 20 mm per minute depending upon the method of measurement. Mucous transport velocity decreases toward the peripheral airways.

The three principal methods for the measurement of tracheobronchial mucociliary function in humans are listed in Table 2. All of these have been used in studies of the effects of cigarette smoke on mucociliary function.

Theoretically, mucociliary dysfunction can result from alterations in ciliary beat frequency and coordination, the quantity and viscoelastic properties of mucus, and the thickness of the periciliary fluid layer. In addition, focal destruction of the respiratory epithelium, producing areas without cilia or mucus, is also associated with impaired or absent mucociliary transport.

Effects of Cigarette Smoke on Mucociliary Function

The irritant effects of cigarette smoke on mucociliary clearance were recognized by Mendenhall and Shreeve (1937). They observed a decrease in the transport rate of carmine particles on the mucosa of excised cat tracheas after bringing them in contact with cigarette smoke, either directly or by dissolving it in the solution in which the tracheas were immersed (Mendenhall and Shreeve 1937, 1940). These early findings were confirmed by Hilding (1956) and Dalhamn

(1959) approximately 25 years ago. Since then, investigations to assess the effects of cigarette smoke on ciliary activity and mucociliary transport have proliferated. Because cigarette smoke can impair mucociliary transport by interfering with ciliary activity or mucus secretion, the studies relating to these two component functions are discussed separately and are complemented by a review of experiments involving mucociliary transport, the ultimate expression of mucociliary function.

The effects of cigarette smoke on mucociliary function have been extensively studied in vitro, in intact animal models, and in human subjects. Comparison among the results of these experimental approaches is difficult, as there are major differences in inhalation patterns even between animal models and human subjects. Cigarette smoke is modified during its passage through the upper airways, and this may vary depending upon the mode of inhalation. By using smoke produced by radio-tracer spiked cigarettes, it has been shown that mice, who are obligatory nose breathers, retain 50 percent of the inhaled radioactivity in the nasal passages, 20 percent in the lungs, and the rest in the esophagus, stomach, and other organs (Page et al. 1973). Using artificial airways to bypass the nasopharynx in experimental animals eliminates the problem of nasal cigarette smoke absorption, but also prevents the oral modification of cigarette smoke that is a typical feature of human smoking. In subjects inhaling cigarette smoke from a smoke dosage apparatus that delivers standard puffs, 86 to 99 percent of most components of gas and particulate phases of cigarette smoke are retained, with the exception of carbon monoxide (CO), of which only 54 percent is retained (Dalhamn et al. 1968). Much of the smoke appears to be retained in the mouth. In human subjects who hold cigarette smoke in their mouth for 2 seconds, 60 percent of the water-soluble components of the gas phase, 20 percent of the water-insoluble components of the gas phase, and 16 percent of particulate matter are absorbed or retained in the upper airways (Frances et al. 1970; Stupfel et al. 1974). This marked modification of cigarette smoke might decrease its ciliotoxic effect in the lower airways. Passing unfiltered cigarette smoke through a chamber with wet surfaces before bringing it in contact with ciliated epithelium decreased the cilioinhibitory capacity of the cigarette smoke (Kaminski et al. 1968). When filtered cigarette smoke was used, the wet surfaces had no additional effect on ciliotoxicity, indicating that the mucosa of the upper airway may serve as a filter (Kaminski et al. 1969). Similar observations have been made when cigarette smoke was passed through a water trap (Albert et al. 1969).

Because of the differences in inhalation pattern between humans and animals, it might be argued that nasal mucociliary function should be measured to assess the effects of inhaled cigarette smoke

TABLE 3.—Effects of cigarette smoke on airway mucociliary system

Exposure	Ciliary dysfunction	Mucus hypersecretion	Impaired mucociliary clearance
Short term	Yes	?	?
Long term	Yes	Yes	Yes

in animal models. However, it has been clearly shown that nasal mucociliary transport is not a good marker of tracheobronchial mucociliary transport because of differential responses at the two sites. For example, exposure to the whole cigarette smoke of up to 30 cigarettes does not impair nasal mucociliary transport in donkeys (Frances et al. 1970), whereas the same number of cigarettes clearly alters tracheobronchial deposition and clearance of radioactive aerosols (Albert et al, 1969). Likewise, Hilding (1965) has concluded from his studies that the nose is not an acceptable organ for the study of the effects of cigarette smoke on mucociliary transport.

Realizing the problems with experimental models of ciliary function in response to cigarette smoke inhalation, Dalhamn (1969) postulated that a proper experimental design should fulfill the following requirements: (1) the exposure pattern and level of cigarette smoke inhalation should simulate that of natural smoking in human subjects, (2) cigarette smoke should be delivered in air and not as an aqueous solution, (3) the components of inhaled cigarette smoke should be analyzed, and (4) exposure should be of long duration. Although these criteria are obviously not met by many of the studies quoted in this review, understanding these principles allows a more critical assessment of the reported results as shown in Table 3.

Short-Term Exposure

The effects of short-term cigarette smoke exposure on the morphology of the respiratory mucosa have not been investigated in man. Cigarette smoke residue has been shown to cause ciliary damage in cultured rabbit tracheal epithelium with a contact-time-dependent effect (Kennedy and Allen 1979). The most consistent abnormalities were cellular desquamation and alterations in mitochrondria, cilia, and microvilli, some of which occurred as early as 1 hour after exposure commenced.

Cytotoxicity has also been observed after short-term exposure of ciliated epithelium to aqueous extracts of cigarette smoke condensate in vitro (Donnelly 1969), but it is difficult to extrapolate data from these in vitro studies to the in vivo conditions that occur during cigarette smoking.

Cilia

With a few exceptions, e.g., Proetz (1939), most investigators have demonstrated an irritant effect of smoke on ciliated epithelium, usually characterized by ciliostasis. Residues of cigarette smoke passed through an aqueous medium have been shown to produce ciliostasis in protozoa (Weiss and Weiss 1964; Wang 1963) and in fragments of human respiratory epithelium (Ballenger 1960). In fragments of rat trachea, brief exposure to whole cigarette smoke appears to elicit a biphasic response, with a short period of stimulation during 1 to 2 minutes followed by a marked decrease in ciliary beat frequency (Guillerm et al. 1961, 1972). In an excised rabbit trachea model, 71 1-ml puffs or 35 10-ml puffs of whole cigarette smoke were necessary to produce ciliostasis; similar relationships were demonstrated in the tracheas of living cats (Dalhamn 1970; Dalhamn et al. 1968). Several investigators have established a stimulus–response relationship between dilutions of aqueous cigarette smoke extract and the time of exposure required for total stoppage of ciliary beat frequency in different experimental models (Donnelly 1969, 1972; Das et al. 1970; Donnelly et al. 1981). The mechanism by which cigarette smoke acutely depresses ciliary function is not clearly known, but may involve enzyme inhibition of adenylate kinase, thereby reducing adenosine triphosphate (ATP), the energy source for ciliary bending (Mattenheimer and Mohr 1975; Schabort 1967). Ciliary function in response to short-term cigarette smoke inhalation has not been studied in man.

Mucus

Very little is known about the quantity and rheologic properties of airway secretions after short-term cigarette smoke exposure. A brief exposure of slugs to cigarette smoke has been reported to stimulate the production of mucus containing an increased number of acid glycoprotein fibers (Wilde 1981). The significance of this observation with respect to the human respiratory tract is not clear, except that an increased number of acid glycoprotein fibers has also been demonstrated in sputum obtained from cigarette smokers.

Mucociliary Interaction

Using a variety of different techniques in animal experiments, ciliary dysfunction and impairment of mucociliary transport by short-term exposure to cigarette smoke have been demonstrated in rats (Iravani 1972; Dalhamn 1964; Ferin et al. 1966), rabbits (Dalhamn 1964; Holma 1969), cats (Carson et al. 1966; Dalhamn 1964, 1969; Kaminski et al. 1968), dogs (Guillerm et al. 1972; Sakakura and Proctor 1972; Isawa et al. 1980), donkeys (Albert et al. 1974, 1969), chickens, and sheep (Stupfel et al. 1974). A few reports

have not demonstrated that short-term exposure to smoke depresses mucociliary function in animal models (La Belle et al. 1966; Bair and Dilley 1967). The reasons for the discrepancy between these and the previously listed studies are not clear, but may be related to methodology and dose of exposure. Stimulus response curves between dose of cigarette smoke and the degree of mucociliary inhibition have been shown in airways of chickens and dogs (Battista and Kensler 1970b; Sakakura and Proctor 1972; Isawa et al. 1980). In one study, for example, 9 puffs of nonfiltered cigarette smoke had variable effects on tracheal mucociliary transport in intact dogs, but tracheal mucociliary transport was consistently inhibited by 12 puffs (Sakakura and Proctor 1972). Likewise, the number of 4-second exposures to cigarette smoke (separated by 1 minute) required to reduce mucus transport in intact chicken tracheas by more than 90 percent has been shown to increase with increasing dilutions (from 50 to 3 percent) of smoke in air (Battista and Kensler 1970b).

Measurements of mucociliary clearance in man immediately after smoking one or more cigarettes have shown conflicting results, with either increased (Albert et al. 1973; Camner et al. 1971; Albert et al. 1975; Camner and Philipson 1971, 1974), inconsistent, or unchanged rates (Yeates et al. 1975; Pavia et al. 1971; Goodman et al. 1978) or decreased (Nakhosteen et al. 1982) rates. Transient effects on mucociliary clearance have been reported in both smokers and nonsmokers (Hilding 1956; Pavia et al. 1971). Such differences between human subjects may reflect a difference in the dose and inhalation pattern of cigarette smoke.

Long-Term Exposure

In dogs inhaling cigarette smoke through a tracheostomy, histologic changes have been observed in the bronchi after 229 to 421 days of exposure (Auerbach et al. 1967b). These changes consisted of epithelial hyperplasia, decreased number of ciliated cells, and areas of squamous metaplasia. This may be criticized as a poor model of cigarette smoking in humans because the upper airway, which absorbs part of the smoke and decreases its toxicity, is bypassed. The irritant effect of cigarette smoke on the tracheobronchial mucosa could be enhanced in this model. However, inflammatory changes in the airways have also been observed in animals that inhaled cigarette smoke via their upper airways (Leuchtenberger et al. 1958; Rylander 1974; Mattenheimer and Mohr 1975; Park et al. 1977; Basrur and Basrur 1976; Jones et al. 1973; Iravani 1973). Various types of lesions have been observed, including tracheal and bronchial epithelial hyperplasia (Park et al. 1977; Frasca et al. 1974), goblet cell proliferation and submucosal gland hypertrophy (Jones et al. 1973; Park et al. 1977), bronchiolar metaplasia of mucus-secreting cells (Basrur and Basrur 1976), increased quantities of airway mucus

that appear to be adherent to submucosal gland openings (Iravani 1973), and a decreased number of ciliated epithelial cells (Basrur and Harada 1979). One study suggested a dose-dependence of the mucosal lesions when comparing hamsters exposed to either four cigarettes per day or eight cigarettes per day for 2 weeks (Basrur and Basrur 1976). The pathologic changes produced by long-term cigarette smoke exposure appear to be reversible if the exposure time is not excessive. Thus, inflammatory changes in the airways of hamsters exposed to cigarette smoke for 4 weeks showed marked reversibility with a recovery time of several weeks (Basrur and Harada 1979).

The histologic changes in the airways of cigarette smokers are similar to those produced by cigarette smoke in animal models, and consist of varying degrees of denudation of the ciliated epithelium, an increase in the number of goblet cells, submucosal gland hypertrophy, and squamous metaplasia (Regland et al. 1976; Jones 1981). Morphometric studies have demonstrated an increased quantity of mucus in the airway lumen without histologic evidence of coexistent emphysema or a history of obstructive lung disease, whereas this is not observed in the lungs of healthy nonsmokers (Niewoehner et al. 1974; Matsuba and Thurlbeck 1971). Electron microscopic examination of ciliated epithelium in surgical lung specimens obtained from cigarette smokers has revealed ciliary abnormalities consisting of compound cilia, single axoneme, intracytoplasmic microtubular doublets, and cilia within periciliary sheaths (McDowell et al. 1976). If bronchial biopsy material is used to detect ciliary abnormality in cigarette smokers, the results must be interpreted with caution, for a single biopsy may be misleading owing to the focal nature of the lesions (Fox et al. 1981).

The morphologic changes of the respiratory mucosa in animals exposed to cigarette smoke for prolonged periods and in human cigarette smokers strongly suggests the presence of mucociliary dysfunction. This has been clearly demonstrated, particularly with respect to the production and clearance of mucus.

Cilia

Ciliary function after long-term cigarette smoke exposure has not been extensively studied. Iravani and Melville (1974) demonstrated a decrease in ciliary beat frequency in the airways of hamsters exposed to cigarette smoke for 1 year; however, in rats also exposed for 1 year under almost identical conditions, ciliary frequency was generally increased, although there were zones of ciliary inactivity or discoordination. A sustained inhibition of adenylate kinase activity in ciliated tracheal cells of hamsters exposed to cigarette smoke for up to 9 months has also been reported (Mattenheimer and Mohr 1975). Because inhibition of this enzyme leads to a decreased generation of adenosine triphosphate, the energy source of ciliary

bending, a decreased ciliary activity might be expected (Mattenheimer and Mohr 1975).

Mucus

Mucus hypersecretion has been clearly demonstrated in the airways of several animal species exposed to cigarette smoke for prolonged periods of time (Battista and Kensler 1970a; Iravani and Melville 1974). Rheologic measurements of airway mucus have not been reported in such animal experiments, but biochemical analysis has revealed the presence of serum proteins that might have cilioinhibitory effect (Dalhamn and Pira 1979; Battista 1980). Mucus hypersecretion may occur as early as 1 month after beginning a smoke inhalation equivalent to as little as one cigarette per day (Battista and Kensler 1970a). Rheologic and biochemical examinations of airway secretions in healthy smokers have not been carried out, primarily because these subjects do not have a productive cough. Once a smoker develops chronic productive cough, he or she is no longer considered healthy, but by definition, has chronic bronchitis.

Mucociliary Interaction

Long-term effects of cigarette smoke on airway mucociliary transport have been studied in different animal species. In purebred beagle dogs exposed to cigarette smoke (100 cigarettes per week) for 13.5 months via a mask that administered cigarette smoke through both the mouth and the nose for 1.5 hours twice daily, tracheal mucus transport rate was decreased to approximately 30 percent of that observed in control animals (Wanner et al. 1973). Pulmonary function did not differ significantly between the two groups. It has subsequently been shown that the abnormality in mucociliary transport in beagles may already be present after 6 months of cigarette smoke exposure (Park et al. 1977). An impairment of mucociliary clearance with long-term cigarette smoke exposure has also been demonstrated in rabbits, guinea pigs, rats, and chickens (Okajima 1971; Rylander 1971b; Iravani and Melville 1974; Battista and Kensler 1970a). In some of those experiments, impaired mucociliary clearance was already observed 4 weeks after the beginning of exposure.

The long-term effects of cigarette smoking on mucociliary function in human subjects has been investigated by aerosol clearance techniques and discrete marker transport techniques. Some of the investigators using radioactive aerosols demonstrated no abnormality of overall clearance in habitual cigarette smokers, particularly in those who already may have had symptoms of chronic bronchitis (Sanchiz et al. 1972; Yeates et al. 1975; Pavia et al. 1970; Pavia and Thomson 1970). However, the deposition of the inhaled radioactive

aerosol is more central in normal smokers and in patients with chronic bronchitis than in nonsmokers (Lippman et al. 1970). Because clearance is faster in central airways than in peripheral airways, this centralization of aerosol deposition may compensate for the overall decrease in mucociliary clearance. Investigations that have related mucociliary clearance to deposition pattern have generally found an impairment of mucociliary clearance in cigarette smokers (Lourenco et al. 1971; Camner et al. 1973a; Camner and Philipson 1972, 1974). Camner and Philipson (1972), in a study of 10 pairs of twins discordant for cigarette smoking, showed a significantly lower average clearance rate in smokers compared with nonsmokers; in 5 pairs clearance was slower in the smoker than in the nonsmoker, whereas in the remaining 5 pairs there was no difference. Analysis of regional clearance has produced further evidence that overall clearance of inhaled radioactive aerosols may fail to detect an abnormality in mucociliary clearance. Thus, Bohning and co-workers (1975) studied the deposition and clearance of 7 μm diameter particles in the tracheobronchial tree of six pairs of monozygotic twins, four of whom were discordant for cigarette smoking. They found comparable overall mucociliary clearance in the smoking and nonsmoking pairs, but more central deposition and slower central clearance in the smokers. Others have reported an impairment of peripheral mucociliary clearance and alveolar clearance as well (Matthys et al. 1983; Cohn et al. 1979).

Discrete particle techniques involving either bronchoscopy or radiography have been used to assess mucus transport in central airways, notably the trachea. Most investigators have reported a decrease of tracheal mucus velocity in healthy smokers, with values ranging between 20 percent and 80 percent of those of nonsmoking controls (Goodman et al. 1978; Toomes et al. 1981; Nakhosteen et al. 1982).

The bulk of the evidence indicates that long-term cigarette smoking alters mucociliary transport mechanisms and that these changes can occur as early as 1 year after smoking onset. Partial recovery of mucociliary transport has been observed in cigarette smokers after cessation for 3 months or more, but not after 1 week of cessation (Camner et al. 1973). These observations have also been supported by animal experiments (Albert et al. 1971).

Fractionation and Filtering of Cigarette Smoke

Whole cigarette smoke is composed of volatile elements and particulate matter, and it has become customary to distinguish between the gas phase and the particulate phase. The gas phase, by definition, consists of the components that remain after cigarette smoke has been "effectively" filtered by passing it through appropriate filters (Dalhamn 1966; Kensler and Battista 1963; Falk et al.

1959). The major constituents of the particulate phase are nicotine, phenols, hydrocarbons, aldehydes and ketones, organic acids, and alcohols. Although 95 percent of the gas phase (approximately 300 ml per cigarette) consists of combustion products and admixed air (nitrogen, oxygen, carbon dioxide, carbon monoxide) in concentrations that do not affect mucociliary transport, some trace gases are important (Battista et al. 1962). These include nitrogen dioxide, ammonia, cyanides, aldehydes, ketones, acrolein, and acids. As is shown below, some controversies still remain about whether the gas phase or the particulate phase of cigarette smoke is primarily responsible for its depressant effect on mucociliary activity. This problem is relevant when comparing the effects on mucociliary clearance of low tar versus high tar cigarettes, low nicotine versus high nicotine cigarettes, and filtered versus nonfiltered cigarettes.

Dalhamn (1966) reviewed the controversy over the separate effects of the gas and the particulate phases of cigarette smoke on mucociliary function. In protozoa, both phases of cigarette smoke have been shown to possess ciliotoxic properties (Kennedy and Elliott 1970). Falk and associates (1959) reported that exposure to whole cigarette smoke for 30 seconds resulted in a biphasic response, with an initial stimulation, followed by depression with a minimum value at about 15 minutes and a tendency toward recovery 45 minutes after exposure. Removal of the particulate matter in cigarette smoke by passing it through filters decreased its depressant effect on mucus transport, indicating that the major effect on mucociliary clearance was related to the particulate phase. Similar observations have been made by others (Rylander 1970; Falk et al. 1959). In contrast, Kensler and Battista (1963) incriminated the gas phase of cigarette smoke; they exposed strips of rabbit trachea to smoke from different cigarettes for 12 seconds and identified various gas phase constituents as having a depressant effect on mucus transport. These findings have also been confirmed by others in in vitro and in in vivo animal experiments (Kensler and Battista 1963; Hee and Guillerm 1973; Dalhamn 1956; Albert et al. 1974; Carson et al. 1966).

The most comprehensive study of individual gas and semivolatile constituents of cigarette smoke has been conducted by Petterson et al. (1982). Using chicken tracheal organ cultures, they showed that at a 5 mm concentration, 36 percent of 316 different compounds caused ciliostasis after 15 seconds of exposure, but 50 percent were without effect after an exposure time of 60 seconds. On the basis of this criterion of separation, either alkylated phenylethers, benzonitriles, benzaldehydes, benzenes, napthalenes and indoles, or α-saturated, β-unsaturated ketones and aldehydes, or aliphatic alcohols, aldehydes, acids, and nitrates were found to be ciliotoxic. Inactive compounds included benzoic acids, esters, polyaromatic hydrocar-

bons, amines, and N-heterocycles (except indoles). With respect to aldehydes, the time to ciliostasis on tissues of rabbit trachea has been reported shortest for formaldehyde, followed by acetaldehyde, acrolein, crotonaldehyde, and methacrolein. The ciliotoxic effects of aldehydes have been confirmed by others using different experimental approaches (Guillerm et al. 1968; Hee and Guillerm 1973; Kensler and Battista 1963). It has also been shown that acute acrolein inhalation causes denudation of ciliated cells, goblet cell discharge, exfoliation of surface epithelial cells, and infiltration of inflammatory cells in the lower airways of several different mammals (Dahlgren et al. 1972). Another volatile constituent of cigarette smoke with marked cilioinhibitory effects is hydrogen cyanide (Wynder et al. 1965a).

Weissbecker et al. (1971) used a different approach to assess the effects of several volatile cigarette smoke constituents on mucociliary transport in the cat trachea. The addition of individual volatile cigarette smoke components (isoprene, nitric oxide, and nitrogen dioxide) to carbon-filtered cigarette smoke either aggravated the impairment of tracheal mucus velocity produced by the filtered smoke or abolished the protection afforded by the carbon filter. When these constituents were added to whole cigarette smoke, no further impairment of mucus transport velocity was observed, indicating a saturation by whole cigarette smoke of receptors responsible for mucociliary depression.

A direct relation has been reported between tar content and the ciliotoxic effect of cigarette smoke (Dalhamn and Rylander 1967; Falk et al. 1959). However, Falk and associates (1959) found no difference between low tar and high tar cigarette residues with regard to in vitro mucociliary transport. The effects of nicotine on mucociliary transport are also controversial, although more investigators have demonstrated a lack of effect (Falk et al. 1959; Guillerm et al. 1972; Rakieten et al. 1952; Donnelly 1972) than a depression of mucociliary transport (Carson et al. 1966). Indeed, a biphasic dose-dependence has been suggested, with stimulation at lower concentrations and depression at higher concentrations (Tsuchiya and Kensler 1959). The stimulation of mucociliary function may be related to stimulation of nicotinic ganglionic receptors causing cholinergic ciliostimulation. This is based on the observation that the stimulating effect of nicotine-containing cigarettes on the metachronal wave frequency in the maxillary sinus of anesthetized rabbits is blocked by atropine and hexamethonium (Hybbinette 1982).

Among the different cigarette tobacco additives, menthol does not interfere with mucociliary transport (Rakieten et al. 1952). With respect to phenols, one investigator has reported that the ciliotoxicity of cigarette smoke produced by freeze-dried tobacco is the same as that produced by conventionally cured tobacco although the former

contains less phenol (Enzell et al. 1971). On the other hand, phenols have been shown to impair mucociliary activity and mucus transport both in vitro (Dalhamn and Lagerstedt 1966; Bernfeld et al. 1964; Dalhamn 1968) and in vivo (Dalhamn 1968). Dalhamn and associates (Dalhamn and Lagerstedt 1966; Dalhamn 1968) have even attempted to relate the toxicity of various phenols to their boiling points. Addition of the anti-inflammatory agents phenylvinyloxadiozole and phenylmethyloxadiozole to tobacco has been shown to reduce the ciliotoxicity of tobacco smoke (Dalhamn and Rylander 1971; Rylander 1971b; Dalhamn 1969), and treatment of rats undergoing long-term exposure to tobacco smoke with phenylmethyloxadiozole has been shown to protect the animals against the cigarette-smoke-induced increase in the number of goblet cells in the respiratory mucosa (Jones et al. 1973).

It can be concluded from these studies that both the particulate phase and the gaseous phase of cigarette smoke impair mucociliary function, that a large number of volatile components are ciliotoxic, that nicotine may or may not contribute to ciliotoxicity, and that the additive phenol is ciliotoxic, but the anti-inflammatory agents phenylmethyloxadiozole and phenylvinyloxadiozole afford partial protection against the deleterious effects of cigarette smoke. The mechanisms by which the various constituents of cigarette smoke interfere with mucociliary transport are unknown. On the basis of experiments in the fresh water mussel, it has been suggested that ciliotoxicity depends on their pH in solution (Wynder et al. 1963). It should be noted, however, that such in vitro experiments requiring an aqueous medium do not necessarily reflect the type of exposure occurring in smokers in whom contact between cigarette smoke and the ciliated epithelium is made by impingement or bypass.

Effects of Filters

Because the toxic effect of cigarette smoke on mucociliary transport mechanisms seems to reside both in the gas phase and in the particulate phase, the filtering of cigarette smoke before inhalation may be protective. It has been clearly shown that a longer exposure time is needed for ciliostasis to occur with smoke from filtered cigarettes than from unfiltered cigarettes, with respect to both ciliary activity in vitro and mucociliary transport in vivo (Dalhamn and Rylander 1964; Dalhamn 1964).

Four major types of filters have been evaluated: cellulose acetate (Cambridge filter), charcoal, glass fiber, and aqua. The histologic changes in the airways of guinea pigs exposed to unfiltered cigarette smoke for 4 to 8 weeks were not seen when cigarette smoke was passed through a Cambridge filter (Rylander 1974). Likewise, Kaminski and coworkers (1968) have shown that cellulose-acetate filters provide protection for the mucociliary activity in the cat

trachea. Similar results have been obtained in other experiments involving in vitro and in vivo systems (Dalhamn and Rylander 1968; Donnelly 1972; Wynder et al. 1965b), and cellulose-acetate filters have been found to reduce the inhibitory effect of cigarette smoke on tracheal epithelial adenylate kinase activity in hamsters exposed for 1 to 5 days (Mattenheimer and Mohr 1975). Charcoal filters are also capable of reducing the ciliotoxicity of cigarette smoke (Kaminski et al. 1968; Kensler and Battista 1963; Battista and Kensler 1970a, b). In one study involving cat tracheas, short-term exposure to a standardized dose of cigarette smoke decreased particle transport rates by 50 percent when unfiltered smoke was used, by 40 percent when the cigarette smoke was passed through a cellulose-acetate filter, and by 20 percent when a carbon-cellulose filter was used (Carson et al. 1966). In another comparison of different studies, a charcoal filter was more effective than a cellulose-acetate filter in reducing the metachronal wave frequency and mucus transport of the eulamellibranch gill in vitro (Wynder et al. 1965b). Glass-fiber and aqua filters were generally less effective (Isawa et al. 1980; Wynder et al. 1965b).

As expected, better protection might be provided by combined filters because they remove components of the particulate and the gaseous phase of cigarette smoke more effectively. Thus, a combination of cellulose-acetate and charcoal filter has been found to be more effective than either filter alone (Dalhamn 1966; Wynder et al. 1965b).

Mucociliary Function in Chronic Bronchitis

Since chronic bronchitis is defined clinically as chronic productive cough rather than by clearly defined morphologic or functional abnormalities (American Thoracic Society 1962), some of the previously reviewed studies of mucociliary function in cigarette smokers may have included patients with chronic bronchitis as well. Conversely, most patients with chronic bronchitis are cigarette smokers or have been cigarette smokers in the past. Although it is very difficult to separate the direct effects of cigarette smoke on mucociliary transport from those related to the pathophysiologic changes of chronic bronchitis, the discussion herein is limited to mucociliary function in chronic bronchitis without considering the direct effects of cigarette smoke on the mucosa.

The histologic changes of the mucociliary apparatus in chronic bronchitis include hypertrophy and hyperplasia of the submucosal glands, an increase in the number and distribution of goblet cells, and goblet cell metaplasia in smaller airways (Reid 1967). In addition, atrophy of the columnar epithelium (Wright and Stuart 1965) and spotty squamous metaplasia (Kleinerman and Boren 1974)

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have been reported. A decrease in both the number of ciliated cells and the mean ciliary length has been noted in the larger airways in patients with chronic bronchitis (Wanner 1977), and electron microscopic examinations of the airway epithelium show subtle abnormalities in bronchial biopsy material (Miskovitz et al. 1974). Auerbach and associates (1962), in a large post-mortem study of cigarette smokers, reported epithelial lesions with loss of cilia in up to 30 percent of random sections, compared with approximately 15 percent of sections from nonsmokers. These ultrastructural changes consisted of swelling and serration of the epithelium with transformation of the goblet cell granules. The capsule surrounding the cilia was irregular, with areas of breakage and outward projections; some cilia showed fibrillar degeneration or were fused to form compound cilia.

The presence of visible respiratory secretions is a frequent endoscopic finding in patients with chronic bronchitis, and increased amount of bronchial secretions can be seen on pathologic sections of the lung (Kleinerman and Boren 1974; Hogg et al. 1968). Thus, the morphologic changes of chronic bronchitis involve both the ciliary apparatus and the mucus-producing structures.

Cilia

In vitro examination of ciliated lower airway epithelial cells obtained from chronic bronchitis patients by brushing has failed to reveal an abnormality in beat frequency (Yager et al. 1980). However, in vitro study of ciliary function is of limited informative value since the ciliated cells are suspended in an artificial medium and are not exposed to their natural milieu. This may explain the discrepancy between this study and one reported by Iravani and Van As (1972), in which ciliary motion was observed in vivo with an incident light technique. In the carefully dissected tracheobronchial tree of rats with experimental chronic bronchitis, the ciliary system showed discoordination and zonal akinesia. In addition, reversals of transport direction, whirlpool formations, and inactive zones without ciliary motion as large as 2 mm by several hundred μm were seen.

Mucus

The distribution, amount, and rheologic properties of mucus within the airways have not been studied in chronic bronchitis, but extensive literature exists on the biochemistry (Boat and Mathews 1973) and rheology of expectorated sputum from patients with chronic bronchitis. These results must be interpreted with caution, partly because of contamination with saliva and the rapid physical alteration of expectorated sputum, and partly because normal respiratory secretions for comparison are virtually impossible to obtain. Mucoid sputum of patients with chronic bronchitis is

biochemically similar to sputum of normal subjects induced by hypertonic saline aerosol, with the exception of a slightly higher fucose and neuraminic acid content in the former (Lopata et al. 1974). In purulent sputum from these patients, biochemical changes typical of inflammatory conditions (increases in the dry weight and deoxyribonucleic acid content and increased cross-linking by hydrogen bonding) were observed. Reid (1968) showed that the neuraminic acid content of sputum is increased in chronic bronchitis, suggesting augmented secretion by the mucus-producing structures. This finding is supported by histochemical studies indicating distended acini of the submucosal glands in patients with chronic bronchitis compared with normal subjects, along with an increase in the volume of both the acid and the neutral mucopolysaccharide-producing acini (Reid 1968).

Impaired mucus transport in chronic bronchitis may, in part, be related to the rheologic abnormalities of respiratory secretions. Deviation from the ideal ratio between viscosity and elasticity may prevent an optimal interaction between cilia and mucus, thereby decreasing mucus transport rates (Dulfano and Adler 1975; Adler and Dulfano 1976). Higher values of sputum viscosity and lower values of sputum elasticity have been observed during exacerbations of chronic bronchitis than during clinical stability (Dulfano et al. 1971). In addition, purulent sputum has a higher viscosity than mucoid sputum (Charman and Reid 1972; Mitchell-Heggs et al. 1974), suggesting a relationship between the concentration of certain mucus constituents and mucus rheology. Indeed, examination of sputum obtained from patients with chronic bronchitis has shown positive correlations between protein content (particularly IgA) and mucus glycoprotein content on the one hand and viscosity on the other (Harbitz et al. 1980; Lopez-Vidriero and Reid 1978). That altered rheologic properties of airway secretions play a role in abnormal mucociliary clearance has been suggested by an observed relationship between in vivo mucociliary clearance, in vitro transportability of expectorated sputum (using the frog palate), and the viscoelastic properties of sputum (Puchelle et al. 1980).

Mucociliary Interaction

Mucus transport has been studied either by directly or indirectly observing the motion of discrete particles placed on the tracheal mucosa (Santa Cruz et al. 1974; Goodman et al. 1978) or by the deposition pattern and clearance rates of inhaled radioactive aerosols (Lourenco 1970; Camner et al. 1973a, b; Luchsinger et al. 1968; Patrick and Stirling 1977; Dulfano et al. 1971). In one study, a marked slacking of tracheal mucus velocity was found in 15 patients with chronic bronchitis who were between 57 and 71 years of age (Santa Cruz et al. 1974). Clinical examination and pulmonary

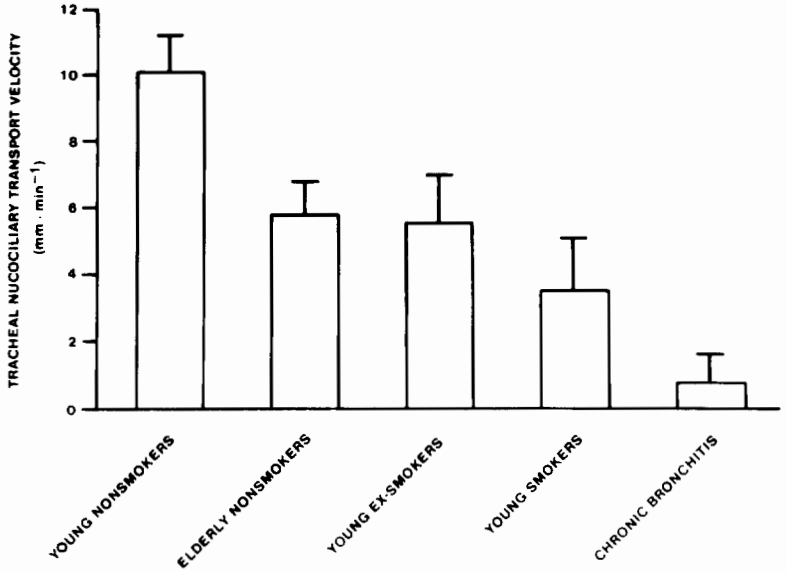

FIGURE 2.—Comparison of mean (S.E. in bracket) tracheal mucociliary transport velocity among young nonsmokers (n=10), elderly nonsmokers (n=7), healthy young ex-smokers (n=9), healthy young smokers (n=15), and patients with chronic bronchitis (n=14)

SOURCE: Goodman et al. (1978).

function tests diagnosed these patients as having both chronic bronchitis and emphysema. Mucociliary clearance of inhaled aerosols is also altered in patients with chronic bronchitis. The clearance of inhaled particles from the lung is influenced by the deposition pattern, which in turn depends on particle size and flow regime in the airways. Clearance rates, therefore, can be interpreted only if particle deposition is carefully monitored (Pircher et al. 1965; Lopez-Vidriero 1973). Coughing, which is difficult to control in such patients, may also contribute to the clearance of particles (Toigo et al. 1963). For these reasons, it is not surprising that mucociliary clearance has been reported to be increased (Muller et al. 1975; Luchsinger et al. 1968), normal (Thomson and Short 1969), or decreased (Lourenco 1970; Camner et al. 1973a, b; Tiogo et al. 1963; Mossberg and Camner 1980; Agnew et al. 1982) in patients with chronic bronchitis.

Once a subject has developed chronic bronchitis, cessation of smoking does not reverse the effect on mucociliary function, and a similar impairment of mucociliary transport has been reported in smokers and ex-smokers with this disorder (Agnew et al. 1982; Santa Cruz et al. 1974; Goodman et al. 1978). Persistence of mucociliary

dysfunction in patients with chronic bronchitis after cessation of smoking has also been reported in a small prospective study (Camner et al. 1973b).

Thus, both patients with chronic bronchitis and healthy smokers exhibit an impaired mucociliary function. However, the magnitude of the impairment is not the same as suggested by Goodman et al. (1978), who demonstrated a greater impairment of tracheal mucociliary transport rates in smokers and nonsmokers with chronic bronchitis than in healthy smokers (Figure 2).

The consequences of airway mucociliary dysfunction have not been satisfactorily examined, but may include increased susceptibility to respiratory infections, airflow obstruction by excessive airway secretions, and increased risk of carcinogenesis resulting from prolonged contact between inhaled carcinogens and the respiratory epithelium (Matthys et al. 1983; Hilding 1957; Moersch and McDonald 1953).

Summary and Conclusions

1. Increased numbers of inflammatory cells are found in the lungs of cigarette smokers. These cells include macrophages and, probably, neutrophils, both of which can release elastase in the lung.
2. Human neutrophil elastase produces emphysema when instilled into animal lungs.
3. Alpha$_1$-antiprotease inhibits the action of elastase, and a very small number of people with a homozygous deficiency of α_1-antiprotease are at increased risk of developing emphysema. The α_1-antiprotease activity has been shown to be reduced in the bronchoalveolar fluids obtained from cigarette smokers and from rats exposed to cigarette smoke.
4. The protease–antiprotease hypothesis suggests that emphysema results when there is excess elastase activity as the result of increased concentrations of inflammatory cells in the lung and of decreased levels of α_1-antiprotease secondary to oxidation by cigarette smoke.
5. Cigarette smokers have been shown to have a more rapid fall in antibody levels following immunization for influenza than nonsmokers. Whole cigarette smoke has been shown to depress the number of antibody-forming cells in the spleens of experimental animals.
6. Cigarette smoke produces structural and functional abnormalities in the airway mucociliary system.
7. Short-term exposure to cigarette smoke causes ciliostasis in vitro, but has inconsistent effects on mucociliary function in man. Long-term exposure to cigarette smoke consistently

causes an impairment of mucociliary clearance. This impairment is associated with epithelial lesions, mucus hypersecretion, and ciliary dysfunction.

8. Chronic bronchitis in smokers and ex-smokers is characterized by an impairment of mucociliary clearance.
9. Both the particulate phase and the gas phase of cigarette smoke are ciliotoxic.

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CHAPTER 6. LOW YIELD CIGARETTES AND THEIR ROLE IN CHRONIC OBSTRUCTIVE LUNG DISEASE

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CONTENTS

Introduction

Following the initial reports in the early 1950s linking cigarette smoke with lung cancer, the pathogenic role of cigarette tar content received considerable emphasis. Because the tar fraction of the smoke contained the bulk of the carcinogenic effect of whole smoke, and because lung cancer risk was closely related to other measures of total smoke exposure (number of cigarettes smoked per day, depth of inhalation, etc.), it was suggested that risk might be related to the amount of tar generated by different cigarettes. This prompted health authorities to advise smokers who were unable to quite smoking to switch to low tar cigarettes (U.S. Senate 1967; Health Department of the United Kingdom 1976). To facilitate this process, the Federal Trade Commission published smoking-machine assays of the tar and nicotine yield of different cigarette brands (Pillsbury et al. 1969). This approach to low tar and nicotine cigarettes was based on the assumption that smoking lower yielding brands, as determined by a smoking-machine, would result in a proportional reduction in the lung's exposure to these toxic substances. This approach to "safer" cigarette smoking has been promoted by the tobacco industry and apparently accepted by the smoking public, as evidenced by the escalation in sales of low tar and nicotine cigarettes. However, there is increasing evidence that this concept of a "less hazardous" cigarette is misleading; although definitive studies are still awaited, it appears that switching from regular to low tar and nicotine cigarettes may not substantially reduce the risk of chronic airflow obstruction.

Problems of Measurement by Machine

The first step in evaluating the relative health risks of different cigarettes is to establish some standardized measure of the toxic substances in different cigarettes in order to facilitate comparison. Quantifying each of the several thousand constituents of cigarette smoke for each brand of cigarette, and assessing the changes in these constituents as the manufacturing and agricultural processes change, would be a truly herculean task; therefore, a more modest goal of quantifying tar and nicotine yields was accepted. To date, the yields determined by the Federal Trade Commission have been the most widely adopted. These measurements are obtained with a laboratory smoking-machine, which consists of a syringe pump that takes a 35 ml bell-shaped puff from a cigarette, over a 2-second period, once per minute until a predetermined butt length is reached, either 23 mm for nonfiltered cigarettes or 3 mm longer than the filter overwrap for filter-tipped cigarettes (Pillsbury et al. 1969). These parameters are based on observations of smoking patterns in seven subjects in Europe in 1933 (Kozlowski 1983). Today's cigarette

is markedly different from that smoked in 1967 when these parameters were established, yet the same parameters are still employed.

Measurements obtained using these parameters indicate a marked reduction in the tar and nicotine yield of cigarettes over the last decade (Figure 1). In addition to the actual tar and nicotine yield of the tobacco, the yield measured by a smoking-machine is influenced by many factors, including cigarette length and diameter, porosity of the cigarette paper, presence of a ventilated or an unventilated filter, butt length, number of puffs, interpuff interval, puff volume, puff duration, puff pressure profile, and frequency of puffing at different stages of cigarette consumption. The number of puffs is important in determining the tar yield of a cigarette, and the number of puffs taken from some brands with the official smoking-machine has significantly declined in recent years (Kozlowski 1981). Since puffs are taken at 1-minute intervals, a more rapidly burning cigarette will have a smaller number of puffs. The burning time of the cigarette is determined by porosity of the cigarette paper, the amount of tobacco in the cigarette, and the diameter of the cigarette column. In a survey of Canadian cigarettes between 1969 and 1974, Kozlowski et al. (1980b) noted a significant reduction in the number of puffs taken in the official assays over this time period, which was strongly correlated with a reduction in tar yield. Omission of the last few puffs can markedly affect tar yield, because tar delivery increases with each puff, and the last few puffs from a cigarette can contain twice as much tar as the first few puffs (Wiley and Wickham 1974). Currently published yields do not indicate the number of puffs taken, which may range from 7 to 12 and may result in a marked variation of the tar yield.

Ventilated cigarette filters, which cause inhaled smoke to be diluted with air, are one of the major methods of achieving low tar yields (Gori and Lynch 1978). Cigarettes with ventilated filters constituted about 25 percent of all cigarette sales in the United States in 1979 (Hoffmann et al. 1980). During systematic interviews, Kozlowski et al. (1980a) found that from 32 to 69 percent of low tar smokers block these filter perforations with their fingers or lips, a feature unaccounted for by smoking-machines. This hole blocking increased the yield of toxic products by 59 to 293 percent.

If a person smokes a cigarette in a manner identical to the smoking-machine, the delivery of tar and nicotine to the mouth will be the same as that estimated by the machine. Human smoking patterns are diverse, however, and show considerable variation from the machine parameters; puff volumes range from less than 20 ml to more than 90 ml (Tobin and Sackner 1982), compared with the fixed 35 ml volume employed by the machine. Differences in puff profile from the bell-shaped puff used by the machine also alter cigarette

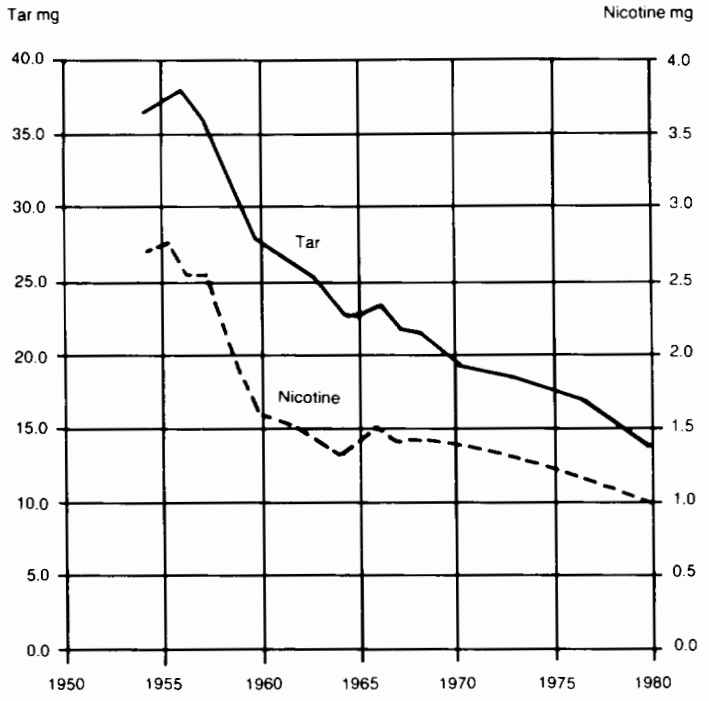

FIGURE 1.—U.S. sales-weighted average tar and nicotine yields

SOURCE: American Cancer Society (1981).

yield. Numerous studies indicate that smokers compensate for lower yielding cigarettes by altering their style of smoking. For each different cigarette brand, smokers may have a different smoking pattern. To provide more meaningful information, smoking-machines should be designed to reproduce variations in the manner of smoking each cigarette brand, and their assays should provide both an average and a range of tar and nicotine yields depending on the individual pattern of smoking (USDHHS 1981).

Many investigators have examined the relationship between the machine-determined nicotine yield of a cigarette and the concentration of nicotine or its metabolites in blood or urine. A fair correlation was observed in some studies (Goldfarb et al. 1976; Herning et al. 1983), but most studies have revealed a poor correlation (Russell et al. 1975, 1980; Sutton 1982; Feyerabend 1982; Benowitz et al. 1983). Machine-determined nicotine yield accounts for only from 4 (Russell et al. 1980) to 25 percent (Herning et al. 1983) of the variation in blood nicotine concentration, whereas 50 to 60 percent of the differences in blood nicotine levels are attributable to individual

smoking behavior. The overriding importance of the pattern of smoking in determining nicotine delivery from a cigarette was underlined in a recent study demonstrating that the nicotine content of the unburned tobacco was similar for cigarettes with high and low nicotine yields determined by smoking-machine assays (Benowitz et al. 1983).

The concept of providing the smoker with information on cigarette yield need not be abandoned. Smoking-machines can be designed to control the puff number, puff volume, puff pressure profile, puff duration, puff interval, butt length, position of the cigarette during and between puffs, and "restricted" or "free" smoking, i.e., whether the butt end is closed or open (Creighton and Lewis (1978a, b). These parameters should be determined and used to obtain an average and a range of yields for each brand. Measurement of cigarette yield should include assays not only of tar and nicotine but also of carbon monoxide and other toxic substances, because compensatory smoking behavior may alter the exposure to each substance beyond that expected on the basis of tar and nicotine delivery.

Effect of Low Tar and Nicotine Cigarettes on Cough and Phlegm Production and Development of Chronic Obstructive Lung Disease

Cigarette smokers account for the vast majority of deaths from chronic obstructive lung disease (COLD) (Peto et al. 1983), and the relative risk for the effects of smoking on mortality from COLD is even greater than that for lung cancer (see the chapter on Mortality in this Report). Chronic obstructive lung disease in smokers may take the following three forms: (1) cough and mucus hypersecretion, (2) airway obstruction, and (3) emphysema. Frequently the three components coexist, as all are related to cigarette smoking, but the agents in cigarette smoke responsible for each type of lung injury may be different. Over the past 25 years, considerable progress has been made in our understanding of the role of cigarette smoking in the pathogenesis and natural history of COLD, but most of the available data have not related lung function to cigarette yield.

Epidemiologic Studies

The cardinal importance of cigarette smoking in the pathogenesis of COLD has been repeatedly documented, and generally the severity of disease increases with increasing cigarette consumption (Ferris et al. 1976). Because of this dose–response relationship, it has been hoped that a reduction in cigarette yield by filtration or other means would reduce the risk of disease (Gori 1976). Available epidemiologic studies of the effect of low yield cigarettes on the development of COLD have shown variable results, which reflects

marked differences between the studies in terms of the population studied, sample size, variation in cigarette brands, reference period of the study, criteria of respiratory involvement, and type of statistical analysis, and whether the study was of a cross-sectional or a longitudinal design. Separating the studies by the three components of smoking-induced COLD indicates that there is a growing body of data on the effect of cigarette yield on the development of mucus hypersecretion and airway obstruction, but currently no information on the development of emphysema.

Several studies have examined the effect of cigarette yield on respiratory symptoms and have observed a relationship between reduction in cigarette yield and the prevalence of cough (Comstock et al. 1970; Freedman and Fletcher 1976; Fletcher et al. 1976; Dean et al. 1978; Schenker et al. 1982) and phlegm production (Comstock et al. 1970; Rimington 1972; Hawthorne and Fry 1978; Higenbottam et al. 1980b). Tar yield was not defined in some of these earlier studies (Comstock et al. 1970; Rimington 1972; Dean et al. 1978; Hawthorne and Fry 1978), but instead a comparison was made between smokers of plain cigarettes and smokers of filter-tipped cigarettes. The tar yield was specified in some studies: in the recent study by Schenker et al. (1982) it ranged from 0.4 to 28 mg; in the studies by Freedman and Fletcher (1976), from 17 to 20 mg; and in the studies by Higenbottam et al. (1980b), from 18 to more than 33 mg, higher than that observed in many of today's cigarettes. In a cross-sectional survey of over 18,000 men (Higenbottam et al. 1980b), the beneficial effect of low tar cigarettes on phlegm production was lost when subjects smoked 20 or more cigarettes per day, as their prevalence of phlegm production increased to that observed in higher tar cigarette smokers. In contrast, in another cross-sectional study of 5,686 women (Schenker et al. 1982), cigarette tar content was a significant risk factor for chronic cough and of borderline significance for phlegm production; this effect of cigarette tar content was independent of the number of cigarettes smoked per day. Chronic cough or phlegm production was approximately twice as common in smokers of high tar (at least 20 mg) cigarettes as it was in low tar (less than 10 mg) smokers. In the latter study, however, multiple logistic regression analysis indicated that the risk of chronic cough and phlegm production is more strongly affected by daily cigarette consumption than by tar content; these symptoms were 4.5 times more common in smokers of 25 or more cigarettes per day than in smokers of less than 15 cigarettes per day.

A small number of studies have examined the importance of cigarette yield on change in pulmonary function. In a prospective study of 680 men, Comstock et al. (1970) noted that smokers of plain cigarettes, compared with smokers of filter-tipped cigarettes, had a lower FEV_1 at entry into the study. Followup measurements showed

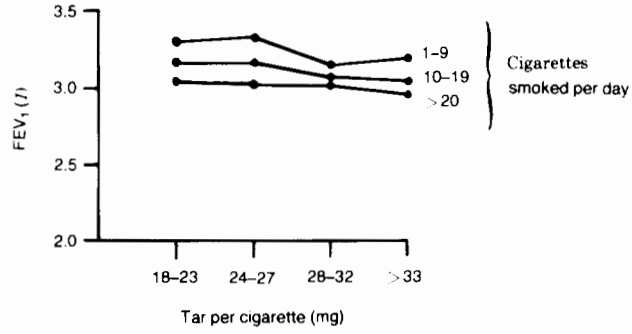

FIGURE 2.—Relationship between mean FEV_1 of asymptomatic smokers (adjusted for height and weight) and tar yield of cigarettes, by number of cigarettes smoked per day

SOURCE: Higenbottam et al. (1980b).

a greater mean reduction of FEV_1 in users of filter-tips, so that the reduction was similar in the two groups after 5 to 6 years of followup. Unfortunately, the variance of the data was not stated, and tests of statistical significance were not performed. In another longitudinal survey of 1,355 men, Sparrow et al. (1983) determined the effect of cigarette tar content, which ranged from less than 16 mg to more than 22 mg, on pulmonary function. Multiple regression analysis indicated that tar content did not significantly influence baseline spirometry or repeat measurements after 5 years of followup. Cross-sectional epidemiologic surveys also indicate no relationship between abnormal pulmonary function and the use of filter-tipped versus plain cigarettes (Beck et al. 1981) or cigarette tar content (Higenbottam et al. 1980b) (Figure 2).

Interpretation of these studies as evidence that cigarette tar and nicotine yield is not an important factor in the development of COLD is premature. First, cross-sectional studies are limited in their capability of defining the natural history of a disease. Second, COLD has a very slow progress, and Fletcher et al. (1976) suggest that a span of approximately 8 years is necessary to establish rates of change of spirometric values with sufficient confidence even to distinguish between smokers and nonsmokers. Third, we have no information on the baseline pulmonary function of smokers at the time they choose between high or low tar and nicotine cigarettes. Significant differences in pulmonary function have been observed between young adults who decide to smoke and those who avoid cigarette smoking (Tashkin et al. 1983), and it is possible that similar

function differences may exist in subjects who choose between high or low tar and nicotine cigarettes. Fourth, the yield of tar and nicotine used in many of these studies does not lie in the same range as that produced by many of today's cigarettes.

However, the possibility that cigarette tar content is related to the development of cough and phlegm, but not of dyspnea or airflow obstruction, is consistent with current concepts of COLD. In a study of 792 men followed over an 8-year period, Fletcher et al. (1976) observed that cigarette smokers were susceptible to two distinct chronic lung diseases—mucus hypersecretion and chronic airflow obstruction. This has recently been confirmed in a large prospective study (Peto et al. 1983) of 2,728 men, followed over 20 to 25 years, which showed that the risk of death from COLD was strongly correlated with initial degree of airflow obstruction, but bore no relationship to initial mucus hypersecretion.

Given the evidence that mucus hypersecretion may depend on the tar fraction of cigarette smoke, while development of airflow obstruction is more closely linked to the number of cigarettes smoked, Higenbottam et al. (1980b) reasoned that these differences might be due to a reduction in the particulate phase products, without a decrease in the gas phase products, in the low tar cigarettes. They hypothesized that tar droplets and soluble gases, such as sulfur dioxide and hydrogen cyanide, are more likely to be deposited or absorbed in the large airways where mucus is produced. The smaller airways, the earliest site of airflow obstruction, are exposed to a lower concentration of tar, but to a full concentration of insoluble gases such as nitrogen dioxide and ozone.

This line of reasoning is in agreement with several studies showing a reduction in lung cancer with the use of low tar and nicotine cigarettes (Wynder et al. 1970; Lee and Garfinkel 1981; Rimington 1981; Hammond et al. 1976). The tar fraction is the component of cigarette smoke particularly linked with the development of both lung cancer and mucus hypersecretion. Although clinicians have long linked chronic bronchitis (mucus hypersecretion) with emphysema, recent evidence indicates that mucus hypersecretion is not predictive of airflow obstruction, but is significantly greater in those smokers who develop lung cancer (Peto et al. 1983).

Mechanisms of Lung Damage

Studies of the mechanism of cigarette-smoke-induced lung damage have contributed significantly to the present understanding of COLD. Cigarette smoke may initiate and aggravate lung injury by a number of mechanisms and may also interfere with the lungs' defense responses.

These mechanisms include the protease-inhibitor imbalance theory for the pathogenesis of emphysema whereby alveolar wall

digestion results from an excess of proteases, a deficiency of their inhibitors, or a combination of both factors (see the chapter on Mechanisms in this Report). The sources of endogenous proteases include polymorphonuclear neutrophils and alveolar macrophages, both of which are found in increased number in the lungs of cigarette smokers. Protease release from both macrophages and neutrophils is increased in the presence of cigarette smoke (Rodriquez et al. 1977; Blue and Janoff 1978). In health, proteases are continually inhibited by α_1-antitrypsin, whereas proteases cause unimpeded digestion of lung tissue in patients with α_1-antitrypsin deficiency, with a markedly increased risk of emphysema. In addition to increasing the protease burden, cigarette smoke causes a functional inhibition of α_1-antitrypsin through the action of oxidants in cigarette smoke (Janoff et al. 1979).

The relative potency of smoke from cigarettes of varying tar and nicotine yields in stimulating protease production and release and in inhibiting α_1-antitrypsin has received scant scientific investigation. Travis et al. (1980) tested the effect of both filtered and unfiltered cigarette smoke on the elastase inhibitory activity of α_1-antitrypsin. Filtered smoke reduced elastase inhibitory activity by 3 percent, and a 19 percent reduction was observed with unfiltered smoke; the tar content of the respective smokes was not stated. The researchers reasoned that this small in vitro effect would be greatly magnified by in vivo conditions in the lung, particularly through its huge surface area. In addition to examining the effect of filters, Cohen and James (1982) recently examined the effect of tar and nicotine content on the elastase inhibitory capacity of α_1-antitrypsin. The oxidant capacity of cigarette smoke was also examined using a chromogenic electron donor. Aqueous condensates of cigarette smoke were obtained from a variety of brands ranging in tar content from about 1 mg to more than 20 mg. Reported tar and nicotine content correlated well with the amount of measured oxidants and the ability of a brand to reduce the elastase inhibitory capacity of α_1-antitrypsin. Filters were found to remove 73 percent of the oxidants from the aqueous smoke solutions. While these findings suggest that low tar and nicotine or filter-tipped cigarettes could reduce a smoker's predisposition to enzymatic lung damage and consequent COLD, it should be noted that neither study examined the effect of lower yield cigarettes on protease production. Morosco and Gueringer (1979) demonstrated a greater increase in elastase in dogs exposed to high nicotine cigarette smoke compared with low nicotine cigarette smoke. More important, these studies have not taken into account the compensatory changes in smoking pattern likely to result with lower yield cigarettes.

The airway response to acute exposure to cigarette smoke has been examined by several investigators employing spirometry (Da Silva and Hamosh 1981), body plethysmograph (Nadel and Comroe 1961),

and breathing pattern analysis (Tobin et al. 1982a). Airway narrowing has been consistently observed by some investigators (Nadel and Comroe 1961; Sterling 1967; Tobin et al. 1982a), but others report a variable response (Higenbottam et al. 1980a; Rees et al. 1982). In some studies, the acute airway response was unrelated to cigarette yield (Higenbottam et al. 1980a), but in most investigations (Robertson et al. 1969; Tobin et al. 1982a; Rees et al. 1982), smoking a low tar or filter-tipped cigarette induced less acute bronchoconstriction. The acute airway response is probably localized to the larger airways, as acute cigarette exposure resulted in no change in the nitrogen washout test of small airway function (Da Silva and Hamosh 1973; Tobin et al. 1982a). These observations on the relative bronchoconstrictor response of various types of cigarettes may be important in our understanding of why some smoking novitiates persist with the habit despite the initial unpleasant reactions (Tashkin et al. 1983), but it is unlikely that repeated episodes of smoking-induced acute airway narrowing finally result in COLD.

Future studies examining the mechanism of smoking-induced lung injury must not only take into account the range of cigarette yields, as determined by a smoking-machine, but also consider variations in smoking behavior. Puff volumes may vary considerably with nominal cigarette tar and nicotine content, thus altering the relative amount of various toxic substances yielded by different cigarettes. Similarly, inhalation profiles are of a diverse nature (Tobin et al. 1982b) and are likely to significantly alter the distribution, penetration, and retention of cigarette smoke constituents in the lungs.

Variation in Smoking Pattern With Switching to Low Tar and Nicotine Cigarettes

Low tar and nicotine cigarettes have gained considerable popularity among the smoking public, partly on the premise that a reduction in the nominal tar and nicotine yield results in a proportional reduction in the health hazards of cigarette smoking. The validity of this approach to cigarette smoking is contingent on the accuracy of smoking-machines in reflecting the actual manner of puffing and also on the smoker not altering smoking behavior to compensate for variations in nominal tar and nicotine content. Should smokers develop compensatory alterations in their smoking behavior, this would not only reduce the relevance of the smoking-machine assays but might also alter the proportionate delivery of the different toxic substances in cigarette smoke and expose the smoker to concentrations beyond those predicted by the smoking-machine.

Smoking Behavior

Nearly 40 years ago, Finnegan et al. (1945) studied the effect of alterations in cigarette nicotine content on smoking behavior and noted no change in cigarette consumption. It is only in the last decade, with the increasing popularity of low tar and nicotine cigarettes, however, that this question has attracted significant interest. The results of 38 studies examining alterations in smoking behavior with a reduction in cigarette yield are shown in Table 1. Considerable differences can be observed between the studies, partly reflecting variations in the level of cigarette yield reduction, alterations in other cigarette constituents, type and duration of switching procedure, parameters evaluated, and techniques used in their measurement.

Most studies agree that smokers rarely increase their daily cigarette consumption upon switching from higher to lower yield brands. Reports are almost equally divided as to whether a smoker increases the number of puffs per cigarette or shows no change on switching to a lower yielding brand. There is an almost unanimous consensus that smokers take a larger puff volume from a lower yielding brand. Studies of puff volume also indicate huge variation between individual subjects (Guillerm and Radziszewski 1978; Herning et al. 1981; Tobin and Sackner 1982; Herning et al. 1983) and that considerable increases in puff volume may occur on switching from a higher to a lower yielding brand, with certain subjects increasing their puff volume by up to 75 percent (Tobin and Sackner 1982). This compensatory increase in puff volume may be observed within a single experimental session (Tobin and Sackner 1982) and maintained over several weeks (Rawbone et al. 1978; Stepney 1981). Full compensation for a lower yielding cigarette is generally not achieved by smokers taking a large puff volume (Rawbone et al. 1978; Herning et al. 1981; Tobin and Sackner 1982).

Instrumentation is required to quantitatively assess the pattern of smoking, but it is important to realize that such instrumentation may, in itself, alter usual smoking behavior. Puff volume has been almost universally measured by using a specialized cigarette holder incorporating different flowmeter designs (Frith 1971; Adams 1977; Rawbone et al. 1978). These devices consist of two tubes connected to a pressure transducer that measures the pressure drop across a small resistance (a filter insert) in the holder; the flow measured is integrated to obtain volume. Use of a cigarette holder has been shown to increase the rate of puffing and puff volume, compared with measurements made with the cheek inductive plethysmography coil (Tobin and Sackner 1982).

Unlike the compensatory increases in puff volume, measurements of the subsequent inhalation volume—which includes the volume of smoke mixed with air inhaled into the lung—have shown no change

TABLE 1.—Effect of smoking low yield cigarettes on smoking pattern

First author	Reference year	Experimental design	Number of cigs smoked	Number of puffs/cig	Puff volume	Volume of inhalation	Duration of inhalation	CO parameters			Nicotine parameters		
								COHb	Expired CO	Relationship to nominal yield	Nicotine/cotinine level (blood/urine/saliva)	Mouth exposure index	Relationship to normal yield
Finnegan	1945	CS	NC										
Ashton	1970	VCF		↑								↑	Poor
Frith	1971	CS			↑								
Cohen	1971	CS						NC		Poor			
Russell	1973	CS	↑					↓		Good			
Turner	1974	CS						↓/NC		Poor			
Russell	1975	CS	↑								↓/NC		Poor
Goldfarb	1976	CS	↑								↓		Good
Forbes	1976	CS										↓	Good
Adams	1977	CS	NC	NC	NC								
Wald	1977	SVS						↑					
Sutton	1978	VCF	NC					↓		Poor	↓		Fair
Rawbone	1978	CS		NC	↑	NC						↓	Poor
Schulz	1978	CS	NC		↑								
Creighton	1978a,b	S			↑								
Adams	1978	CS		↑	↑								
Guillerm	1978	CS		↑	NC	NC		↑		Poor			
Jarvik	1978	CS	↑	↑									
Ashton	1979	CS	NC					↓		Poor	↓	↓	Poor
Garfinkel	1979	SVS	NC										
Hill	1980	CS						NC		Poor	↓		Good
Robinson	1980	SVS										↓	Good
Russell	1980	SVS									NC		Poor
Henningfield	1980	VCF	NC	↑				↑	NC				
Wald	1980	SVS						↑					

TABLE 1.—Continued

First author	Reference year	Experimental design	Number of cigs smoked	Number of puffs/cig	Puff volume	Volume of inhalation	Duration of inhalation	CO parameters			Nicotine parameters		
								COHb	Expired CO	Relationship to nominal yield	Nicotine/cotinine level (blood/urine/saliva)	Mouth exposure index	Relationship to normal yield
Herning	1981	CS		NC	↑				↑				
Wald	1981	SVS	NC					↑		Poor			
Stepney	1981	CS	NC	↑	↑				↓	Fair	↓	↓	
Jaffe	1981	SVS	NC/↑						NC	Poor			
Tobin	1982	CS		NC	↑	NC	NC						
Battig	1982	SVS	NC		↑				NC				Poor
Sutton	1982	SVS			↑					Good			
Griffiths	1981	CS		NC	↑								
Jaffe	1982	CS	NC/↑						NC	Poor			
Feyerabend	1982	SVS											Poor
Herning	1983	CS											Fair
Benowitz	1983	SVS											

NOTE: CS = controlled switching; VCF = variable cigarette filters; SVS = spontaneous voluntary switching; NC = no change; ↑ = increase; ↓ = decrease; CO = carbon monoxide.

on switching to a low yield cigarette. Likewise, in one short-term study (Tobin and Sackner 1982), duration of inhalation showed no relationship to nominal cigarette yield. Perhaps compensatory changes in inhalation parameters require a longer period of time than puff volume does.

Measurement of carboxyhemoglobin (COHb) concentration has been proposed as an index of the pattern of inhalation (Wald et al. 1975, 1978). While COHb provides valuable information on the amount of carbon monoxide absorbed from the lung during compensatory alterations in smoking behavior, it is an indirect index and provides complementary information on cigarette smoke inhalation rather than replacing direct measurements of the volume of inhalation.

Carbon Monoxide Uptake

Unlike tar and nicotine, which are present in the particulate phase, carbon monoxide (CO) is a constituent of the vapor phase of cigarette smoke. For this reason, cigarettes purported to produce a low tar and nicotine yield may not necessarily provide a lower yield of carbon monoxide. Compared with tar and nicotine yield, carbon monoxide yield is more dependent on cigarette design, including such features as paper porosity and perforations in the filter tips. These factors regulate the dilution of smoke with air and the burning profile of the cigarette, and thus can significantly reduce carbon monoxide yield. Wald (1976) showed that the carbon monoxide yield of filter-tipped cigarettes was 28 percent higher than that of plain cigarettes, although the average nicotine yield was lower in the filter-tipped cigarettes. He reasoned that smoke passing through a cigarette is diluted by air entering through the porous cigarette paper. However, the filter of filter-tipped cigarettes is surrounded by relatively nonporous paper, resulting in a higher content of carbon monoxide exiting from the proximal cigarette end. Perforations in the filter tip circumvent this problem and significantly reduce carbon monoxide yield (Hoffmann et al. 1980; Wald and Smith 1973).

Many investigators have measured COHb or carbon monoxide concentration in expired gas following cigarette smoking and compared the levels achieved in smoking brands with different nominal yields (see Table 1). An increase, decrease, or no change in carbon monoxide intake has been observed, depending on relative differences in cigarette design and experimental procedure. As expected, unventilated filter-tipped cigarettes produced higher COHb levels than those observed with unfiltered cigarettes (Wald et al. 1977). This is in agreement with information provided by smoking-machine assays (Wald et al. 1973), but the use of ventilated filter-tipped cigarettes may produce COHb levels similar to those observed with unfiltered cigarettes despite lower carbon monoxide

yields on smoking-machine assay (Wald et al. 1977). Comparison of cigarettes with a marked difference in nominal carbon monoxide yield usually results in a lower COHb level when the lower yielding brand is being smoked (Russell et al. 1973; Turner et al. 1974; Sutton et al. 1978; Ashton et al. 1979); but over the range of different carbon monoxide yields there is a poor correlation between levels of COHb and measured carbon monoxide yield. Similar information has been observed using expired carbon monoxide concentrations.

Nicotine Uptake

It has been long considered that nicotine might serve as a primary reinforcer of cigarette smoking and that smokers might adjust their smoking behavior to regulate their level of nicotine intake. Several investigators have measured the blood, urinary, or salivary levels of nicotine or its major metabolite cotinine during the smoking of cigarettes of varying nominal nicotine yields (see Table 1). A reduction in blood (Russell et al. 1975; Sutton et al. 1978; Ashton et al. 1979; Hill and Marquardt 1980) and urinary (Goldfarb et al. 1976; Ashton et al. 1979; Stepney 1981) nicotine levels or in plasma (Hill and Marquardt 1980; Stepney et al. 1981) and urinary (Ashton et al. 1979; Hill and Marquardt 1980) cotinine levels has generally been observed on switching to a cigarette with a lower nominal nicotine yield. However, smokers show variable degrees of compensation for the lower yield, as there is generally a poor relationship between nominal nicotine yield and measured blood nicotine levels (Russell et al. 1980; Sutton et al. 1982; Feyerabend et al. 1982; Benowitz et al. 1983).

Relating nominal nicotine yield and blood nicotine levels, Ashton et al. (1979) estimated that smokers compensated for about two-thirds of the difference in nominal yields when they switched from medium nicotine cigarettes to high or low nicotine brands. Using a stepwise multiple regression analysis of nicotine yield and blood nicotine concentration, Russell et al. (1980) observed a significant, but very weak, correlation ($r=0.21$) between the two measurements, but the nominal nicotine yield of the cigarettes accounted for only 4.4 percent of the variability in blood nicotine concentrations. The use of absolute rather than logarithmic analysis in this study has been criticized (Kozlowski et al. 1982; Herning et al. 1983), and the criticism involved the problems of trying to predict doses to individuals rather than the dose to groups. In another study using log-linear regression analysis (Herning et al. 1983), a better correlation was observed between nominal nicotine yield and the increasing blood nicotine after smoking ($r=0.5$), but this study used Kentucky reference cigarettes rather than commercial brands, and these low yield cigarettes have less nicotine in the unburned tobacco than commercial low yield brands. Such a relationship still accounted for

only 25 percent of the individual differences in blood nicotine levels, whereas 50 to 60 percent was accounted for by individual differences in smoking behavior (Herning et al. 1983).

Additional information on compensatory alterations in nicotine intake has been provided by studying the mouth exposure index, which is calculated from analysis of cigarette butts for nicotine content and a knowledge of the retention efficiency of the filter tip (Ashton and Watson 1970). Because the amount of nicotine retained by a filter is proportional to the amount that passes through, it is possible to estimate the amount of nicotine presented to the smoker from the nicotine content of the filter. Results using this index have revealed a greater variation between individual studies (see Table 1) than observed with blood nicotine measurements. This may be related to the fact that filter efficiency is usually determined by a machine, but retention of nicotine is also dependent on the way the cigarette is smoked; therefore, the retention efficiency of the filter may vary between smokers.

Role of Tar Content

The observations that smokers adapt their smoking behavior according to the nicotine delivery of a cigarette and that many of the toxic effects of smoking appear to be related to tar rather than nicotine content has led to the suggestion that altering the tar to nicotine ratio might produce a cigarette less hazardous to health (Russell 1976; Stepney 1981). A cigarette with a medium nicotine, low tar, and low carbon monoxide yield might be advantageous. While nicotine has been the component most extensively studied, it may not be the only substance responsible for the addictive power of tobacco. It is not possible to separate the effects of tar and nicotine in most studies, as their respective yields usually show a very close correlation.

Using research cigarettes providing three different yields of nicotine and two different yields of tar, Goldfarb et al. (1976) found evidence of compensation for nicotine but not for tar content. The authors urged cautious interpretation of the results because of the limited range of tar yields examined. Examining a large number of subjects smoking cigarettes of varying tar and nicotine yield, Wald et al. (1981) found that both tar and nicotine were significantly related to blood COHb, taken as an index of cigarette smoke inhalation. Two-way analysis of variance of the data indicated that after allowing for the effect of either tar or nicotine yield, the COHb index was no longer significantly influenced by the other. A cross-over study of medium tar smokers who were switched to low nicotine, low tar cigarettes and medium nicotine, low tar cigarettes has been reported by Stepney (1981). While the intake of carbon monoxide was least with the medium nicotine, low tar cigarette, the mouth exposure

index to tar was similar among the brands. Indeed, the pattern of smoking adopted by the subjects was more effective in reducing the difference in tar delivery between the cigarettes than in compensating for nicotine delivery. Further evidence indicating the importance of cigarette tar delivery in determining smoking behavior was reported by Sutton et al. (1982). Using multiple regression analysis, they observed that when nicotine yield was controlled, smokers of lower tar cigarettes had higher blood nicotine levels than smokers of higher tar cigarettes, indicating that they inhaled a greater volume of smoke. In contrast, when tar yield was controlled, smokers of lower nicotine cigarettes had lower blood nicotine concentrations than smokers of higher nicotine cigarettes, indicating that they inhaled less smoke. These results suggest some compensation for tar over and above any compensation for nicotine. It may be that nonpharmacologic, sensory stimulation by factors such as the flavor of cigarette smoke may be more important than nicotine in determining smoking behavior.

These new observations, especially on the role of tar delivery, require further investigation. Most published research consists of controlled switching experiments in which the subject smokes cigarettes of varying yields (see Table 1). Further studies of smoking behavior in subjects who have voluntarily chosen cigarettes of different yields are needed. The absence of an acceptable, palatable "standard" research cigarette continues to be an impediment to research in this area.

Variations in Pattern of Cigarette Smoke Inhalation

While cigarette smoking is the single most important factor in the development of COLD, the majority of smokers never develop clinically significant airflow obstruction (Fletcher et al. 1976). Despite the clear dose–response relationship between number of cigarettes smoked and death from COLD, attempts at identifying the individual susceptible smoker on the basis of number of cigarettes smoked have had very limited success.

Another approach to identifying the susceptible smoker is to study the manner of smoking, as this is probably a major determinant of the lung's exposure to cigarette smoke. Cigarette smoking consists of two phases: initially, the smoker takes a puff into the mouth, and after a variable 1 to 4 second pause, the smoke mixed with air is inhaled into the lungs (Rawbone et al. 1978; Higenbottam et al. 1980a; Tobin and Sackner 1982). Individual differences in the pattern of cigarette smoking such as the size of the puff volume, the duration of holding the smoke in the oral cavity before inhalation, and the depth and duration of inhalation are among the important factors determining the relative concentration of smoke constituents

that reach the lung. Despite its significance in determining the distribution and deposition of cigarette smoke, the mode of inhalation following the puff has received scant scientific investigation.

A number of epidemiologic studies have examined the relationship between cigarette smoke inhalation, based on the smoker's subjective estimation, and the severity of pulmonary disease. Results of these studies are conflicting; some investigators reported an association between smoke inhalation and the presence of mucus hypersecretion (Rimington 1974; Schenker et al. 1982; Dean et al. 1978) and decline in pulmonary function (Ferris et al. 1976; Bosse et al. 1975), and others observed no relationship between inhalation and pulmonary dysfunction (Beck et al. 1981; Schenker et al. 1982). The inconsistencies in these epidemiologic studies may be due to the smokers' inability to accurately describe their inhalation pattern.

There are three reports of the relationship between subjective estimations of cigarette smoke inhalation and direct objective measurement. Rawbone et al. (1978) found that the rating on a visual analog scale was a good predictor of inhalation volume ($r=0.65$). Conversely, Tobin et al. (1982a) noted no relationship between inhalation volume and the smoker's perception of depth of inhalation, indicated on a visual analog scale ($r=0.04$); a similar finding was reported by Adams et al. (1983) ($r=0.04$). Standardizing the inhaled volume for vital capacity did not improve the relationship. Other investigators using measurements of COHb observed a weak relationship between self-estimated inhalation and COHb concentration (Stepney 1982; Wald et al. 1978). Measurements of COHb reflect the amount of cigarette smoke absorbed by the lung. In addition to being affected by the depth of inhalation, COHb concentration is influenced by the varying carbon monoxide yields of different cigarettes, the number of puffs per cigarette, puff volume, pulmonary function—particularly diffusing capacity and alveolar ventilation—and hemoglobin concentration (Wald et al. 1978; Rickert et al. 1980). Therefore, it yields valuable complementary information, but it does not provide a direct measure of the pattern of inhalation (Tobin et al. 1982a; Guyatt et al. 1983).

Direct measurements of the pattern of cigarette smoke inhalation have been reported for a small number of smokers. Initially, the puff from the cigarette is taken into the mouth, and after a variable pause of 1 to 4 seconds, it is inhaled into the lungs (Rawbone et al. 1978; Higenbottam et al. 1980a; Tobin and Sackner 1982; Tobin et al. 1982a; Adams et al. 1983). Higenbottam et al. (1980a) reasoned that this pause, while holding the smoke in the mouth, minimized the irritant qualities of cigarette smoke. In a group of five subjects who were requested to inhale smoke directly into their lungs, without an intervening pause in the mouth, consistent acute airway narrowing was observed. In contrast, smokers adopting the usual two-phase

smoking pattern showed a variable airway response. The authors suggested that buccal absorption of water-soluble compounds, such as sulfur dioxide and acrolein, together with precipitation of tar, minimized the irritating qualities of cigarette smoke. They observed no relationship between the acute airway response and amount of smoke inhaled in the regular two-phase smokers, although there appeared to be a relationship in those directly inhaling smoke into their lungs. However, there is a marked discrepancy in the inhalation volumes reported in this study compared with the values reported in other studies of cigarette smoke inhalation, probably due to the inaccuracy of the magnetometers employed for the measurements; therefore, a statement regarding the relationship between depth of smoke inhalation and the acute airway response may be misleading.

The report that acute airway narrowing is uncommon after cigarette smoking is in disagreement with the findings of several investigators who have observed bronchoconstriction to be a common phenomenon after acute smoke exposure (Nadel and Comroe 1961; Sterling 1967; Da Silva and Hamosh 1981; Tobin et al. 1982a); however, it is certainly plausible that the response is greater in smokers who inhale smoke directly into the lungs than in two-phase smokers. The frequency of direct inhalation of cigarette smoke into the lungs is unknown. In a small study of 10 smokers, Tobin and Sackner (1982) observed 1 subject who showed an approximately 50 ml expansion of the abdominal compartment simultaneously with taking the puff from the cigarette.

Adams et al. (1983) studied the relationship between puffing, cigarette smoke inhalation, and partitioning of airflow between the nose and mouth in 10 smokers. After taking the puff into the mouth, two subjects actively exhaled 80 ml and 200 ml volumes, respectively, before the subsequent inhalation. In this situation, the volumes of smoke might be expelled from the mouth, and little, if any, would be available for subsequent inhalation into the lungs. The frequency of this smoking pattern was not given, but another report from the same laboratory (Rawbone et al. 1978) indicated that it was uncommon. There was marked intersubject variation in the partitioning of airflow between the nose and mouth during smoking, with four subjects inhaling almost exclusively through the mouth, four inhaling predominantly through the nose, and the other two demonstrating both patterns of inhalation. The importance of factors in determining whether cigarette smoke is inhaled as a bolus followed by a subsequent "chaser" of air or is evenly distributed throughout the inhaled volume of air remains to be determined.

Considerable discrepancies exist between published reports of the volume of air mixed with smoke that is inhaled into the lungs, with reported mean inhalation volumes of 34 to 152 ml (Higenbottam et

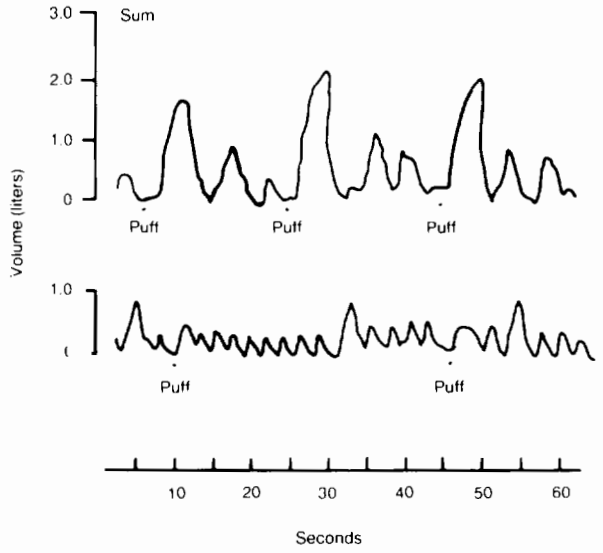

FIGURE 3.—Pattern of inhalation of cigarette smoke mixed with air, in two smokers

SOURCE: Modified from Tobin et al. (1982b).

al. 1980a), 450 to 485 ml (Guillerm and Radziszewski 1978), 389 to 1,136 ml (Adams et al. 1983), 750 to 2,000 ml (Rawbone et al. 1978), and 170 to 1,970 ml (Tobin et al. 1982b). A major factor in the discrepancies between these studies is probably the inaccuracies inherent in some of the methods employed in the measurements, as discussed by Tobin and Sackner (1982). When inhalation volumes are standardized for body size by relating them to vital capacity, marked interindividual variation is still observed (Figure 3), with inhalational volumes ranging from 9 to 47 percent of the vital capacity and a group mean value of 20 percent (Tobin et al. 1982b). Smokers show considerable variation in inhaled volumes while smoking a single cigarette. The volume of inhalation bears no relationship to cigarette consumption in terms of pack-years (Tobin et al. 1982b). Similarly, duration of inhalation shows considerable variation between subjects, with mean individual values ranging from 1.7 to 7.3 seconds (Adams et al. 1983; Tobin et al. 1982b). Repeat measurements at intervals of up to 10 months apart indicate that individual subjects tend to maintain a fairly constant inhalation volume, duration of inhalation, and associated breathhold time (Tobin et al. 1982b; Adams et al. 1983).

The pattern of cigarette smoking shows a wide degree of intersubject variability, including differences in the number of puffs, puff volume, holding pause in the mouth, exhalation of smoke from the mouth before inhalation, partitioning of airflow between the nose and mouth, and volume and duration of inhalation. Given this degree of variation, it is not surprising that smokers might show wide differences in their individual susceptibilities to lung injury. In a study relating inhalation volume—standardized for vital capacity—to the time-volume and flow-volume components of a forced vital capacity maneuver, no significant correlation was observed (Tobin et al. 1982b). Although this lack of a relationship might be interpreted as indicating that the pattern of smoking is unimportant in the development of lung disease, it may also reflect the fact that pulmonary function was normal or near normal in the majority of subjects and that the study was of a cross-sectional design.

Use of Additives in Low Tar and Nicotine Cigarettes

The nominal tar and nicotine yield of cigarettes has continually decreased since the time of the initial reports linking smoking with lung cancer (USDHHS 1981). In 1954, the average tar yield per cigarette was 38 mg, and in 1980 it was less than 14 mg. Initially, tar reduction was achieved by decreasing the cigarette tobacco content or removing tar by smoke filtration, both of which probably resulted in a lower smoke exposure. Since 1971, the reduction in tar yield has exceeded the relative reduction in the weight of tobacco per cigarette; this difference has increased since 1975 (USDHHS 1981). Manufacturing technology has progressed beyond simple reduction in tobacco content: the yield and composition of smoke can be modified by genetic modification of the tobacco leaf (Tso 1972a), changes in its cultivation and processing (Tso 1972b), changes in the porosity of cigarette paper, and alterations in filter design (Kozlowski et al. 1980b).

When initially introduced, lower yield cigarettes lacked palatability and acceptability. Advertisements for the current low tar and nicotine cigarettes emphasize their flavor, presumably achieved by the use of additives in the processing of the tobacco. Additives employed may include artificial tobacco substitutes (Freedman and Fletcher 1976), flavor extracts of tobacco and other plants, exogenous enzymes, powdered cocoa (Gori 1977), and other synthetic flavoring substances. Perhaps more additives are being used in the new lower tar and nicotine cigarettes than in the older brands, and new agents may also be in use. Some of the substances, such as powdered cocoa, have been shown to further increase the carcinogenicity of tar (Gori 1977), and others may result in increased or new and different health risks. The pyrolytic products of these additive agents may

produce novel toxic constituents. A characterization of the chemical composition and adverse biologic potential of these additives is urgently required, but is currently impossible because cigarette companies are not required to reveal what additives they employ in the manufacture of tobacco (USDHHS 1981). No government agency is empowered with supervisory authority in the manufacture of tobacco products. With this lack of basic information and the usually prolonged latent period before manifestation of the adverse effects of smoking, it is likely that a long time period will elapse before we know the hazards of the new cigarettes in current use.

Research Recommendations

1. Longitudinal epidemiologic studies are needed to determine the risk for pulmonary symptoms and dysfunction in smokers of cigarettes with the low tar and nicotine yields found in currently popular brands.
2. Further research is needed to determine the relative potency of high and low tar and nicotine cigarettes in inducing elastase release and producing functional inhibition of α_1-antitrypsin activity.
3. Development of an animal model of cigarette-smoke-induced emphysema would be advantageous in determining the relative risk of lung injury of cigarettes of different composition.
4. More information is required on the smoking behavior of smokers who have voluntarily switched from high to low tar and nicotine cigarettes.
5. The role of cigarette tar, as opposed to nicotine content, in determining smoking behavior needs to be defined.
6. Standard research cigarettes of varying tar and nicotine contents that are palatable and acceptable to smokers need to be developed.
7. The role of variation in smoking behavior in determining susceptibility to lung injury needs to be defined. Studies are required to determine the effect of smoking patterns on the distribution and penetration of the smoke aerosol into the lung.
8. More information is needed on the composition and adverse biologic effects of flavor additives in cigarettes and their pyrolytic products.

Summary and Conclusions

1. The recommendation for those who cannot quit to switch to smoking cigarette brands with low tar and nicotine yields, as determined by a smoking-machine, is based on the assumption that this switch will result in a reduction in the exposure of the

lung to these toxic substances. The design of the cigarette has markedly changed in recent years, and this may have resulted in machine-measured tar and nicotine yields that do not reflect the real dose to the smoker.

2. Smoking-machines that take into account compensatory changes in smoking behavior are needed. The assays could provide both an average and a range of tar and nicotine yields produced by different individual patterns of smoking.
3. Although a reduction in cigarette tar content appears to reduce the risk of cough and mucus hypersecretion, the risk of shortness of breath and airflow obstruction may not be reduced. Evidence is unavailable on the relative risks of developing COLD consequent to smoking cigarettes with the very low tar and nicotine yields of current and recently marketed brands.
4. Smokers who switch from higher to lower yield cigarettes show compensatory changes in smoking behavior: the number of puffs per cigarette is variably increased and puff volume is almost universally increased, although the number of cigarettes smoked per day and inhalation volume are generally unchanged. Full compensation of dose for cigarettes with lower yields is generally not achieved.
5. Nicotine has long been regarded as the primary reinforcer of cigarette smoking, but tar content may also be important in determining smoking behavior.
6. Depth and duration of inhalation are among the most important factors in determining the relative concentration of smoke constituents that reach the lung. Considerable interindividual variation exists between smokers with respect to the volume and duration of inhalation. This variation is likely to be an important factor in determining the varying susceptibility of smokers to the development of lung disease.
7. Production of low tar and nicotine cigarettes has progressed beyond simple reduction in tobacco content. Additives such as artificial tobacco substitutes and flavoring extracts have been used. The identity, chemical composition, and adverse biological potential of these additives are unknown at present.

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CHAPTER 7. PASSIVE SMOKING

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CONTENTS

Introduction

This chapter explores recent data that relate involuntary cigarette smoke exposure to the occurrence of physiologic changes, symptoms, and diseases in nonsmoking adults and children. Health effects related to fetal exposure in utero, a subject that has been extensively studied, are not discussed, although instances where such exposure may relate to potential development are pointed out. The interested reader is referred to several excellent recent reviews for a more complete treatment of this issue (USDHEW 1979; USDHHS 1980; Abel 1980; Weinberger and Weiss 1981).

Differences in Composition of Sidestream Smoke and Mainstream Smoke

Involuntary (passive) smoking is defined as the exposure of nonsmokers to tobacco combustion products from the smoking of others. Analysis of the health effects of passive smoking requires not only some knowledge of the constituents of tobacco smoke, but also some quantitation of tobacco smoke exposure. Tobacco smoke in the environment is derived from two sources: mainstream smoke and sidestream smoke. Mainstream smoke emerges into the environment after having first been drawn through the cigarette, which filters some of the active constituents. The smoke is then filtered by the smoker's own lungs, and exhaled. Sidestream smoke arises from the burning end of the cigarette and enters directly into the environment. Differences in the temperature of combustion, the degree of filtration, and the amount of tobacco consumed all lead to marked differences in the concentration of the constituents of mainstream smoke and sidestream smoke (USDHEW 1979; Sterling et al. 1982; Brunneman et al. 1978; National Academy of Sciences 1981; Rylander et al. 1984). Many potentially toxic gas phase constituents are present in higher concentration in sidestream smoke than in mainstream smoke (Brunneman et al. 1978) (Table 1), and nearly 85 percent of the smoke in a room results from sidestream smoke. Smaller amounts of smoke are contributed to the environment from the nonburning end of the cigarette by diffusion through the paper wrapping and by the smoke exhaled by the smoker. Therefore, both active and passive smokers may be similarly exposed to sidestream smoke. Mainstream smoke is inhaled directly into the lungs and is diluted only by the volume of air breathed in by the smoker when he or she inhales. Sidestream smoke is generally diluted in a considerably larger volume of air. Thus, passive smokers are subjected to a quantitatively smaller and qualitatively different smoke exposure than active smokers. The quantification of the exposure of a passive smoker to these sidestream smoke constituents is often difficult. Factors such as the type and number of cigarettes burned, the size of

the room, the ventilation rate, and the smoke residence time are all important variables in determining levels of exposure. Thus, no single variable accurately characterizes exposure to smoke constituents.

Repace and Lowrey (1980, 1982, 1983) have shown that, to a reasonable approximation, exposure to the particulate phase is predicted by the ratio of the smoker density to the effective ventilation rate of the area in which the smokers are located.

Measurement of Exposure

Levels of indoor byproducts of tobacco smoke, with measurements made under realistic exposure conditions, are presented in Table 2. Among the constituents that have been measured, nitrogen oxide, carbon monoxide, nicotine and respirable particulates, nitrosamines, and aldehydes have been shown to be significantly elevated indoors as a result of cigarette smoking. Nitrogen oxide is rapidly oxidized to nitrogen dioxide (NO_2) in air, and reaches equilibrium with outdoor levels of NO_2, provided there are suitable air exchange rates and no other indoor sources, such as a gas stove. The particulate concentration indoors clearly increases with increasing numbers of smokers, although the background level is determined by the outdoor level. The conclusions from the few studies that actually measure ventilation rates during exposure suggest that under "normal" air circulation conditions, carbon monoxide (CO) levels will be relatively low, but still may exceed the ambient air quality standard of 9 ppm (NIOSH 1971). However, even modest reductions in ventilation rates can lead to CO accumulation.

A variety of measures have been utilized to quantify the nonsmoker's exposure to tobacco smoke. No single measure has been uniformly accepted as characterizing the level of smoke. Nicotine is the most tobacco-specific of these measures, but it is relatively complicated and expensive to measure and settles out of the air with the particulate phase, making it a poor measure of gas phase constituents. In addition, nicotine may rapidly deposit on surfaces and subsequently evaporate into the environment (Rylander et al. 1984), making it a poor measure of acute smoke exposure levels. Measurements of total particulate matter are a broader measure of smoke exposure, particularly if the measurements are limited to particles in the respirable range and to environments without other major sources of respirable particles. The smoke particles also settle out of the air and therefore may not reflect the levels of gas phase constituents, and a wide variety of other dusts may contribute particulates to the air, particularly in the occupational setting. A number of authors have measured levels of CO. This measurement is relatively simple and a measure of absorption (carboxyhemoglobin)

TABLE 1.—Ratio of selected constituents in sidestream smoke (SS) to mainstream smoke (MS)

Gas phase constituents	MS	SS/MS ratio	Particulate phase constituents	MS	SS/MS ratio
Carbon dioxide	20–60 mg	8.1	Tar	1–40 mg	1.3
Carbon monoxide	10–20 mg	2.5	Water	1–4 mg	2.4
Methane	1.3 mg	3.1	Toluene	108 μg	5.6
Acetylene	27 μg	0.8	Phenol	20–150 μg	2.6
Ammonia	80 μg	73.0	Methylnaphthalene	2.2 μg	28
Hydrogen cyanide	430 μg	0.25	Pyrene	50–200 μg	3.6
Methylfuran	20 μg	3.4	Benzo[a]pyrene	20–40 μg	3.4
Acetonitrile	120 μg	3.9	Aniline	360 μg	30
Pyridine	32 μg	10.0	Nicotine	1.0–2.5 mg	2.7
Dimethylnitrosamine	10–65 μg	52.0	2-Naphthylamine	2 ng	39

Adapted from U.S. Department of Health, Education, and Welfare (*1979*).

TABLE 2a.—Acrolein measured under realistic conditions

Study	Type of premises	Occupancy	Ventilation	Monitoring conditions	Levels	
					Mean	Range
Badre et al.	Cafes	Varied	Not given	100 mL samples		0.03–0.10 mg/m³
(*1978*)	Room	18 smokers	Not given	100 mL samples	0.185 mg/m³	
	Hospital lobby	12 to 30 smokers	Not given	100 mL samples	0.02 mg/m³	
	2 train compartments	2 to 3 smokers	Not given	100 mL samples		0.02–0.12 mg/m³
	Car	3 smokers	Natural, open	100 mL samples	0.03 mg/m³	
		2 smokers	Natural, closed	100 mL samples	0.30 mg/m³	
Fischer et al.	Restaurant	50–80/470 m³	Mechanical	27 × 30 min samples	7 ppb	
(*1978*) and	Restaurant	60–100/440 m³	Natural	29 × 30 min samples	8 ppb	
Weber et al.	Bar	30–40/50 m³	Natural, open	28 × 30 min samples	10 ppb	
(*1979*)	Cafeteria	80–150/574 m³	11 changes/hr	24 × 30 min samples	6 ppb (5 ppb nonsmoking section)	

TABLE 2b.—Aromatic hydrocarbons measured under realistic conditions

Study	Type of premises	Occupancy	Ventilation	Monitoring conditions	Levels		Nonsmoking controls	
					Mean	Range	Mean	Range
					Benzene (mg/m³)			
Badre et al. (*1978*)	Cafes	Varied	Not given	100 mL samples		0.05–0.15		
	Room	18 smokers	Not given	100 mL samples	0.109			
	Train compartments	2 to 3 smokers	Not given	100 mL samples		0.02–0.10		
	Car	3 smokers	Natural, open	100 mL samples	0.04			
		2 smokers	Natural, closed	100 mL samples	0.15			
					Toulene (mg/m³)			
	Cafes	Varied	Not given	100 mL samples		0.04–1.04		
	Room	18 smokers	Not given	100 mL samples	0.215			
	Train compartments	2 to 3 smokers	Not given	100 mL samples	1.87			
	Car	2 smokers	Natural, closed	100 mL samples	0.50			
					Benzo[a]pyrene (ng/m³)			
Elliott and Rowe (*1975*)	Arena	8,647–10,786 people	Mechanical	Not given	7.1			
		12,000–12,844 people	Mechanical	Not given	9.9			
		13,000–14,277 people	Mechanical	Not given	21.7			
				Separate non-activity days			0.69	
Galuskinova (*1964*)	Restaurant	Not given	Not given	20 days in summer 18 days in the fall	6.2	28.2–144		

TABLE 2b.—Continued

Study	Type of premises	Occupancy	Ventilation	Monitoring conditions	Levels		Nonsmoking controls	
					Mean	Range	Mean	Range
Just et al. (*1972*)	Coffee houses	Not given	Not given	6 hr continuous	0.25–10.1		4.0–9.3 (outdoors)	
					Benzo[e]pyrene (ng/m³)			
					3.3–23.4		3.0–5.1 (outdoors)	
					Benzo[ghi]perylene (ng/m³)			
					5.9–10.5		6.9–13.8 (outdoors)	
					Perylene (ng/m³)			
					0.7–1.3		0.1–1.7 (outdoors)	
					Pyrene (ng/m³)			
					4.1–9.4		2.8–7.0 (outdoors)	
					Anthanthrene (ng/m³)			
					0.5–1.9		0.5–1.8 (outdoors)	
					Coronene (ng/m³)			
					0.5–1.2		1.0–2.8	
					Phenols (μ/m³)			
					7.4–11.5			
					Benzo[a]pyrene (ng/m³)			
Perry (*1973*)[a]	14 public places	Not given	Not given	Samples, 5 outdoor locations	<20–760			<20–43

[a] The correctness of the data is doubtful (Grimmer et al. 1977).

TABLE 2c.—Carbon monoxide measured under realistic conditions

Study	Type of premises	Occupancy	Ventilation	Monitoring conditions	Levels (ppm)		Nonsmoking controls (ppm)	
					Mean	Range	Mean	Range
Badre et al. (*1978*)	6 cafes	Varied	Not given	20 min samples		2–23	(outdoors)	0–15
	Room	18 smokers	Not given	20 min samples	50		0 (outdoors)	
	Hospital lobby	12 to 30 smokers	Not given	20 min samples	5			
	2 train compartments	2 to 3 smokers	Not given	20 min samples		4–5		
	Car	3 smokers	Natural, open	20 min samples	14		0 (outdoors)	
		2 smokers	Natural, closed	20 min samples	20		0 (outdoors)	
Cano et al. (*1970*)	Submarines 66 m^3	157 cigarettes per day	Yes		< 40 ppm			
		94–103 cigarettes per day	Yes		< 40 ppm			
Chappell and Parker (*1977*)	10 offices	Not given	Values not given	17 × 2–3 min samples	2.5 ± 1.0	1.5–4.5	2.5 ± 1.0 (outdoors)	1.5–4.5
	15 restaurants	Not given	Values not given	17 × 2–3 min samples	4.0 ± 2.5	1.0–9.5	2.5 ± 1.5 (outdoors)	1.0–5.0
	14 nightclubs and taverns	Not given	Values not given	19 × 2–3 min samples	13.0 ± 7.0	3.0–29.0	3.0 ± 2.0 (outdoors)	1.0–5.0
	Tavern	Not given	Artificial	16 × 2–3 min samples	8.5			
			None	2 × 2–3 min samples		35 (peak)		
	Office[a]	1440 ft^3	Natural, open	2–3 min samples 30 min after smoking	1.0	10.0 (peak)		

TABLE 2c.—Continued

Study	Type of premises	Occupancy	Ventilation	Monitoring conditions	Levels (ppm)		Nonsmoking controls (ppm)	
					Mean	Range	Mean	Range
Coburn et al. (*1965*)	Rooms	Not given	Not given	Not given		4.3–9.0		
				Nonsmokers' rooms			2.2 ± 0.98	0.4–4.5
Cuddeback et al. (*1976*)	Tavern 1	10–294 people	6 changes/hr	8 hr continuous	11.5	10–12	2 (outdoors)	
				2 hr after smoking	~1			
	Tavern 2	Not given	1–2 changes/hr	8 hr continuous	17	~3–22	Values not given	
				2 hr after smoking	~12		Values not given	
U.S. Dept. of Transportation (*1971*)[b]	18 military planes	165–219 people	Mechanical	6–7 hr continuous		<2–5		
	8 domestic planes	27–113 people	Mechanical	$1^1/_4$–$2^1/_2$ hr continuous	≤2			
Elliott and Rowe (*1975*)[c]	Arena 1	11,806 people	Mechanical	Not given	9.0		3.0 (nonactivity day)	
	Arena 2	2,000 people	Natural	Not given	25.0		3.0 (nonactivity day)	
				Nonsmoking arena			9.0	
Fischer et al. (*1978*) and Weber et al. (*1979*)	Restaurant	50–80/470 m^3	Mechanical	27 × 30 min samples	5.1	2.1–9.9	4.8 (outdoors)	
	Restaurant	60–100/440 m^3	Natural	29 × 30 min samples	2.6	1.4–3.4	1.5 (outdoors)	
	Bar	30–40/50 m^3	Natural, open	28 × 30 min samples	4.8	2.4–9.6	1.7 (outdoors)	
	Cafeteria	80–150/574 m^3	11 changes/hr	24 × 30 min	1.2	0.7–1.7	0.4 (outdoors)	
				Nonsmoking room			0.5	0.3–0.8
Godin et al. (*1972*)	Ferryboat	Not given	Not given	11 grab samples	18.4 ± 8.7		3.0 ± 2.4 (nonsmoking room)	
	Theater foyer	Not given	Not given	Grab samples	3.4 ± 0.8		1.4 ± 0.8 (auditorium)	

TABLE 2c.—Continued

Study	Type of premises	Occupancy	Ventilation	Monitoring conditions	Levels (ppm)		Nonsmoking controls (ppm)	
					Mean	Range	Mean	Range
Harke (1974a)	Office[d]	~72 m³	236 m³/hr	30 min samples		<2.5–4.6		
	Office[e]	~78 m³	Natural	30 min samples		<2.5–9.0		
Harke and Peters *(1974)*[f]	Car	2 smokers (4 cigs)	Natural	Samples		42 (peak)	(Nonsmoking runs) 13.5 (peak)	
			Mechanical	Samples		32 (peak)	(Nonsmoking runs) 15.0 (peak)	
Harmsen and Effenberger *(1957)*[b]	Train	1–18 smokers	Natural	Not given		0–40		
Perry *(1973)*[b]	14 public places	Not given	Not given	One grab sample	<10			
Portheine *(1971)*[g]	Rooms	Not given	Not given	Not given		5–25		
Sebben et al. *(1977)*	9 nightclubs	Not given	Varied	77 × 1 min samples	13.4	6.5–41.9		
				Outdoors			9.2	3.0–35.0
	14 restaurants	Not given	Not given	Spot checks	9.9 ± 5.5		Values not given	
	45 restaurants	Not given	Not given	Spot checks	8.2 ± 2.2		7.1 ± 1.7 (outdoors)	
	33 stores	Not given	Not given	Spot checks	10.0 ± 4.2		11.5 ± 6.9 (outdoors)	
	3 hospital lobbies	Not given	Not given	Spot checks		4–8	Values not given	

TABLE 2c.—Continued

Study	Type of premises	Occupancy	Ventilation	Monitoring conditions	Levels (ppm)		Nonsmoking controls (ppm)	
					Mean	Range	Mean	Range
Seiff (*1973*)	Intercity bus	Not given	15 changes/hr, 23 cigarettes burning continuously		33 ppm			
			3 cigarettes burning continuously		18 ppm			
Slavin and Hertz (*1975*)	2 conference rooms	Not given	8 changes/hr	Continuous, morning		8 (peak)	1-2 (separate nonsmoking day)	
			6 changes/hr	Continuous, morning		10 (peak)	1-2 (separate nonsmoking day)	
Szadkowski et al. (*1976*)	25 offices	Not given	Not given	Continuous	2.78 ± 1.42		2.59 ± 2.23 (separate nonsmoking offices)	

[a] Three cigarettes and one cigar smoked in 20 minutes.
[b] The Drager tube used is accurate only within ± 25 percent.
[c] The MSA Monitaire Sampler used is accurate only within ± 25 percent.
[d] About 40 cigarettes/day were smoked.
[e] About 70 cigarettes/day were smoked.
[f] Four filter cigarettes were smoked.
[g] No experimental description given.

TABLE 2d.—Nicotine measured under realistic conditions

Study	Type of premises	Occupancy	Ventilation	Monitoring conditions	Levels (μg/m³)		Nonsmoking controls	
					Mean	Range	Mean	Range
Badre et al. (*1978*)	6 cafes	Varied	Not given	50 min sample		25–52		
	Room	18 smokers	Not given	50 min sample	500			
	Hospital lobby	12 to 30 smokers	Not given	50 min sample	37			
	2 train compartments	2 to 3 smokers	Not given	50 min sample		36–50		
	Car	3 smokers	Natural, open	50 min sample	65			
			Natural, closed	50 min sample	1010			
Cano et al. (*1970*)	Submarines 66m³	157 cigarettes per day	Yes		32 μg/m³			
		94–103 cigarettes per day	Yes		15–35 μg/m³			
Harmsen and Effenberger (*1957*)	Train	Not given	Natural, closed	30–45 min samples		07.–3.1		
Hinds and First (*1975*)[a]	Train	Not given	Not given	2½ hr samples	4.9		Values not given	
	Bus	Not given	Not given	2½ hr samples	6.3		Values not given	
	Bus waiting room	Not given	Not given	2½ hr samples	1.0		Values not given	
	Airline waiting room	Not given	Not given	2½ hr samples	3.1		Values not given	
	Restaurant	Not given	Not given	2½ hr samples	5.2		Values not given	
	Cocktail lounge	Not given	Not given	2½ hr samples	10.3		Values not given	
	Student lounge	Not given	Not given	2½ hr samples	2.8		Values not given	
Weber and Fischer (*1980*)[b]	44 offices	Varied	Varied	140 × 3 hr samples	0.9 ± 1.9	13.8 (peak)	Values not given	

[a] Background levels have been subtracted.

[b] Control values (unoccupied rooms) have been subtracted.

TABLE 2e.—Nitrogen oxides measured under realistic conditions

Study	Type of premises	Occupancy	Ventilation	Monitoring conditions	Levels		Nonsmoking controls (ppb)	
					Mean	Range	Mean	Range
Fischer et al. (*1978*) and Weber et al. (*1979*)	Restaurant	50–80/470 m^3	Mechanical	27 × 30 min samples	NO_2: 76	59–105	63 (outdoors)	
					NO: 120	36–218	115 (outdoors)	
	Restaurant	60–100/440 m^3	Natural	29 × 30 min samples	NO_2: 63	24–99	50 (outdoors)	
					NO: 80	14–21	11 (outdoors)	
	Bar	30–40/50 m^3	Natural, open	28 × 30 min samples	NO_2: 21	1–61	48 (outdoors)	
					NO: 195	66–414	44 (outdoors)	
	Cafeteria	80–150/574 m^3	11 changes/hr	24 × 30 min samples	NO_2: 58	35–103	34 (outdoors)	
					NO: 9	2–38	4 (outdoors)	
				Other—non-smokers room			NO_2: 27	15–44
							NO: 5	2–9
Weber and Fischer (*1980*)[a]	44 offices	Varied	Varied	348–354 samples	NO_2: 24 ± 22	115 (peak)	Values not given	
					NO: 32 ± 60	280 (peak)	Values not given	

[a]Control values (unoccupied rooms) have been subtracted.

TABLE 2f.—Nitrosamines measured under realistic conditions

Study	Type of premises	Occupancy	Ventilation	Monitoring conditions	Levels (ng/L)	
					Mean	Range
					N-Nitrosodimethylamine	
Brunneman and Hoffmann (*1978*)	Train bar car	Not given	Mechanical	90 min continuous	0.13	
	Train bar car	Not given	Natural	90 min continuous	0.11	
Brunneman et al. (*1977*)	Bar	Not given	Not given	3 hr continuous	0.24	
	Sports hall	Not given	Not given	3 hr continuous	0.09	
	Betting parlor	Not given	Not given	90 min continuous	0.05	
	Discotheque	Not given	Not given	2¾ hr continuous	0.09	
	Bank	Not given	Not given	5 hr continuous	0.01	
	House	Not given	Not given	4 hr continuous	<0.005	
	House	Not given	Not given	4 hr continuous	<0.003	

TABLE 2g.—Particulates measured under realistic conditions

Study	Type of premises	Occupancy (active smokers per 100 m^3)	Ventilation	Monitoring conditions (min)	Levels ($\mu g/m^3$) Mean	Levels ($\mu g/m^3$) Std. dev.	Nonsmoking controls ($\mu g/m^3$) Mean	Nonsmoking controls ($\mu g/m^3$) Std. dev.
Repace and Lowrey (*1980*)	Cocktail party	0.75	Natural	15	351	± 38	24	
	Lodge hall	1.26	Mechanical	50	697	± 28	60[1]	
	Bar and grill	1.78	Mechanical	18	589	± 28	63[1]	
	Firehouse bingo	2.77	Mechanical	16	417	± 63	51[1]	
	Pizzeria	2.94	Mechanical	32	414	± 58	40[1]	
	Bar/cocktail lounge	3.24	Mechanical	26	334	± 120	50[1]	
	Church bingo game	0.47	Mechanical	42	279	± 18	30	
	Inn	0.74	Mechanical	12	239	± 9	22[1]	
	Bowling alley	1.53	Mechanical	20	202	± 19	49[1]	
	Hospital waiting room	2.15	Mechanical	12	187	± 52	58[1]	
	Shopping plaza restaurant							
	Sample 1	0.18	Mechanical	18	153	± 8	59[1]	
	Sample 2	0.18	Mechanical	18	163	± 4	36[1]	
	Barbeque restaurant	0.89	Mechanical	10	136	± 17	40[1]	
	Sandwich restaurant A							
	Smoking section	0.29	Mechanical	20	110	± 36	40[1]	
	Nonsmoking section	0	Mechanical	20	55	± 5	30	
	Fast-food restaurant	0.42	Mechanical	40	109	± 38	24[1]	
	Sports arena	0.09[2]	Mechanical	12	94	± 13	55[1]	
	Neighborhood restaurant/bar	0.40	Mechanical	12	93	± 17	55[1]	
	Hotel bar	0.59	Mechanical	12	93	± 2	30	
	Sandwich restaurant B							
	Smoking section	0.13	Mechanical	8	86	± 7	55	
	Nonsmoking section	0	Mechanical	21	51			
	Roadside restaurant	1.12	Mechanical (9.5 ach[3])	18	107[4]		30	
	Conference room	3.54	Mechanical (4.3 ach[3])	6	1947[4]		55	

TABLE 2g.—Continued

Study	Type of premises	Occupancy (active smokers per 100 m³)	Ventilation	Monitoring conditions (min)	Levels (μg/m³) Mean	Levels (μg/m³) Std. dev.	Nonsmoking controls (μg/m³) Mean	Nonsmoking controls (μg/m³) Std. dev.
Repace and Lowrey (*1982*)	Dinner theater	0.14	Mechanical	44	145	± 43	47	± 10
	Reception hall	1.19	Mechanical	20	301	± 30	33[1]	
	Bingo hall	0.93[2]	Natural	2	1140		40[1]	
		0.93[2]	Mechanical (1.39 ach[3])	6	443[4]		40[1]	

[1] Sequential outdoor measurement (5 minute average).

[2] Estimated.

[3] Air changes per hour.

[4] Equilibrium level as determined from concentration vs. time curve.

TABLE 2g.—Continued

Study	Type of premises	Occupancy	Ventilation	Monitoring conditions	Levels (μg/m³)		Nonsmoking controls (μg/m³)	
					Mean	Range	Mean	Range
Cuddleback et al. (*1976*)	Tavern	Not given	6 changes/hr	4 × 8 hr continuous	310	233–346		
	Tavern	Not given	1–2 changes/hr	8 hr continuous	986			
U.S. Dept. of Transportation (*1971*)	18 military planes	165–219 people	Mechanical	72 × 6–7 hr samples		<10–120		
	8 domestic planes	27–113 people	Mechanical	24 × 1¼–2½ hr samples	Not given			
Dockery and Spengler (*1981*)	Residences	Not given	Varied	24 hr samples	32			
Elliott and Rowe (*1975*)	Arena 1	11,806 people	Mechanical	During activities	323		42 (nonactivity day)	
	Arena 2	2,000 people	Natural	During activities	620		92 (nonactivity day)	
	Arena 3 (smoking prohibited)	11,000 people	Mechanical	During activities	148		71 (nonactivity day)	
Harmsen and Effenberger (*1957*)	Trains	15–120 people	Natural	Not given		46–440 particles/cm³		
				Nonsmokers' cars				20–75 particles/cm³
Just et al. (*1972*)	4 coffee houses	Not given	Not given	6 hr averages	1150	500–1900	570 (outdoors)	100-1900
Neal et al. (*1978*)	Hospital unit	Not given	Mechanical	48 hr samples	21 ± 14	3–58	73 ± 25	
	Hospital unit	Not given	Mechanical	48 hr samples	40 ± 21	13–79	72 ± 25	

TABLE 2g.—Continued

Study	Type of premises	Occupancy	Ventilation	Monitoring conditions	Levels (μg/m³)		Nonsmoking controls (μg/m³)	
					Mean	Range	Mean	Range
Spengler et al. (*1981*)	Residences	2+ smokers	Natural	24 hr samples	70 ± 43		21 ± 12 (outdoors)	
		1 smoker	Natural	24 hr samples	37 ± 15		21 ± 12 (outdoors)	
Weber and Fischer (*1981*)	44 offices	Varied	Natural and mechanical	429 × 2 min samples	133 ± 130[1]	962[1] (peak)		
Quant et al. (*1982*)	Office No. 1	0.82[2]	Mechanical	Five 10 hr workday averages; continuous monitoring	45	39-54		5–15
	Office No. 2	0.68[2]	Mechanical		45	37–50		15–20
	Office No. 3	1.46[2]	Mechanical		68	42–89		15–20
Brunekreef and Boleij (*1982*)	26 houses	1–3 smokers	Natural	2 mo averages	153[3]	60–340	55	20–90

[1] Values above background.

[2] Habitual smokers per 100 m².

[3] Weighted mean.

TABLE 2h.—Residuals measured under realistic conditions

Study	Type of premises	Occupancy	Ventilation	Monitoring conditions	Levels		Nonsmoking controls	
					Mean	Range	Mean	Range
					Acetone (mg/m³)			
Badre et al. (*1978*)[a]	6 cafes	Varied	Not given	100 mL samples		0.91–5.88		
	Room	18 smokers	Not given	100 mL samples	0.51			
	Hospital lobby	12 to 30 smokers	Not given	100 mL samples	1.16			
	2 train compartments	2 or 3 smokers	Not given	100 mL samples		0.36–0.75		
	Car	3 smokers	Natural, open	100 mL samples	0.32			
	Car	2 smokers	Natural, closed	100 mL samples	1.20			
					Sulfates (μg/m³)			
Dockery and Spengler (*1981*)	Residences	Not given	Varied	24 hr samples	4.81			
					Sulfur dioxide (ppb)			
Fischer et al. (*1978*)	Restaurant	50–80/470 m³	Mechanical	27 × 30 min samples	20	9–32	12 ppb	
	Restaurant	60–100/440 m³	Natural	29 × 30 min samples	13	5–18	6	
	Bar	30–40/50 m³	Natural, open	28 × 30 min samples	30	13–75	8	
	Cafeteria	80–150/574 m³	11 ch/hr	24 × 30 min samples	15	1–27	12	
				Other nonsmokers' room			7	3–13
Just et al. (*1972*)	4 coffee houses	Not given	Not given	6 hr continuous	12.0–15.3			

[a] See original paper for nine other residuals.

SOURCE: Sterling et al. (*1982*).

is also readily available. CO reflects the gas phase components of smoke and thus may not reflect the levels of particulate phase constituents. There are also a number of other CO sources in addition to cigarettes, both in the external environment (e.g., automobiles) and in the indoor environment (e.g., gas stoves). As a result, even the subtraction of external atmospheric levels may not entirely eliminate the contribution of other sources of CO to the indoor environment.

Given these problems, use of several of these measures, or the tailoring of the measurement to the phenomenon being measured, seems appropriate. The measurement of total particulate matter may be a reasonable indicator of exposure to the particulate phase of smoke, once the measurement is limited to respirable particulates and once background levels with the same level of activity, but without smoke, are subtracted. Relatively precise methods have been developed to predict the levels of exposure to carbon monoxide (Jones and Fagan 1975; Coburn et al. 1965) and total particulate matter (Repace and Lowrey 1980) that would be expected in rooms of different size and ventilation with different rates of smoking. Stewart et al. (1974), using blood donors, found the median blood carboxyhemoglobin level for smokers and nonsmokers in selected populations to be 5.0 and 1.2 percent, respectively. This corresponds to a steady state ambient CO level of 7 ppm, which represents a combination of atmospheric pollution from cigarette smoke and the background level of urban pollution and is consistent with the levels described in Table 2. Exposure levels to carbon monoxide are highly dependent on ventilation, occupancy, smoking rates, and background levels in the ambient air. The half life of carboxyhemoglobin is approximately 4 hours, making blood carboxyhemoglobin a useful biologic monitor of acute exposure to passive smoking, but one that does not provide useful data for chronic exposure.

Assessment of chronic exposure with a biologic marker requires the ability to measure some accumulating product of smoke. To date, substances such as cotinine (Matsukura et al. 1979; Langone et al. 1973; Williams et al. 1979; Feyerabend and Russell 1980; Russell et al. 1982), thiocyanate (Bottoms et al. 1982; Cohen and Bartsch 1980), and polonium-210 (Radford and Hunt 1964; Little and McGendy 1966) have been measured in active smokers. Plasma and urinary nicotine, plasma and urinary cotinine, and salivary nicotine and cotinine have been reported in nonsmokers exposed to tobacco smoke (Jarvis and Russell 1984; Russell and Feyerabend 1975; Feyerbend et al. 1982). Of these measures, it would appear that urinary cotinine offers the most promise as an index of exposure. However, there are no published data using these measures as biologic markers of chronic involuntary smoke exposure.

In contrast to physiologic investigations, epidemiologic studies have used the number of smokers in the home or in the working environment as the principal exposure variable. These relatively crude indices, in general, ignore time spent with the smoker and the environmental factors known to influence ambient smoke concentration noted above.

In summary, involuntary smoking research deals with an exposure that is qualitatively and quantitatively different from that of active smoking. Adequate characterization of passive exposure in both epidemiologic and physiologic studies is substantially more difficult for involuntary exposure than for active smoking exposure. While the active smoker's total current cigarette consumption is relatively easily quantitated, the lower dose and greater influence of ventilation and ambient environment for involuntary smoke exposure makes assessment of exposure one of the most important methodologic issues of this research. Clearly, a biologic marker of chronic exposure that reflects the amount of tobacco smoke to which nonsmoking persons are exposed would be a useful tool. In addition, carefully formulated questionnaires quantifying passive smoking are also necessary, and may prove equally valid for assessing exposure. No single index has yet been accepted by all investigators, and comparison between studies remains difficult. However, Repace and Lowrey (1983) have estimated that the nonsmoking population may be exposed to from 0 to 14 mg of tar per day, with an average exposure of 1.43 mg per day.

Acute Physiologic Response of the Airway to Smoke in the Environment

Relatively little acute exposure data exist concerning the effects of passive inhalation of cigarette smoke on pulmonary function (Table 3). The data that are available have been obtained in exposure chambers under carefully monitored and controlled circumstances (Pimm et al. 1978; Shephard et al. 1979; Dahms et al. 1981).

Pimm and colleagues (1978) exposed nonsmoking adults to smoke in an exposure chamber. Relatively constant levels of carbon monoxide (approximately 24 parts per million) were achieved in the chamber during involuntary smoking. Peak blood carboxyhemoglobin levels were always less than 1 percent in subjects before smoke exposure, but were significantly greater during the study exposure. Lung volumes, flow volume curves, and heart rate were measured for all subjects. Measurements were made at rest and following exercise under control conditions and smoke-exposure conditions. Flow at 25 percent of the vital capacity decreased significantly with smoke exposure at rest in men and with exercise in women. The magnitude of the change was small: a 7 percent decrease in flow in

TABLE 3.—Acute effects on pulmonary function of passive exposure to cigarette smoke

Study	Type of exposure	Magnitude of exposure	Effects	Comments
Pimm et al. (*1978*)	Chamber 14.6 m^3 with sparse furniture; smoking machine in room	Peak [CO] ~ 24 ppm; particulates >4 mg/m^3	Men: 5% increase FRC, 11% increase RV, 4% decrease $\dot{V}_{max25}$ during exercise Women: 7% decrease $\dot{V}_{max25}$ post exercise; no effects on VC, TLC, FVC, FEV_1, $\dot{V}_{max50}$	Nonsmokers; average age of men = 22.7, women = 21.9; sham exposure as control
Shepard et al. (*1979*)	As above	Low exposure: peak [CO] ~ 20 ppm, particulates ~ mg/m^3; high exposure: [CO] ~ 31 ppm	Low exposure: 3% decrease FEV_1, 4% decrease $\dot{V}_{max50}$, 5% decrease $\dot{V}_{max25}$ with exercise; no increased effect with high exposure	Nonsmokers; average age of men = 23, women = 25; sham exposure as control; subjects estimated to have inhaled ~ 1/2 cigarette/2 hours
Dahms et al. (*1981*)	Chamber 30 m^3; climate controlled	Room levels not measured; estimated at peak [CO] ~ 20 ppm	0.9% increase in FVC, 5.2% increase in FEV_1, 2.2% increase in FEF_{25-75} at 1 hour	10 nonsmokers; age range 24–53 years; not blinded; no sham exposure

men and 14 percent in women. No other consistent changes in lung function were observed. Shepard and coworkers (1979) utilized a similar crossover design in a chamber of exactly the same size as Pimm's. Their results were almost identical, with a small (3 to 4 percent) decrease in FVC, FEV_1, $\dot{V}_{max50}$, and $\dot{V}_{max25}$. They concluded that these changes were of the magnitude anticipated from an exposure of less than 1/2 cigarette in 2 hours (the exposure anticipated for a passive smoker).

Dahms et al. (1981) used a slightly larger chamber with an estimated peak CO level of approximately 20 parts per million. They found no change in FVC, FEV_1, or FEF_{25-75} after 1 hour of exposure in normal subjects. This experiment was not blinded and had no sham exposure.

The data from these studies suggest that involuntary smoke exposure can probably produce measurable, albeit small, changes in the airways of normal individuals. This response is consistent with the acute response to the inhalation of cigarette smoke by the active smoker, and it is not surprising that high dose involuntary exposure to tobacco smoke might produce similar results. The magnitude of these changes is small, even at moderate to high exposure levels, and it is unlikely that this change in airflow per se results in symptoms; however, it may be only one manifestation of a broader irritant response to smoke in nonsmokers.

Symptomatic Responses to Chronic Passive Cigarette Smoke Exposure in Healthy Subjects

Eye irritation is the most common complaint experienced by normal people acutely exposed to cigarette smoke. In one study, 69 percent of subjects reported ever experiencing this symptom (Speer 1968). Headache, nasal irritation, and cough were reported by approximately one-third of the subjects in this and other investigations (Weber and Hertz 1976; Slavin and Hertz 1975). Several factors may alter the prevalence of irritant symptoms, including the amount of smoking, the size of the area involved, the humidity and temperature of ambient air, and the extent of ventilation (Johansson 1976). No longitudinal studies of these irritant effects (e.g., development of increased sensitivity or tolerance) have been reported.

Weber (1984) has examined the effect of dose and duration of exposure to environmental tobacco smoke on subjective reporting of eye irritation and objective measurement of eye blink rate. Figure 1 reveals that both eye irritation and blink rate increase with increasing dose of smoke exposure, and that substantial subjective irritation and objective increase in blink rate occur at levels of smoke exposure (CO levels of 20 to 24 ppm) equivalent to those used to evaluate pulmonary function changes in response to environmen-

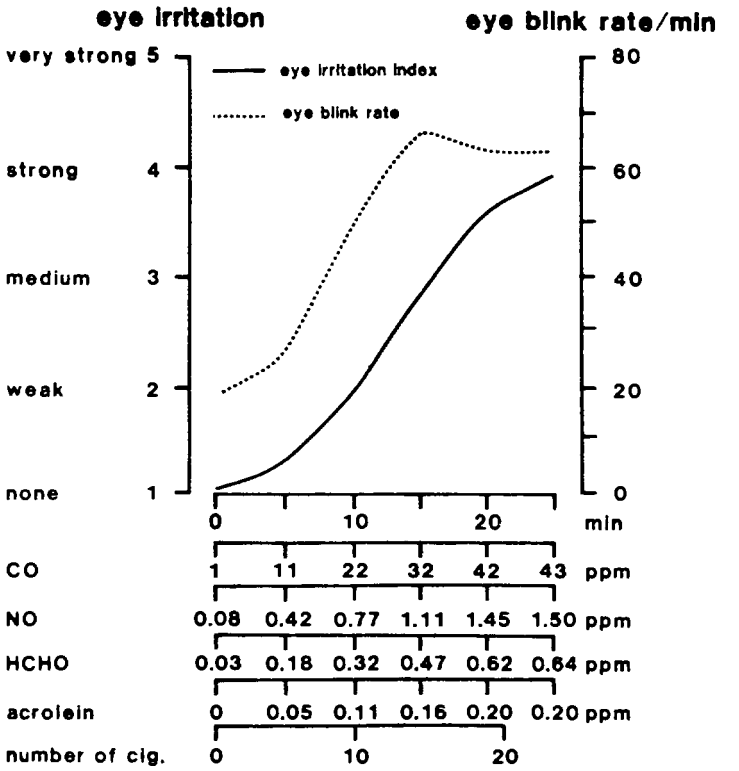

FIGURE 1.—Mean subjective eye irritation, mean eye blink rate, and concentrations of some pollutants during continuous smoke production in an unventilated climatic chamber

NOTE: Thirty-three subjects; ventilation rate 0.01 h^{-1}; eye irritation index calculated from the answers to four questions concerning eye irritation; 0 min = measurement before smoke production.

SOURCE: Weber (1984).

tal tobacco smoke exposure. Both irritation and blink rate increase with duration of exposure to environmental tobacco smoke (Figures 2 and 3). After 60 minutes of exposure, distinct changes are evident in level of irritation with a smoke exposure of 1.3 ppm CO, and the blink rate increased with smoke exposures as low as 2.5 ppm CO. These levels of smoke exposure (1.3 to 2.5 ppm CO) are well within those measured under realistic conditions (see Table 1). Therefore, it is possible to demonstrate an objective irritant response in normal subjects at levels of smoke exposure substantially lower than the levels where an airway response (also presumably an irritant response) has been demonstrated. Whether this difference represents a difference in threshold for irritation in the eye and airway or a limitation in the ability to measure subtle changes in the airway is uncertain.

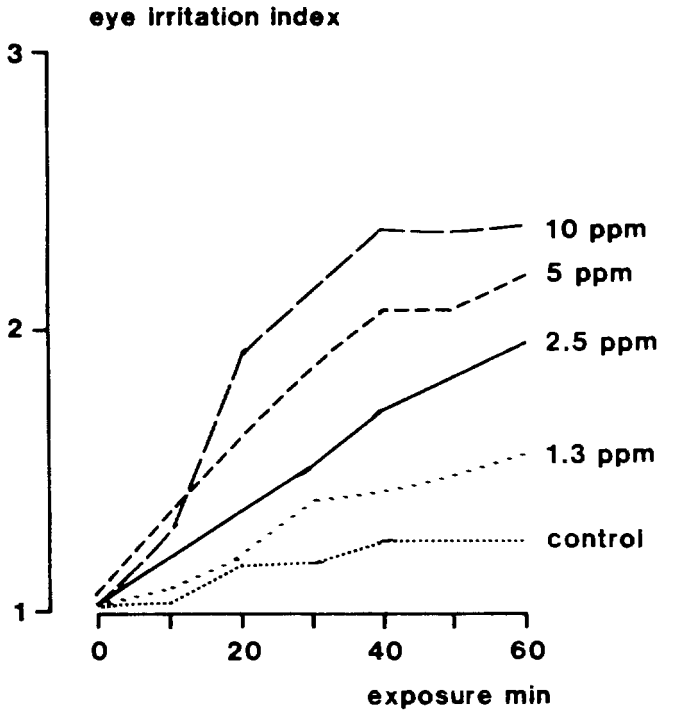

FIGURE 2.—Subjective eye irritation due to environmental tobacco smoke, related to smoke concentration and duration of exposure

NOTE: CO values are levels during smoke production minus background level before smoke production; 32 to 43 subjects; 0 min = measurements before smoke production.

SOURCE: Weber (1984).

Chronic respiratory symptoms have been reported most commonly in children. Studies from several different countries (Table 4) have shown a positive relationship between parental cigarette smoking and the reporting of the symptoms of chronic cough, chronic phlegm, and persistent wheeze (Colley et al. 1974; Bland et al. 1978; Lebowitz and Burrows 1976; Weiss et al. 1980; Ware et al. 1984; Schilling et al. 1977; Kasuga et al. 1979; Schenker et al. 1983). Some of these studies may be confounded by an increased reporting of symptoms in the child by parents who smoke and have symptoms (Colley et al. 1974; Bland et al. 1978; Kasuga et al. 1979) or by the child's own smoking habits (Colley et al. 1974; Bland et al. 1978; Kasuga et al. 1979). Not all studies show statistical significance for all symptoms (Lebowitz and Burrows 1976; Schilling et al. 1977; Schenker et al. 1983). However, a consistent finding in all reported data is an increase in symptoms with an increased number of smoking parents in the

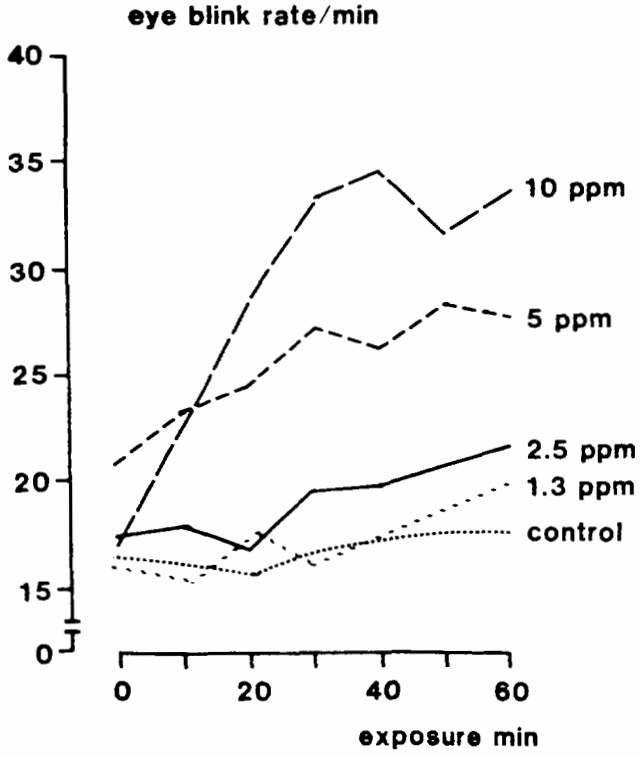

FIGURE 3.—Effects of environmental tobacco smoke on eye blink rate

NOTE: CO values are levels during smoke production minus background level before smoke production; 32 to 43 subjects; 0 min = measurements before smoke production.

SOURCE: Weber (1984).

home. This effect persists after controlling for parental cough and is most marked in the first year of life.

British researchers, studying a birth cohort, demonstrated an increased incidence of wheezing over a 5-year period among nonasthmatic children who had two parents who smoked. However, when examined by logistic regression, parental smoking was not a significant predictor of occurrence of wheeze or the future occurrence of asthma (Bland et al. 1978). In a subgroup of the cohort—861 children of asymptomatic parents, Leeder and colleagues (1976a) found no significant trend in asthma–wheeze symptoms with increasing levels of parental smoking over a 5-year period. In a study of 650 children aged 5 to 10 years (Weiss et al. 1980), a significant trend in the reported prevalence of chronic wheezing with current parental smoking was found; the rates were 1.85 percent, 6.85 percent, and 11.8 percent for zero, one smoking parent, and two smoking parents, respectively. Although the data given are for all

TABLE 4.—Respiratory symptoms in children in relation to involuntary smoke exposure

Study	Subjects	Respiratory symptoms or illness	Rates per 100 by number of smoking parents 0	1	2	Comment
Colley et al. (*1974*)	2,426 children, aged 6–14, England	Chronic cough assessed by questionnaire completed by parent	15.6	17.7	22.2	Trend significant; possible that symptoms in parents could result in reporting bias; active smoking in children could also bias results; bias unlikely to explain full effect of trend
Bland et al. (*1978*)	3,105 children, aged 12–13, who did not admit to ever smoking cigarettes, England	Cough during day or at night	16.4	19.0	23.5	Self-reported symptoms and smoking history collected simultaneously from children; difference between morning and daytime cough suggested as different diseases, but could be difference in exposure, in that exposure more likely in daytime than when asleep
		Morning cough	1.5	2.8	2.9	
Weiss et al. (*1980*)	650 children, aged 5–9, United States	Chronic cough and phlegm	1.7	2.7	3.4	Trend not significant
		Persistent wheeze	1.8	6.8	11.8	Trend significant
Ware et al. (*1984*)	8,528 children, aged 5–9, with two parents of known smoking status, six U.S. cities	Chronic cough	7.7	8.4	10.6	Adjusted for age, sex, and city cohort effects; significant trends
		Persistent wheeze	9.9	11.0	13.1	

TABLE 4.—Continued

Study	Subjects	Respiratory symptoms or illness	Rates per 100 by number of smoking parents 0	1	2	Comment
Dodge (*1982*)	628 children, grades 3–4, in two-parent households; questionnaire response of parents, United States	Wheeze	27.6	27.9	40.0	All trends significant; some of effect might relate to parental symptoms, but not likely to influence trends
		Phlegm	6.4	10.9	12.0	
		Cough	14.6	23.0	27.8	
Schenker et al. (*1983*)	4,071 children, aged 5–14, in western Pennsylvania	Chronic cough	6.3	7.0	8.3	None of these rates significant; data not adjusted for parental symptoms
		Chronic phlegm	4.1	4.8	4.0	
		Persistent wheeze	7.2	7.7	5.4	
			Never smoking		Parent smoking	
Lebowitz and Burrows (*1976*)	1,252 children, <15 years old, United States	Persistent cough	3.7		7.2	Higher rates in symptomatic households with trends persisting, but not significant for asymptomatic households
		Persistent phlegm	10		12.8	
		Wheeze	23.4		24.1	
Schilling et al. (*1977*)	816 children, age 7+, United States	Cough, phlegm, wheeze	No significant effect			Specific data not provided
Kasuga et al. (*1979*)	1,937 children, aged 6–11, Japan	Wheeze, asthma	Increased prevalence in families with a heavy smoker (≥21 cig/day); less clear effect in family with a light smoker (<21 cig/day)			Data adjusted for distance of home from main traffic, highway

households, when the analysis was restricted to those households where neither parent reported symptoms, the results were identical, suggesting that in this population, significant reporting bias was not responsible for the observed results. Lebowitz and Burrows (1976), in a group of 463 current-smoking and never-smoking households with children below age 15, found trends—but no statistically significant differences—for a variety of symptoms, including wheeze most days, in households with smokers. In the same study, among 849 households with older children and adults, there were no significant differences for any symptom prevalence between current-smoking and never-smoking household members. In a general population study, Schilling et al. (1977) reported no association between wheeze and involuntary smoking.

A preliminary report from one of the largest studies currently under way (Speizer et al. 1980) indicated no association of persistent wheeze with the presence of smoking in the household for approximately 8,000 children aged 6 to 11 in six communities. However, subsequent analyses of these same cohorts with the addition of approximately 2,000 more children and a more detailed assessment of the smoking behavior of each parent revealed a positive relationship that increased with the amount of maternal smoking and was only modestly affected by taking into account the parents' own symptoms (Ware et al. 1984). Dodge (1982), studying third and fourth grade children, found that symptoms, including wheeze, were related to both the presence of symptoms in the parents and the number of smokers in the household. The gradient of the wheeze effect persisted even after excluding the potential effect of reporting bias by symptomatic parents. Few data are available on the level of exposure necessary to produce symptoms or on the implication of these symptoms for future lung growth and development. No data are currently available on the relationship of passive smoking to other putative risk factors for wheezing such as atopy, respiratory infection, and increased levels of airways responsiveness, nor are sufficient data available to estimate whether these early exposures affect the occurrence of respiratory disease later in life. The characteristics of the child who may be susceptible to this type of exposure are unknown. However, the data are sufficiently consistent to suggest that pediatricians should routinely inquire about smoking habits of parents when caring for children with chronic or recurrent respiratory symptoms and illnesses. It would also be prudent to advise parents of children who are suffering from recurrent respiratory illnesses or persistent wheeze or asthma not to smoke.

Respiratory Infections in Children of Smoking Parents

Bronchitis and pneumonia and other lower respiratory illnesses are significantly more common in the first year of life in children who have one or two smoking parents (Table 5). Bonham and Wilson (1981) showed that in 1970 the majority of homes with children under 17 years of age had at least one smoker. Thus, passive smoking by children, even in early childhood, is widespread. Harlap and Davies (1974) studied 10,672 births in Israel between 1965 and 1968 and observed that infants whose mothers said they smoked (as determined at a prenatal visit) experienced a 27.5 percent greater hospital admission rate for pneumonia and bronchitis than children of nonsmoking mothers. In addition, they demonstrated a dose–response relationship between the amount of maternal smoking and the number of hospital admissions for these conditions. It should be noted that the mothers were reporting prenatal smoking and not postnatal smoking for the first year of life.

British investigators studying live births between 1963 and 1965 in London also observed an increased frequency of bronchitis and pneumonia in the first year of life associated with involuntary smoking that did not carry over to years 2 to 5 (Colley et al. 1974). This effect was independent of parents' own symptoms and increased with the amount of smoking by parents. Bronchitis and pneumonia also increased with an increased number of siblings, and this was not controlled in the analysis.

Fergusson et al. (1981), studied 1,265 New Zealand children from birth to age 3. They demonstrated an increase in both bronchitis and pneumonia and lower respiratory illness during the first 2 years of life in children whose mothers smoked. Corrections for maternal age, family size, and socioeconomic status did not affect the linear relationship between the degree of maternal smoking and the rate of respiratory illness. This effect declined with the increasing age of the child.

Leeder and colleagues (1976b) studied a British cohort of children born between 1963 and 1965 and demonstrated that parental cigarette smoking was associated significantly with bronchitis and pneumonia during the first year of life. A dose–response association persisted after correction for parental respiratory symptoms, sex of the child, number of siblings, and a history of respiratory illness in the siblings.

Pullan and Hey (1982) studied children who were hospitalized with documented respiratory syncytial virus (RSV) infection in infancy. They found a significant difference in the smoking habits of mothers at the time of the infection, compared with children hospitalized for other illnesses—including respiratory diseases for which RSV infection was not documented. These children reported an excess occurrence of wheeze and asthma and had lower levels of pulmonary

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TABLE 5.—Early childhood respiratory illness and involuntary cigarette smoking

Study	Subjects	Findings	Illness rates per 100				Comments
			By cigarettes per day				
			0	1–10	11–20	20+	
Harlap and Davies (*1974*)	10,672 births, 1965–1968, West Jerusalem, Israel	Hospitalized for bronchitis/pneumonia in first year of life RR[1] = 1.38	9.5	10.8	16.2	31.7	Smoking history obtained antenatally; maternal smoking only
Colley[2] (*1974*)	2,205 births, 1963–1965, London, England	Questionnaire on bronchitis/pneumonia in first year of life RR = 1.73 for one parent smoker RR = 2.60 for two parent smokers	7.6 10.3	10.4 15.1	11.1 14.5	15.2 23.2	= Asymptomatic parents = Symptomatic parents Neither controlled for number of siblings or sex of smokers
Fergusson et al. (*1981*)	1,265 births, 4 months, 1977, Christchurch, New Zealand	Questionnaires on doctor or hospital visits for bronchitis/pneumonia; check by hospital records Assessment at 4 months, 1, 2, and 3 years RR = 2.04 if mother smoked	7.0 7.0	12.8 4.6	13.4 8.8	Maternal only Paternal only	Combined effect significant for maternal smoking in first year of life only
			By number of smoking parents				
			0	1	2		
Ware et al. (*1984*)	8,528 children, aged 5–9, with two parents of known smoking status, six U.S. cities	Respiratory illness in last year	12.9	13.7	14.8		Adjusted for age, sex, and city cohort effect; significant trends

TABLE 5.—Continued

Study	Subjects	Findings	Illness rates per 100	Comments
Said et al. (*1978*)	3,920 children, aged 10–20, France	Tonsillectomy and/or adenoidectomy, generally before age 5, as indicator of frequent respiratory tract infection	28.2 41.4 50.9	Self-reporting by children; not clear that smoking habits of parents at time of reporting directly related to exposure approximately 10+ years earlier
Schenker et al. (*1983*)	4,071 children, aged 5–14, western Pennsylvania	Chest illness before age 2 Chest illness >3 days in past year	6.7 7.9 11.5 8.8 11.8 13.6	Trends for both significant
Cameron et al. (*1969*)	158 children, aged 6–9; parents completed telephone questionnaire, United States	Respiratory illness with restricted activity and/or medical consultation in last year	1.33 7.4	Illness reporting not verified; not clear how reporting adult was related to child
Leeder et al. (1976a, b)	2,149 infants, born 1963–1965, Harrow, England	RR ~ 2.0 for infants with two smoking parents	Not provided	Parents answered for children, but response bias seems unlikely because effects were observed for infants of asymptomatic parents; effects of maternal vs. paternal smoking not investigated
Sims et al. (*1978*)	35 children hospitalized with RSV bronchiolitis, 35 controls, England	Borderline significant increase in maternal smoking during first year of life RR=2.65	Not provided	No significant effect for paternal smoking; average amount smoked greater for parents of cases than for controls

TABLE 5.—Continued

Study	Subjects	Findings	Illness rates per 100	Comments
Rantakallio (*1978*)	1,821 children of smoking mothers, 1,823 children of nonsmoking mothers	Significant increase in hospitalization for respiratory illness during first 5 years of life RR=1.74	Not provided	Prospective followup of doctor visits, hospitalizations, deaths up to age 5; only maternal smoking evaluated
Pullan and Hey (*1982*)	130 children admitted to hospital during first year of life with RSV infection, 111 nonhospitalized controls	Significant effect of maternal (RR=1.96) and paternal (RR=1.53) smoking at time of study; significant maternal effect of smoking during first year of life (RR=1.55)	Not provided	

[1] Relative risk for children of smoking mothers versus children of nonsmoking mothers calculated from published data provided by J.M. Samet, M.D.

[2] These data are considered in a more expanded analysis provided by Leeder et al. (*1976*).

function that persisted to age 10. The authors could not distinguish between the possibilities that infection caused damage that persisted and affected the maturation of the lung or that these children were already more susceptible to severe RSV infection. Greenberg et al. (1984) examined the tobacco smoke exposure of infants in the first year of life by measuring urinary cotinine-to-creatinine ratios. They found that infants of mothers who smoked had a ratio of 351 ng per mg, as contrasted with a ratio of 4 ng per mg in infants of mothers who did not smoke. Breast-fed infants were excluded because of the presence of nicotine in the breast milk of mothers who smoke. A dose–response relationship was present between the cotinine-to-creatinine ratio and the reported level of maternal smoking in the previous 24 hours. This study suggests that infants of mothers who smoke absorb measurable amounts of the smoke from this environmental exposure.

Rantakallio (1978) studied over 3,600 children for 5 years, half of whom had mothers who smoked and half of whom did not. Children of mothers who smoked had a 70 percent greater chance of being hospitalized for a respiratory illness than children of nonsmoking mothers.

Some of these studies may be confounded by the increased reporting of symptoms in the child by parents who smoke and have symptoms (Cameron et al. 1969; Said et al. 1978; Leeder et al. 1976b), but in those studies in which parental symptoms were controlled, the effects persisted. Other studies may be influenced by the child's own smoking habits (Said et al. 1978), although the majority of research examined children in an age range in which smoking would be unlikely.

In summary, several studies suggest important increases in severe respiratory illnesses, particularly in the very young (less than 2 years old) children of smoking parents. Young children may represent a more susceptible population for adverse effects of involuntary smoking than older children and adults. The amount of time spent with active smokers, particularly by children under 2 years of age with smoking mothers, may be an important factor. How in utero exposure influences this risk is unknown.

Pulmonary Function in Children of Smoking Parents

In recent years, a number of studies have examined the relationship of parental cigarette smoking to pulmonary function in children (Table 6). The majority of these studies have been cross sectional (Tager et al. 1979; Weiss et al. 1980; Vedal et al., in press; Burchfiel et al., 1983; Tashkin et al. 1983; Hasselblad et al. 1981; Ware et al. 1984) and have demonstrated decreases in level of pulmonary function ($FEV_{0.75}$, FEV_1, FEF_{25-75}, and flows at low lung volumes) in

children of smoking mothers compared with children of nonsmoking mothers.

In some studies, there seems to be a dose–response relationship (Tager et al. 1979; Weiss et al. 1980); i.e., the greater the number of smokers in the home, the lower the level of function. When analyzed by multiple regression techniques, maternal smoking has the greatest impact (as would be expected from the greater contact time with the child), and a dose–response relationship with the amount smoked seems to exist (Weiss et al. 1980; Tager et al. 1979; Ware et al. 1984; Vedal et al., in press). Younger children seem to be more adversely affected than older children (Tager et al. 1979; Weiss et al. 1980), and clearly there is an added effect in older children if they themselves smoke (Tager et al. 1979).

Tager and colleagues (1983) followed 1,156 children for 7 years to determine the effect of maternal smoking on growth of pulmonary function in children. After correcting for previous level of FEV_1, age, height, personal cigarette smoking, and correlation between mother's and child's pulmonary function, maternal smoking was associated with a reduced rate of annual increase in FEV_1 and FEF_{25-75}. The magnitude of the effect was consistent with a 3 to 5 percent decrease in expected lung growth due to the maternal smoking effect, constant over the time period of the study. Because so few mothers changed their smoking habits, the study did not attempt to differentiate between postnatal and in utero effects of involuntary smoke exposure.

Ware et al. (1984) followed 10,106 white children for two successive annual examinations. The FEV_1 was 0.6 percent lower in the children of smoking mothers at the first examination and 0.9 percent lower at the second examination. These differences were statistically significant, but represent very small absolute differences. In this study, and in the other studies that show small changes in pulmonary function, it is not clear whether these changes represent small changes occurring uniformly among the children of smoking mothers or somewhat larger changes occurring in a small subpopulation of susceptible children.

The available data demonstrate that maternal smoking affects lung function in young children. However, the absolute magnitude of the difference in lung function is small; it is unlikely that this small difference, per se, is of functional significance. The concern generated by the demonstration of even small differences is directed at the future lung function of those children, particularly if they become active cigarette smokers as adults. The possibility that this difference in lung function may result from pathophysiologic mechanisms similar to those present in active smokers raises the concern that these children may be "sensitized" to smoke at an early age, and that this "sensitization" may result in a more rapid decline in lung

TABLE 6.—Pulmonary function in children exposed to involuntary smoking

Study	Subjects	Pulmonary function measure	Outcome	Comments
Schilling et al. (*1977*)	816 children, aged 7–17, Connecticut and South Carolina	FEV_1 as percent predicted	No effect of parental smoking	No control for sibship size or correlation of siblings' pulmonary function; when analysis restricted to children who never smoked, $\dot{V}_{max50}$ significantly less in children with smoking mothers
Tager et al. (*1979*)	444 children, aged 5–19, East Boston, Massachusetts	MMEF in standard deviation units	Significant effect of parental smoking	Analysis controlled for sibship size and correlation of siblings' pulmonary function
Weiss et al. (*1980*)	650 children, aged 5–9, East Boston, Massachusetts	MMEF in standard deviation units	Significant effect of parental smoking	Analysis controlled for sibship size and correlation of siblings' pulmonary function
Vedal et al. (in press)	4,000 children, aged 6–13	FEV_{75}, FVC, $\dot{V}_{max50}$, $\dot{V}_{max75}$, $\dot{V}_{max90}$	FVC positively associated, flows negatively associated	Flows dose–response with amount smoked by mother
Lebowitz and Burrows (*1976*)	271 households with complete histories of parents' smoking and of pulmonary function of children $\geq$ age 6, Tucson, Arizona	FEV_1, FVC, $\dot{V}_{max50}$, $\dot{V}_{max75}$ derived from MEF_1 $\dot{V}$ curves, expressed as standard deviation units	No effect of parental smoking	Suggestion that real differences in indoor levels of exposure compared with more northerly climates may be occurring

TABLE 6.—Continued

Study	Subjects	Pulmonary function measure	Outcome	Comments
Dodge (*1982*)	558 children, aged 8–10, Arizona	FEV_1 by age change FEV_1/H^3 per year	No effect of parental smoking	Potential bias in participation rates; cross-sectional data not controlled for children's height; annual change in FEV_1/H^3 at ages 8, 9, and 11 consistently greater in nonsmoking households than in two-parent smoking households; statistical test not significant, however
Tager et al. (*1983*)	1,156 children, aged 5–19 at initial survey, East Boston, Massachusetts	FEV_1, FEF_{25-75}	Significant decreased rate of growth in FEV_1 and FEF_{25-75} for children of smoking mothers	7-year followup; no effect of paternal smoking; maximum effect of maternal smoking on fully developed lung not more than 4 or 5 percent
Burchfiel et al. (*1983*)	4,378 children, aged 0–19, Tecumseh, Michigan	FVC, FEV_1, $\dot{V}_{max50}$	Decreased FEV_1 and FVC for boys and $\dot{V}_{max50}$ for girls with increased number of smoking parents	Abstract; no distinction between effects of maternal and paternal smoking; effects most prominent for boys and youngest age groups
Tashkin et al. (*1983*)	1,070 nonsmoking, nonasthmatic children, Los Angeles	$\dot{V}_{max}$, $\dot{V}_{max75}$, $\dot{V}_{max25}$, FEF_{25-75}	Decreased $\dot{V}_{max}$, $\dot{V}_{max25}$ for boys and FEF_{25-75}, $\dot{V}_{max75}$ for girls with at least a smoking mother	No effect of paternal smoking
Hasselblad et al. (*1981*)	16,689 children, aged 5–17, seven geographic regions, United States	FEV_{75} as percent predicted	Significant effect of maternal smoking, but not paternal smoking	Large number of children excluded because of invalid pulmonary function data or missing parental smoking data

TABLE 6.—Continued

Study	Subjects	Pulmonary function measure	Outcome	Comments
Speizer et al. (*1980*)	8,120 children, aged 6–10, in six U.S. cities	FVC and FEV_1 as percent predicted	No effect for FEV_1 or FVC	Recent analysis of this cohort demonstrated an effect for FVC and FEV_1
Ware et al. (*1984*)	10,000 children, aged 6–11, in six U.S. cities	FEV_1 and FVC	FVC positively associated with smoking, FEV_1 negatively associated	FEV_1 dose–response with amount smoked by mother

function as adults, particularly if they become smoking adults. No data are currently available to establish the role, if any, of the small physiologic changes in children on the development of adult obstructive lung disease.

Pulmonary Function in Adults Exposed to Involuntary Cigarette Smoke

White and Froeb (1980) reported on 2,100 asymptomatic adults drawn from a population about to enter a physical fitness program. They demonstrated statistically significant decreases in FEV_1 and MMEF as a percent of predicted in nonsmokers exposed to tobacco smoke in the work environment compared with nonexposed workers. The decrement was comparable to that seen in smokers inhaling 1 to 10 cigarettes per day. However, the absolute magnitude of the difference in mean levels of function in the smoke-exposed and unexposed groups was quite small: 160 ml (5.5 percent) for FEV_1 and 465 ml/sec (13.5 percent) for MMEF. Carbon monoxide levels were measured in the workplace and ranged from 3.1 to 25.8 ppm. The population was self-selected, response was related to current workplace exposure and did not account for people who changed jobs, and it is unclear how the ex-smokers in the population were handled in the analysis.

Comstock et al. (1981) examined 1,724 subjects drawn from two separate studies in Washington County, Maryland. They found no statistically significant greater risk of having an FEV_1 less than 80 percent of predicted in male nonsmokers exposed to wives' cigarette smoke at home. Schilling et al. (1977) did not find an effect of passive smoking exposure in adults. Both of these studies included adults in their samples who were relatively young and generally would not have had a long-term passive exposure in adult life. This point was brought out by a recently reported large study from France. Kauffmann et al. (1983) reported on a seven-city investigation in which a total of 7,818 adults were studied. In a subsample of 1,985 nonsmoking women aged 25 to 29, in which 58 percent were exposed to smoking husbands, there was a significant difference in level of MMEF between truly nonsmoking women and women of comparable ages exposed to passive smoking. This effect did not become apparent until age 40. These changes were small, and although not adjusted for differences in body size, may suggest a possible effect of long-term exposure in adult life.

The physiologic and clinical significance of these small changes in pulmonary function in adults remains to be determined. In addition, variables such as ventilation, room size, number of rooms in the home, duration of contact with the active smoker, and number of cigarettes smoked could significantly influence total exposure and

need to be explored more fully. Differences in these exposure variables and the characterization of exposure may explain some of the differences in these study results (Table 7).

The Effect of Passive Smoke Exposure on People With Allergies, Asthma, and COLD

There are very limited data on the effects of passive smoke exposure in patients with preexisting pulmonary disease, and the available data are conflicting. Clinical studies have suggested a relationship between respiratory symptoms in asthmatics and exposure to parental cigarette smoke, but methodologic problems complicate the interpretation of the limited available data.

O'Connell and Logan (1974) identified 37 asthmatic children who were "bothered" by parental cigarette smoke. Parents of 20 of the children stopped smoking and 18 (90 percent) of the 20 children had an improvement in symptoms. The control group consisted of 15 children (2 were not followed up) whose parents did not stop smoking. Only 4 (27 percent) of the children in the control group improved. The self-selection of those parents who quit, subjective criteria for improvement, and an unclear duration of followup limit the interpretation of this data. Gortmaker and coworkers (1982) studied two populations of children aged newborn to 17 years. They found a significant association between parental reporting of children's asthma and maternal smoking. Maternal smoking alone was associated with approximately 20 percent of all asthma. The effect persisted when age and sex of the child, allergies, and family income and education were controlled in the analysis. No control was attempted for the children's own smoking habits or for increased reporting of symptoms in children of symptomatic parents. Other population-based studies (Lebowitz and Burrows 1976; Speizer et al. 1980; Schilling et al. 1977) have not shown such results.

Dahms et al. (1981) studied 10 patients with bronchial asthma and 10 normal subjects passively exposed to smoke in an environmental chamber. Pulmonary function was measured at 15-minute intervals for 1 hour after smoke exposure. Blood carboxyhemoglobin levels were measured before and after the 1-hour exposure. Carboxyhemoglobin levels in subjects with asthma increased from 0.82 to 1.20 percent. In normal subjects the increase was from 0.62 to 1.05 percent. The increases in carboxyhemoglobin in the two study groups were not significantly different. Asthmatic subjects had a decrease in forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), and maximum mid expiratory flow rate (MMEF) to a level significantly different from their preexposure values. The decreases in asthmatic subjects were present at 15 minutes, but worsened over the course of the hour to approximately 75 percent of

TABLE 7.—Pulmonary function in adults exposed to involuntary smoking

Study	Subjects	Pulmonary function measure	Outcome	Comments
White and Froeb (*1980*)	2,100 adults, San Diego, California	FVC, FEV_1, and MMF as percent predicted	Significant effect of office exposure to involuntary smoke	Potential bias in selection; assessed only current cigarette smoke exposure
Comstock et al. (*1981*)	1,724 adults, Washington County, Maryland	FEV_1 as percent predicted	No effect of wives' smoking on husbands' pulmonary function	Includes adults aged 20+
Kauffmann et al. (*1983*)	7,818 adults, seven French cities, selected subgroups	FEV_1, FVC, and MMEF	Significant effect in wives of smoking husbands in all measures; significant only for MMEF in husbands of smoking wives	Not adjusted for height; dose–response to amount of husbands' smoking for MMEF in wives; no effect below age 40

the preexposure values. Normal subjects had no change in pulmonary function with this level of exposure. In this study, subjects were not blinded as to the exposure and were selected because of complaints about smoke sensitivity. Shephard et al. (1979), in a very similar experiment, subjected 14 asthmatic subjects to a 2-hour cigarette smoke exposure in a closed room (14.6 m^3). The carbon monoxide levels (24 ppm) were similar to those predicted in the study of Dahms and coworkers. No blood carboxyhemoglobin levels were measured. Subjects were randomized and blinded to sham (no smoke) and smoke exposure and tested on two separate occasions. Data were expressed as a percentage change from the sham exposure. No significant changes in FVC or FEV_1 were observed between sham and smoke exposure periods, although 5 of 12 subjects did report wheezing or tightness in the chest on the day of smoke exposure.

The limited existing data yield conflicting results concerning the relationship between passive smoke exposure and symptoms in patients with known pulmonary disease. Further study of this important question is warranted.

Summary and Conclusions

1. Cigarette smoke can make a significant, measurable contribution to the level of indoor air pollution at levels of smoking and ventilation that are common in the indoor environment.
2. Nonsmokers who report exposure to environmental tobacco smoke have higher levels of urinary cotinine, a metabolite of nicotine, than those who do not report such exposure.
3. Cigarette smoke in the air can produce an increase in both subjective and objective measures of eye irritation. Further, some studies suggest that high levels of involuntary smoke exposure might produce small changes in pulmonary function in normal subjects.
4. The children of smoking parents have an increased prevalence of reported respiratory symptoms, and have an increased frequency of bronchitis and pneumonia early in life.
5. The children of smoking parents appear to have measurable but small differences in tests of pulmonary function when compared with children of nonsmoking parents. The significance of this finding to the future development of lung disease is unknown.
6. Two studies have reported differences in measures of lung function in older populations between subjects chronically exposed to involuntary smoking and those who were not. This difference was not found in a younger and possibly less exposed population.

7. The limited existing data yield conflicting results concerning the relationship between passive smoke exposure and pulmonary function changes in patients with asthma.

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CHAPTER 8. DEPOSITION AND TOXICITY OF TOBACCO SMOKE IN THE LUNG

CONTENTS

CIGARETTE SMOKE DEPOSITION IN THE LUNG

Introduction

Previous Reports of the Surgeon General on the health consequences of smoking have focused on characterizing and quantifying responses to the inhalation of cigarette smoke. Typically, dose is given in terms of packs per day or cumulative pack years. However, a more accurate description of dose would include how much smoke is inspired into the respiratory tract, how much is deposited and fails to exit with the expired air, and the fate of the deposited smoke.

A commonly held fallacy is that "living in New York is like smoking two packs per day." Is the amount of particles produced by smoking comparable to that encountered in urban air pollution? A person who smokes two packs of cigarettes per day with an average tar rating of 20 mg per cigarette would breathe in 800 mg of material per day, or 292 g of tar per year. A reasonable value for urban air would be 100 μg, or 0.1 mg per cubic meter. The average person breathes approximately 20,000 liters, or 20 cubic meters, of air per day. Thus, 2 mg of material per day, or 0.73 g of particulate per year, would be inspired. At the outset, it is evident that the amount of smoke entering the lungs is considerably greater than the amount of particulates from air pollution.

This chapter emphasizes the size and aerodynamic properties of smoke and relates them to the fraction of the inspired smoke that deposits in the lungs. Also considered is where the smoke deposits, and its possible fate is described.

The particulate phase of cigarette smoke, commonly known as tar, is inhaled as an aerosol into a smoker's respiratory tract. An aerosol is defined as a suspension of solid or liquid particles in a gas (Hinds 1982). In the case of cigarette smoke, the aerosol contains ambient air as well as the gases, liquids, and solids produced during tobacco combustion. The particulates include a wide variety of organic and metallic compounds, many of which are toxic to lung tissues. Hydrocarbons, aldehydes, ketones, organic acids, alcohols, nicotine, and phenols are among them. Metallic compounds such as radioactive lead and polonium are also present. The gas phase is also complex; in addition to the nitrogen and oxygen in the air, considerable amounts of carbon dioxide and carbon monoxide are present, and also significant amounts of cyanides, acrolein, nitrogen oxides, and ammonia. The precise quantitative composition of the tobacco smoke varies with many different factors, including the type of tobacco plant grown, the soil used to grow the plant, the method of curing the leaves, the temperature of combustion during smoking, and the composition and physical properties of the cigarette paper

and other additives. As the cigarette butt length decreases, many substances that have previously condensed on the remaining tobacco are revaporized. Generally, as butt length shortens, the smoke from the cigarette contains an increasing concentration of these substances. Most of these constituents in smoke are toxic to lung tissues. Their toxicity extends from impairment of mucociliary transport, critical for clearing particles from the lungs, to carcinogenic and cocarcinogenic activities (Wynder and Hoffmann 1979; Battista 1976). To understand where the numerous particulates in cigarette smoke deposit in the lungs and how they are removed is important for determining the pathologic effects of chronic cigarette smoking.

Characterization of an Aerosol

To predict the deposition patterns of any aerosol, such as cigarette smoke, it is necessary to know the size, shape, and density of the individual particles or droplets. Describing the distribution of particle diameters is essential. It is convenient to describe particle size as an aerodynamic diameter rather than as an actual particle size based on optical measurements, because the former is a better predictor of aerodynamic behavior (Hinds 1982). Aerodynamic diameter is defined as the diameter of a sphere of unit density that has the same settling velocity as the particle being measured. This may be expressed as a count median aerodynamic diameter (CMAD) and a mass median aerodynamic diameter (MMAD). These are, respectively, the diameters for which half of the number or mass of the particles are less than that diameter and half are more.

Characterization of Cigarette Smoke Aerosols

The particulates in cigarette smoke have been measured by several investigators using a variety of analytical devices. Because of different apparatus and different methods of smoke generation and dilution, results vary but are reasonably consistent. McCusker et al. (1983) used a device called the single particle aerodynamic relaxation time (SPART) analyzer to determine the size of particulates from several brands of cigarettes, with and without filters. The mass median aerodynamic diameter (MMAD) for all brands averaged approximately 0.46 μm; it was not markedly different when the filters were removed. These measurements showed that, even with a filter, billions of particles are present in an average 35 ml puff of cigarette smoke generated by an automatic smoking-machine. Particulate concentrations per ml ranged from 0.3×10^9 to 3.3×10^9, depending on whether the cigarettes were rated ultra-low, low, or medium in tar content. The reduced particulate concentration reported for low tar cigarettes results principally from filter

efficiency and air dilution of the smoke. When the specially designed filters were removed or the vent holes were covered, as could be accomplished by the smoker's fingers, particulate concentrations per milliliter increased to levels comparable to that for higher tar content cigarettes.

Hinds (1978) compared the particulate size distribution in cigarette smoke using an aerosol centrifuge and a cascade impactor. Although these devices are based upon different physical principles, Hinds found that the results were comparable. The MMAD values ranged from 0.37 to 0.52 μm. Variations depended primarily upon the dilution of the smoke. The MMAD and concentration values reported by Hinds and coworkers (1983) were similar to those reported by Keith and Derrick (1960), who used a specially modified centrifuge, called a conifuge, to analyze cigarette smoke. Particulate analysis by a light scattering photometer yielded an MMAD of 0.29 μm and particulate concentrations of 3×10^{10} per ml (Okada and Matsunuma 1974). Carter and Hasegawa (1975) "fixed" cigarette particulates with methyl cyanoacrylate, a method that may produce artifacts, and measured a mean diameter of 0.48 μm from electron micrographs of the particulates. Earlier methods of measurement were based upon the collection of smoke particulates on various surfaces. Harris (1960) reported a range of 0.16 to 0.54 μm from a replica of cigarette smoke particulates that included a correction for droplet-spreading during sample preparation. Langer and Fisher (1956) found a median range of 0.6 μm, but made no correction for droplet-spreading during sample collection.

Time and concentration are important modifiers of tobacco smoke. Cigarette smoke aerosols contain volatile components, and evaporation gradually reduces particle diameters. It is also true that with the extremely high particle concentrations encountered in mainstream smoke, the aerosol can agglomerate rapidly because nearby particles collide with each other and coalesce. If smoke is cooled (reducing the vapor pressure of the volatile components) and diluted (reducing the probability of particle collisions) the particle size will be more stable. Thus, it is difficult to reliably measure the size and concentration of particles in cigarette smoke produced under realistic experimental conditions.

The size and concentration of the particulates are also affected by the decreasing length of a cigarette as it is smoked. McCusker et al. (1983) found the particulate concentration to be 67 percent greater in the last three puffs of a filtered cigarette than in the first three. Ishizu et al. (1978) also reported that particulate concentrations in unfiltered cigarettes increased and that the mean geometric diameter of the particles decreased with decreasing cigarette length. They attributed the former effect to the decreased filtration by the tobacco column and the latter effect to the shorter length traveled by the

particles to reach the butt end and, hence, the decreased time for particulate coagulation. In addition, their results illustrate that filters may trap the larger particles and generate more uniform aerosols; McCusker et al. (1983) noted no change in MMAD between the first and last three puffs of filtered cigarettes. Ishizu et al. (1978) also reported that larger puff volumes decreased the average particulate diameters. This can affect interpretation of experimental data in that standard cigarette smoking-machines draw 35 ml puff volumes, whereas Hinds et al. (1983) reported that 54 ml was the average puff volume measured in smoking subjects.

Particle size is a critical factor in determining what fraction of the particles that enter the respiratory tract will deposit there and fail to exit with the expired air, as well as where they will deposit. Submicrometric particles will deposit not only in small and large airways, but also in alveoli. Breathing pattern is also important (see review by Brain and Valberg 1979). Large tidal volumes will favor alveolar deposition. Higher inspiratory flows will promote deposition at bifurcations. Breath-holding is important, because the greater the elapsed time before the next expiration, the higher the fraction deposited (collection efficiency).

Individual anatomic differences may influence the amount and distribution of deposited particles. The cross-section of airways will influence the linear velocity of the inspired air. Increasing alveolar size decreases alveolar deposition.

Factors That Affect Particulate Deposition

A typical puff volume is approximately 30 to 70 ml. It is usually inspired with a volume of ambient air that is one to two times the normal tidal volume. Particle size not only can change in experimental equipment as described above, but also may change within the human respiratory tract.

After a volume of smoke is drawn into the mouth and upper respiratory tract of a smoker, it may be retained in that humidified air before deep inhalation. Here too, the particulates can change in size through coagulation or evaporation. They can also grow because of the particulates' affinity for water, termed hygroscopicity (Davies 1974; Hiller 1982b). Other aspects of each smoker's behavior may also influence dose. Most manufacturers achieve low tar yields by the use of ventilated cigarette holders; this causes the inhaled smoke to be diluted with air. However, 32 to 69 percent of interviewed smokers of "low" tar cigarettes reported that they blocked these filter preparations with their fingers or lips. This causes dramatic increases in the amount of tar and nicotine in a way not predicted by studies using smoking-machines (Kozlowski et al. 1980).

Such individual differences in cigarette use as well as other strategies designed to increase the inhalation of tar and nicotine probably account for the poor correlation between the machine-determined nicotine yield of a cigarette and the concentration of nicotine or its metabolites in blood or urine (Russell et al. 1975, 1980; Sutton et al. 1982; Feyerabend et al. 1982; Benowitz et al. 1983). For example, Herning and coworkers (1981) demonstrated that when low nicotine cigarettes are used, most smokers compensate by increasing the puff volume. In addition, Tobin and Sackner (1982) reported that some subjects increase their puff volume by up to 70 percent after switching to low tar cigarettes. In some instances, this compensatory increase occurred during a single experimental session. In contrast, a few smokers may reduce smoke deposition in their lungs by retaining the smoke in their mouth for several seconds before inhaling it. Stupfel and Mordelet-Dambrine (1974) showed that if a smoker holds the smoke in his mouth for 2 seconds, 16 percent of the particulate matter is removed. Also, 60 percent of the water-soluble components of the gas phase are absorbed by the upper airways.

Chronic smoking also causes alterations in lung structure that affect deposition patterns. Sanchis et al. (1971) studied the deposition of an aerosol of radioactively labeled albumin inhaled by smokers and nonsmokers. They found less aerosol deposition in the alveolar region of smokers than of nonsmokers and suggested that the difference may be the result of alterations in the small airways produced by chronic smoking. Similar results were reported for hamsters exposed to cigarette smoke for 3 weeks prior to a single exposure of radioactively labeled cigarette smoke (Reznik and Samek 1980). More labeled smoke concentrate was found in the lungs of hamsters not previously exposed to cigarette smoke.

The rate and pattern of breathing can also affect the total dose of cigarette particulates deposited in the lungs. Dennis (1971) reported that exercise increased the percent deposition of two experimentally generated aerosols in human subjects. Increased deposition was also measured in exercising hamsters that inhaled a radiolabeled aerosol (Harbison and Brain 1983). These results are most relevant to those who smoke when ventilation is increased while working or shortly after a period of exercise.

Deposition of Cigarette Smoke Particulates

The factors discussed in the previous section illustrate that experimental measurements of the size and concentration of cigarette aerosols are insufficient for the prediction of deposition patterns. Cigarette smoke is a mutable aerosol, which complicates the collection of accurate and reproducible data regarding its particulate composition. In addition, alterations in respiratory

structure and respiratory rate can affect the deposition of particulates. These complexities stress the importance of actual measurement of the regional deposition of cigarette smoke particulates in human lungs. However, few data have been published on this important area, despite the prevalence of smoking and its impact on human health. Most of the available information on the deposition of cigarette smoke particulates is based upon theoretical or physical models of the lungs and measurements of differences in the concentration of aerosol between inhaled air and exhaled air.

A model to predict the percent deposition of particles based upon MMAD was presented by the Task Group on Lung Dynamics of the International Commission on Radiological Protection (1966). The respiratory tract was divided into three main regions: nasopharynx, trachea and bronchi, and alveoli. In conjunction with estimates of particulate clearance, deposition calculations were made for these regions at three different inhalation volumes. This model suggests that 30 to 40 percent of the particles within the size range present in cigarette smoke will deposit in the alveolar region and 5 to 10 percent will deposit in the tracheobronchial region. This model also emphasizes the impact of particle solubility on the total integrated dose over time. Brain and Valberg (1974) developed convenient nomograms and a computer program to demonstrate how particle solubility and particle size significantly affect the net amount of particulates retained in the lungs.

Aerosol deposition has also been studied in airway casts. Physical models of the upper airways of human lungs have been made by a double casting technique in order to study particulate deposition at several airway generations (Schlesinger and Lippmann 1972). Lungs obtained at autopsy were filled with wax or alloy. When these materials became solid, the tissue was removed and the casts were coated with silicon rubber or latex. The wax or alloy was then melted and removed, leaving a cast of the original airways. Different flow rates and particulate sizes were used to study deposition patterns. Schlesinger and Lippman (1978) reported a correlation between the deposition sites of test aerosols in the lung casts and the most common sites of origin of bronchogenic carcinoma in humans. Both occurred preferentially at bifurcations. Martonen and Lowe (1983) added an oropharyngeal compartment and a replica cast of the larynx to the tracheobronchial casts in order to better simulate air flow patterns in the upper respiratory tract. They used these models to evaluate the amount of cigarette smoke condensate deposited in the airways at different flow rates. More condensate was present at branching regions, especially at carinal ridges. Aerosol was also deposited preferentially along posterior airway walls.

Most experiments designed to determine aerosol deposition in human subjects measure differences in aerosol concentration before

and after inhalation. Hinds and associates (1983) measured the percent mass of inhaled tobacco smoke particulates that deposited in male and female smokers. A transducer placed in the filter of a smoked cigarette relayed information to an automatic smoking-machine to duplicate inhaled puff volume. This method was used to produce a more natural smoking pattern. Comparisons were then made between particulate mass concentrations in the machine-generated smoke and the amount of smoke actually exhaled by the smoker. With these measurements, a 57 percent deposition of particulate mass was seen in men. This was greater than the significant 40 percent collection efficiency measured in women ($p < 0.01$). No data regarding particulate size or deposition sites were reported. Hiller and coworkers (1982b) also measured the deposition fraction of an aerosol containing three different sizes of polystyrene latex spheres in nonsmoking humans. They measured a 10 percent deposition for 0.6 μm (MMAD) spheres, which is similar to the results of Davies et al. (1972) and Muir and Davies (1967) using 0.5 μm aerosols and of Heyder et al. (1973) using aerosols with a 0.2 to 1.0 μm range. The size ranges of these aerosols are comparable to those experimentally measured in cigarette smoke, as previously discussed. These percentages are lower than those observed by Hinds et al. (1983), probably reflecting differences in breathing patterns. The measurements of Hinds et al. (1983) were made with realistic breathing patterns used during smoking; the other investigators had used normal breathing patterns. Increased breath-holding following inspiration probably accounts for the enhanced collection efficiencies.

Particulate Retention in the Lung

The amount of particulates retained in the lung at different times following the inhalation of an aerosol such as cigarette smoke depends upon the balance between the amount that deposits in the respiratory tract and the efficiency of the lung clearance mechanisms in the airways and alveoli. Particles depositing in the airways are entrained in the mucus layer lining these passages. This layer is swept toward the mouth by the action of ciliated cells and eventually swallowed. Macrophages present in the airways may also phagocytose deposited particulates and are also carried toward the mouth by the mucociliary transport system. Particulates reaching the alveolar region—those that are usually smaller than several micrometers in size—are soon engulfed by alveolar macrophages. These cells gradually migrate toward the airways and exit the lung via the mucociliary escalator. Dissolution is also an important clearance mechanism for soluble particles. Clearance mechanisms are a dynamic component of normal lung function and operate to keep the lung sterile.

Lung disease and cigarette smoking itself can affect particulate clearance and retention in smokers' lungs. Previous studies have shown that smokers have different aerosol deposition patterns and slower clearance rates than nonsmokers (Albert et al. 1969; Cohen et al. 1979; Sanchis et al. 1971). These alterations in clearance are, in part, caused by components in cigarette smoke that are ciliotoxic (Battista 1976) and impair phagocytosis by alveolar macrophages (Ferin et al. 1965). Clearance mechanisms in smokers may be further compromised by lung diseases, such as emphysema and fibrosis, and by exposure to air pollutants. Oxidants in photochemical smog, such as ozone and nitrogen oxides, are toxic to ciliated cells and macrophages (Bils and Christie 1980).

Measurements of retention of cigarette particulates in the lungs over time are difficult to estimate from data obtained with airway casts or from differences in the aerosol concentration of inhaled and exhaled smoke because these methods do not take clearance mechanisms into account. Unfortunately, few data are available regarding the actual retention and sites of deposition of cigarette smoke particulates in either humans or animals. The most accurate method is quantification of particulate deposits in individual pieces of tissue dissected from the lung. Impossible in living animals, this is a tedious procedure with animal lungs or human material obtained at surgery or autopsy and is especially difficult with large lungs. Little et al. (1965) examined lungs from humans at autopsy and suggested a correlation between the sites of bronchogenic carcinoma in the lungs of smokers with the deposition of polonium^{210}, a radioactive component of cigarette smoke. Resnik and Samek (1980) used a radioactive marker to study the retention of smoke in hamster lungs. They exposed hamsters to the smoke from cigarettes containing a labeled component in the tobacco and then measured the amount of radioactivity present in different lobes. They found that more radioactivity was present in the lung tissue of hamsters not previously exposed to unlabeled cigarette smoke. However, the clearance of the labeled component from the lungs was slower in the group previously exposed to smoke. There are problems with using animal models for smoke uptake. Most rodents are obligatory nose breathers, and significant fractions of the smoke may be taken up as it passes through the upper airways. Page et al. (1973) studied mice using radiolabeled cigarettes. They found that 50 percent of the deposited smoke was recovered from the nasal passages. About 30 percent was recovered from the esophagus, stomach, and other organs, and only 20 percent was present in the lungs. Exposing animals via a tracheostomy avoids this excessive and unnatural deposition in the nose, but it bypasses the mouth and larynx, which may remove some particles during smoking in man.

Passive Smoking

Recently concern has increased regarding the health effects of cigarette smoke inhaled by nonsmokers, a phenomenon called passive smoking. The smoke is composed of that exhaled by the smoker and the sidestream smoke produced by the burning cigarette between inhalations. The concentration of respirable particulates in areas where there are smokers can range from 100 to 700 $\mu g/m^3$. This is up to 25 times higher than that found in nonsmoking areas (Repace and Lowrey 1980). Using mean deposition values of 11 and 70 percent for the passive smoker and the active smoker, respectively, from the data presented by Hiller et al. (1982), the deposition would be approximately 0.55 mg for a nonsmoker over an 8-hour day in a room with 500 $\mu g/m^3$ of smoke. In comparison, a smoker would deposit approximately 400 mg of tar in his or her lungs if he or she smoked two packs of cigarettes with an average tar rating of 20 mg per cigarette during the same time period. As has been discussed earlier, the rate and pattern of breathing can also affect the total dose of cigarette particulates deposited in the lungs.

Although the amount of smoke depositing in the lungs of nonsmokers during passive smoking is small compared to that encountered by the active smoker, large numbers of people are involved. In the United States in 1979, 36.9 percent of men and 28.2 percent of women were current smokers (USDHEW 1980).

Conclusions

Cigarette smoke is the most important cause of chronic obstructive lung disease. This significant response is matched by the significant dose of toxic particulates received by the respiratory tract of smokers. The particle size of cigarette smoke is so small that little protection is offered by the filtering capacity of the upper airways. Cigarette smoke penetrates deep into the lungs and reaches the small airways and alveoli. The fraction of the smoke deposited is high because most smokers employ some breath-holding following inhalation of a puff. Their attempt to enhance deposition of smoke is successful, resulting in increased lung burdens of toxic smoke products.

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CIGARETTE SMOKE TOXICOLOGY

Introduction

The inhalation toxicity of tobacco smoke has become one of the major public health problems of the 20th century. The chemical complexity of tobacco smoke confounds the task of identifying its toxic constituents. Tobacco smoke is comprised of thousands of chemical components arising primarily from volatilization and pyrolysis of the tobacco leaf (Stedman 1968; Green 1977). The chemical gamut runs from traces of elemental metals, such as cadmium, to nonvolatile whole tobacco leaf components that have escaped degradation during the burning process (USDHHS 1981). Approximately 90 percent of the individual constitutents are organic compounds associated with both the particulate phase and the gas phase (Guerin 1980). It is not surprising that chronic inhalational exposure to this diverse mixture of potentially bioactive compounds can evoke a wide variety of toxicologic responses. Over the years, scientific and public concern has centered primarily on the carcinogenic and atherogenic effects of tobacco smoke. In contrast, relatively little is known about the involvement of tobacco smoke constituents in the pathogenesis of chronic obstructive lung disease (COLD) (USDHHS 1981).

For the most part, smoke constituent toxicity studies, both epidemiologic (Dean et al. 1977; Higenbottam et al. 1980) and toxicologic (Walker et al. 1978; Lewis et al. 1979; Coggins et al. 1980), have been confined to a comparison of the varying amounts of particulate matter or tar delivered by smoke. In studies of this nature, attempts have been made to distinguish between the relative toxicities of the vapor phase and the particulate phase of tobacco smoke. The general conclusion reached is that gas phase components that penetrate to the small airways and alveoli may play a significant role in the production of peripheral airway and parenchymal diseases such as emphysema, whereas particulate phase components that deposit in larger airways may play a role in the development of disorders of the more proximal airways such as chronic bronchitis (USDHHS 1981). This generalization may not always hold, however. For example, in a review of the effects of smoking on mucociliary clearance, Newhouse (1977) noted considerable disagreement among investigators with regard to whether the vapor phase or the particulate phase was the major factor in smoke-induced dysfunction of the mucociliary transport system. Also, Coggins and associates (1980) observed an increase in both peripheral and central airway goblet cell number in rats after exposure to tobacco smoke from which most of the vapor phase had been removed. Cohen and James (1982) found that the level of oxidants in tobacco smoke (oxidants have been implicated in the pathogenesis of

emphysema) correlated with the amount of particulate matter in smoke from various brands of cigarettes. At present, therefore, attempts to associate a specific toxicologic response solely with either the vapor phase or the particulate phase of tobacco smoke are not recommended.

Because so little is known regarding the role of specific constituents or phases of tobacco smoke in the pathogenesis of COLD, this section of the Report is organized on the basis of specific insults to the respiratory system that may be brought on by exposure to whole tobacco smoke and that may lead to structural and functional changes within the lung. Included, as available information permits, are data on the known contribution of individual smoke constituents or phases to a specific insult. Human and animal studies are described separately to provide a perspective on the extent to which animal research has verified or extended clinical research and vice versa.

Preliminary Considerations

Tobacco smoking is generally accepted as the major cause of COLD (USDHEW 1979; USDHHS 1981). COLD is often subdivided into three categories: (1) uncomplicated bronchitis, characterized by mucus hypersecretion and cough, (2) chronic bronchitis with bronchiolar inflammation and obstruction of distal airways, and (3) pulmonary emphysema, characterized by distal air space enlargement with loss of alveolar interstitium. These three pathologic conditions are often considered collectively within the context of COLD because they can coexist in the lungs of smokers and because signs and symptoms associated with one condition may presage the development of another.

Effects on Airway Function and Ventilation

Human Studies

Cigarette smoke appears to have both chronic and acute effects on airway function. In adults, smoking over a period of years leads to narrowing of and histopathologic abnormalities in small airways (Ingram and O'Cain 1971; Cosio et al. 1980; Suzuki et al. 1983). Even in teenagers, regular smoking for 1 to 5 years is sufficient to cause demonstrable changes in tests of small airway function in some smokers (Seely et al. 1971); the lungs of young cigarette smokers who die suddenly show definite pathologic changes in the peripheral airways (Niewoehner et al. 1974).

The acute response to cigarette smoke has been reported to involve large airways, small airways, or both. Costello and associates (1975), in a study of asymptomatic smokers and nonsmokers, found that

tests of small airway function (maximum expiratory flow volume curves, closing volume, and frequency dependence of compliance) were unaltered after smoking one cigarette; however, specific airways conductance, a measure of large airway function, fell significantly in both groups. Essentially the same results were obtained by Gelb and associates (1979), who reported a decrease in airways conductance but little or no change in volume of isoflow (another test of small airway function) in healthy nonsmokers after smoking one cigarette. Likewise, McCarthy and colleagues (1976), using several different tests, found no evidence for an acute effect of intensive cigarette smoking on small airways, but did demonstrate increased large airways resistance. The decrease in conductance caused by cigarette smoke has been shown to occur within 7 or 8 seconds of a single inhalation (Rees et al. 1982), and filtration seems to reduce the degree of bronchoconstriction (Da Silva and Hamosh 1980). Irritant effects of tobacco smoke are not limited to the particulate phase, because exposure to oxides of nitrogen at levels present in cigarette smoke also can precipitate acute bronchospasm (Tate 1977). Nicotine does not appear to be responsible for the acute bronchoconstriction that accompanies cigarette smoking (Nadel and Comroe 1961).

Zuskin and coworkers (1974) showed that in healthy human subjects, smoking one or two cigarettes decreased flow rates on maximum and partial flow-volume curves, and concluded that smoking causes acute narrowing of small airways. Da Silva and Hamosh (1973) and Sobol and colleagues (1977) measured airways conductance, as well as maximum mid-expiratory flow rates, and concluded that both large and small airways are probably affected by the acute inhalation of cigarette smoke.

Though the bronchoconstrictive response to cigarette smoke has most often been attributed to a cholinergic reflex originating with stimulation of irritant receptors in the airways, there are data suggesting that histamine may also be involved. Walter and Walter (1982b) found a significant increase in the number of degranulated basophils in the blood of smokers 10 minutes after smoking compared with just before smoking. There is also some evidence to indicate that smokers may differ from nonsmokers in their responsiveness to inhaled histamine (Brown et al. 1977; Gerrard et al. 1980) as well as methacholine (Malo et al. 1982; Kabiraj et al. 1982; Buczko et al. 1984), but smoking immediately prior to an inhalation test does not appear to affect bronchial responsiveness to either histamine or methacholine (McIntyre et al. 1982).

Asthmatic subjects have a greater than normal susceptibility to the bronchoconstrictive effects of cigarette smoke when the smoke is actively inhaled. The question whether tobacco smoke plays a role in

allergic asthma has yet to be resolved completely (USDHEW 1979; Shephard 1982; Burrows et al. 1984).

Animal Studies

Binns and Wilton (1978) studied the acute ventilatory response to cigarette smoke in rats. They found that within the first 3 minutes after initiation of smoke exposure, tidal volume fell to 80 percent of the preexposure level, then rose to 160 percent after 9 minutes of exposure; respiratory rate dropped to 40 percent of the preexposure level within 1 minute and remained there for the duration of the exposure period. There was no adaptation of the acute ventilatory response after 4 weeks of daily smoke exposures. In a similar study, Coggins and associates (1982) found that rats exposed to a relatively low dose of cigarette smoke demonstrated a persistent depression in tidal volume and breathing frequency, whereas animals exposed to a relatively high dose exhibited an increase in tidal volume with no change in frequency.

Acute airway responses to cigarette smoke have not been studied as extensively in animals as they have been in man. Experiments in anesthetized dogs (Aviado and Palecek 1967), rabbits (Sellick and Widdicombe 1971), and cats (Boushey et al. 1972) indicate that acute smoke exposure elicits reflex bronchoconstriction. There also is evidence from experiments with isolated monkey lungs that smoke exposures stimulate histamine release (Walter and Walter 1982a). Histamine appears to be responsible, at least in part, for mediating the increase in collateral resistance in dogs following administration of cigarette smoke (Gertner et al. 1982).

The chronic effects of cigarette smoking on pulmonary function in dogs were studied by Park and coworkers (1977). Active inhalation of 100 and 200 puffs of diluted (1:4) smoke 5 days per week for periods of 6 months and 1 year, respectively, did not produce any noteworthy changes in pulmonary function. The effects of chronic cigarette smoke exposure on ventilation in rats were studied by Loscutoff and coworkers (1982). Animals exposed for up to 24 months to cigarette smoke containing various amounts of tar and nicotine were found to have higher tidal volumes and lower respiratory rates than sham-exposed animals. The most pronounced changes were seen in animals exposed to smoke from low tar, high nicotine cigarettes. Histopathologic examination of lungs taken from these animals revealed primarily granulomatous lesions with no evidence of emphysematous changes (Wehner et al. 1981). Roehrs and colleagues (1981) used operant conditioning techniques to get baboons to smoke 40 cigarettes per day for 3 years. Measurements of lung volumes, compliance, and expiratory flow showed no differences between smoking animals and sham animals, but airway reactivity to inhaled methacholine was decreased in animals that had smoked. Subse-

quently, Wallis and associates (1982) reported that both acute and chronic inhalation of nicotine mimicked this effect of cigarette smoke on bronchial reactivity in baboons.

Effects on Permeability of the Pulmonary Epithelium

The pulmonary epithelium functions to protect underlying structures from injurious agents deposited in the airway lumen. Cigarette smoke has been shown to diminish this protective function by increasing epithelial permeability in all regions of the tracheobronchial tree (Simani et al. 1974). In the airways, irritant receptors located just beneath epithelial tight junctions are more accessible following exposure to tobacco smoke. Stimulation of these receptors is thought to initiate rapid changes in ventilation and to induce bronchoconstriction (Widdicombe 1977). Likewise, mast cells, a source of potent bronchoconstrictive mediators, become more accessible to inhaled toxicants after smoke exposure (Guerzon et al. 1979). In the alveolar region, an increase in epithelial permeability may promote the transfer of noxious smoke constituents and endogenous proteases to the interstitium, thereby facilitating disruption of alveolar septa.

Human Studies

Subepithelial structures of the lung are important targets for smoke-induced injury, and research has shown that tobacco smoke alters epithelial permeability to allow offending agents to gain access to these structures. Minty and colleagues (1981) showed that, compared with nonsmokers, smokers had significantly shorter half-time lung clearance as measured with inhaled radiolabeled aerosols. After cessation of smoking, half-time clearance increased, but at 21 days it was still significantly less than that reported in nonsmokers. Using similar techniques, Kennedy and colleagues (1984) compared pulmonary epithelial permeability and bronchial reactivity to inhaled histamine in smokers and nonsmokers. These researchers found increased permeability in smokers, but could find no evidence of increased reactivity. Although the mechanism by which cigarette smoke induces an increase in alveolar epithelial permeability is not fully understood, it has been suggested that carbon monoxide may play an important role, with possible additional contributions from nicotine and oxides of nitrogen (Jones et al. 1980).

Animal Studies

In studies of rabbit tracheal rings exposed in vitro, just a few puffs of diluted cigarette smoke have caused ultrastructural changes in tracheal epithelial cells and an increase in the size of intracellular spaces, but junctional complexes between cells remain intact (Davies

and Kistler 1975). Boucher and associates (1980) found that, compared with controls, guinea pigs exposed to 100 or more puffs of cigarette smoke exhibited a significantly faster transfer rate for horseradish peroxidase across tracheal epithelium. These animals also demonstrated a progressive disruption of epithelial tight junctions as a function of the dose of tobacco smoke. Hulbert and associates (1981) reported that smoke-induced increases in guinea pig airway permeability were transient, reaching maximum levels at 30 minutes after acute exposure to 100 puffs and returning to control levels 12 hours later. Gordon and associates (1983) reported that acute exposure (48 hours) of hamsters to NO_2 caused a marked increase in bronchiolar and alveolar epithelial permeability to horseradish peroxidase. Restoration of the epithelial barrier was noted 48 hours after exposure in these animals. Ranga and associates (1980) demonstrated a similar increase in guinea pig tracheal epithelial permeability upon exposure to NO_2 for 14 days.

Effects on Mucociliary Structure and Function

The mucociliary system provides the lung with one of its most effective lines of defense against inhaled pollutants. Disruption of this system enables pollutants to remain in contact with the respiratory membranes for prolonged periods and increases the risk of toxic damage. Tobacco smoke can adversely affect mucociliary function by increasing the amount or viscosity of respiratory tract secretions or by depressing ciliary activity directly (Newhouse 1977; Wanner 1977).

Effects on Cells: Pulmonary Alveolar Macrophages and Polymorphonuclear Leukocytes

Pulmonary emphysema is believed to result from the slow degradation of the elastin framework of lung parenchymal tissue. Degradation of elastin is most likely initiated by elastolytic enzymes released locally in the lung and not adequately inhibited by endogenous antiproteases. Recent studies of the effects of cigarette smoke on these cellular sources of elastolytic enzymes have provided additional insights into the relationships between smoking and pulmonary emphysema. (See chapter 5.)

Human Studies

Normally, pulmonary alveolar macrophages (PAMs) function as a defense mechanism against particulate material deposited on the respiratory surfaces of the lung. However, cigarette smoke can induce a number of changes in PAMs that may promote excessive degradation of native lung tissue. For example, PAMs from smokers

have elevated elastase levels, and these cells may secrete elastase in vitro (Harris et al. 1975; Rodriguez et al. 1977; Hinman et al. 1980). Further, PAMs from smokers have been shown in vitro and in vivo to bind and internalize elastase released from polymorphonuclear leukocytes (PMNs) (Campbell et al. 1979; White et al. 1982). It has been suggested that during the phagocytosis of smoke particulates by PAMs, elastolytic enzymes may be released into extracellular spaces (Hocking and Golde 1979; Brain 1980; Kuhn and Senior 1978). Numerous investigators have reported significantly greater yields of PAMs from the lungs of smokers compared with nonsmokers (Green et al. 1977; Roth et al. 1981; Hoidal and Niewoehner 1982). The effects of smoking on PAM mobility are unclear. Some researchers have reported a significant increase in chemotactic migration of PAMs from smokers versus PAMs from nonsmokers (Warr and Martin 1974), but others have been unable to observe such an effect (Demarest et al. 1979).

Macrophages from smokers exhibit various morphologic, metabolic, and functional abnormalities. Structural changes noted in the PAMs of smokers include a slight increase in cellular diameter, the presence of "smokers inclusions" consisting predominantly of kaolinite particles (which have been shown to be cytotoxic to human PAMs in vitro (Green et al. 1977)) and increased numbers of lysosomes and phagolysosomes (Brody and Craighead 1975). Perturbations in several metabolic pathways have been observed in PAMs from smokers, and acrolein in smoke has been implicated in this toxicity (Green et al. 1977; Laviolette et al. 1981). The production of superoxide radicals and hydrogen peroxide (H_2O_2), both of which inhibit lung antiproteases, has been reported to be enhanced in the PAMs of smokers (Hoidal et al. 1981). Smokers' PAMs have also been shown to release chemotactic substances for PMNs (Gadek et al. 1978; Hunninghake et al. 1980). Additionally, there is evidence suggesting that PAMs from smokers secrete factors that promote the release of elastases from PMNs (Cohen et al. 1982).

As with PAMs, PMNs have been found in elevated numbers in the lungs of smokers (Reynolds and Newball 1975; Hunninghake et al. 1980a; Hunninghake and Crystal 1983). Exposure of PMNs to cigarette smoke condensate in vitro has been shown to promote the release of elastolytic enzymes (Blue and Janoff 1978). Hutchison and coworkers (1980) found that the particulate phase of cigarette smoke stimulated the release of lysosomal enzymes from human PMNs, but they did not quantitate this release specifically for elastases. A recent study by Totti and colleagues (1984) showed that nicotine was chemotactic for human PMNs and that it enhanced PMN responsiveness to other chemotactic factors. These results are in contrast with a previous study by Bridges and coworkers (1977) showing that nicotine, when used in higher concentrations than those employed

by Totti and colleagues, inhibited the chemotactic response of PMNs to casein.

In a preliminary laboratory study, Janoff and colleagues (1983) found that smokers have elevated levels of PMN elastase in their lung fluids compared with nonsmokers. This finding is of particular interest in that human PMN elastase has been shown to induce emphysema in animals (Janoff et al. 1977; Senior et al. 1977; Snider et al. 1984). There is also evidence that cigarette smoke alters PMN metabolism in such a way as to favor the release of toxic oxygen metabolites. PMNs from smokers with an elevated white blood cell count show a marked increase in the release of superoxide anions compared with PMNs from nonsmokers or with PMNs from smokers with a normal white cell count (Ludwig and Hoidal 1982). These unstable oxygen metabolites have harmful effects on various cells and tissues in vivo and in vitro (Sachs et al. 1978; Fridovich 1978), and are capable of injuring phagocytes and promoting the release of proteolytic enzymes (Hoidal and Niewoehner 1982). Oxidants derived from PMNs are also capable of inactivating lung antiproteases in vitro; this may be yet another mechanism by which smoke-affected PMNs contribute to the development of emphysema (Zaslow et al. 1983).

Animal Studies

Laboratory animal studies of the effects of cigarette smoke on lung free-cell population and integrity have yielded results similar to those obtained from human studies. Recruitment of PAMs to the lungs following cigarette smoke exposure has been demonstrated in a number of animal species, including mice (Matulionis and Traurig 1977; Guarneri 1977); hamsters (Hoidal and Niewoehner 1982), and monkeys (DeLucia and Bryant 1980). In the rat, PAM recruitment in response to smoke exposure appears variable. In two relatively similar studies, one group of investigators (Drath et al. 1978) found a depression in the number of PAMs in the lungs of rats exposed to smoke for 30 days, whereas another group (Walker et al. 1978) reported a significant increase in the number of PAMs after 6 weeks of smoke exposure.

Several authors have described the effects of cigarette smoke exposure on the morphology of rat PAMs. Observed changes include increases in PAM size, lipid vacuoles, and lysosomes, as well as the presence of "smokers inclusions" (Walker et al. 1978; Davies et al. 1978; Lewis et al. 1979). Cigarette smoke exposure of mice induces a similar pattern of morphological changes in PAMs (Matulionis 1977).

Alterations of PAM phagocytic capacity have been demonstrated in animals exposed to cigarette smoke. Fogelmark and colleagues (1980) reported a dose-related increase in the rate of phagocytosis of fungal spores in vitro by PAMs from hamsters and rats that had

been exposed to cigarette smoke. The ability of rats to mobilize PAMs in response to a bacterial challenge does not appear to be altered by cigarette smoke exposure (Guarneri 1977), nor is there a significant effect upon PAM phagocytosis of Staphylococcus aureus in rats after 30 days of smoke exposure (Drath et al. 1981). Macrophages from mice exposed to cigarette smoke for 4 weeks secrete significantly higher amounts of elastase than PAMs from controls. However, it is not known whether this effect is due to the stimulation of resident macrophages or to the recruitment of a highly exudative population of macrophages to the lungs (White et al. 1979).

A number of metabolic abnormalities have been noted in PAMs from smoke-exposed animals (Low et al. 1977). Among these is an increase in oxidative metabolism resulting in an increased production of superoxide anions. Hoidal and Niewoehner (1982) showed that enhanced oxidative metabolism in hamster PAMs was diminished if the particulates were filtered from the smoke. However, other workers (Drath et al. 1981) studying smoke enhancement of rat PAM oxidative metabolism have attributed this effect to the vapor phase of smoke. In another study of PAM oxidative metabolism in rats exposed to cigarette smoke for 180 days (Huber et al. 1980), it was reported that metabolism was activated after 30 days, and at the same time PAM superoxide dismutase (an enzyme that detoxifies superoxide radical) activity was depressed by 30 percent.

Animal PAMs, like human PAMs, can secrete PMN-directed chemotactic factor in response to various stimuli. For example, Gadek and colleagues (1980) demonstrated that noninfectious particulate material stimulated the release of PMN-specific chemotactic factor from guinea pig PAMs. Perhaps tobacco smoke particulates might evoke a similar response.

Owing to the ease with which PMNs can be harvested from peripheral blood, most research concerning the effects of tobacco smoke on PMNs has been conducted using human cells. In one laboratory study, hamsters exposed to cigarette smoke for 2, 8, and 20 hours showed a progressive recruitment of PMNs to the lungs. Control saline aerosol and filtered smoke did not stimulate recruitment of PMNs, suggesting that this effect of cigarette smoke resides in the particulate phase (Kilburn and McKenzie 1975).

Effects on Protease Inhibitors

In addition to efforts to characterize the effects of tobacco smoke on cellular sources of elastolytic enzymes, considerable research has gone into delineating the effects of tobacco smoke on the protease inhibitor defense mechanism in the lungs. While several protease inhibitors have been identified, α_1-protease inhibitor (α_1Pi) is consid-

ered to be the most important in neutralizing the effects of elastase (Gadek et al. 1981). Chemical oxidants are known to inactivate α_1Pi and diminish its capacity to inhibit elastase both in vitro and in vivo (Abrams et al. 1980). Cigarette smoke is an abundant source of chemical oxidants that can exert the same effect on α_1Pi and thereby reduce lung defenses against endogenous elastases.

Human Studies

The toxic effect of tobacco smoke on protease inhibitors has been demonstrated in a variety of experimental situations. Janoff and Carp (1977) reported that tobacco smoke condensate suppressed the inhibitory action of human serum, purified α_1Pi, and bronchopulmonary lavage fluids on both porcine and human elastase. The suppression of human serum elastase inhibitory capacity by smoke condensate solutions in vitro has also been demonstrated by others (Ohlsson et al. 1980).

Comparison of the protease inhibitory capacity of serum samples from smokers and nonsmokers has revealed a significant depression in smokers that is correlated with smoking history (Chowdhury 1981; Chowdhury et al. 1982). The latter studies also reported that the depression of serum protease inhibitors was related to an effect of smoke on the inhibitors per se, and not to a decrease in serum antiprotease concentration. Still, the effect of tobacco smoke on serum and lung lavage fluid antiprotease concentration and activity remains controversial. Several investigators have reported that smokers have elevated serum protease inhibitor levels (Rees et al. 1975; Ashley et al. 1980); others (Olsen et al. 1975; Warr et al. 1977), like Chowdhury and colleagues, have shown no difference in serum or lavage fluid protease inhibitor concentrations between smokers and nonsmokers.

Gadek and associates (1979) compared α_1Pi activity of lung lavage fluids taken from smokers and nonsmokers and found that smokers had a twofold depression of functional α_1Pi activity. The activity of α_1Pi in this study was tested against porcine pancreatic elastase. In a similar study (Carp et al. 1982), in which human neutrophil elastase was used, bronchoalveolar lavage fluids obtained from smokers had 40 percent less α_1Pi activity than fluids from nonsmokers. However, Stone and colleagues (1983) found that smokers' bronchoalveolar lavage fluids did not exhibit decreased functional α_1Pi activity when tested against either porcine pancreatic elastase or human neutrophil elastase, and suggested that increased elastase derived from neutrophils may be the main factor in the genesis of emphysema in smokers.

Smokers may have a functional deficiency in bronchial mucus protease inhibitor (BMPi) activity. A comparison of BMPi obtained from tracheal aspirates of smokers with BMPi from nonsmokers

revealed that smokers' BMPi was 20 percent less active against PMN elastase than nonsmokers' BMPi (Carp and Janoff 1980a).

Specific cigarette smoke constituents that may be responsible for the inactivation of lung protease inhibitors have not been identified. Nicotine and acrolein were studied for their ability to suppress α_1Pi activity and were found to be ineffective (Janoff and Carp 1977). Several studies have shown that oxidizing compounds such as chloramine-T and N-chlorosuccinimide can oxidize methionine groups on α_1Pi and reduce its activity against porcine pancreatic and human PMN elastases (Cohen 1979; Johnson and Travis 1979; Satoh et al. 1979; Abrams et al. 1980; Beatty et al. 1980). This has led to the current belief that oxidants in cigarette smoke may be involved in the inactivation of protease inhibitors (Janoff et al. 1983). In addition to free radicals (Pryor 1980), cigarette smoke contains oxides of nitrogen possessing their own free radical properties and able to react with olefins in the gas phase or with peroxides to generate potent oxy-radicals (Dooley and Pryor 1982; Pryor et al. 1983).

As mentioned previously, smoke condensate solution suppresses the elastase inhibitory capacity of serum α_1Pi in vitro. This suppression can be prevented by the incorporation of phenolic antioxidants into the test media (Carp and Janoff 1978). Similarly, BMPi suppression by smoke condensate can be prevented by antioxidants (Carp and Janoff 1980a). Cohen and James (1982) used o-dianisidine oxidation to quantify the levels of oxidants in tobacco smoke condensates from various brands of cigarettes and found that oxidant levels correlated with capacity to suppress α_1Pi deactivation of elastase. Further, this study provided evidence that peroxides and superoxide anions were responsible for the loss of α_1Pi activity, because inclusion of catalase and superoxide dismutase in the test system reduced smoke condensate effects on α_1Pi activity. Bronchoalveolar fluid from smokers contains some amount of oxidant-inactivated α_1Pi, as evidenced by the presence of methionine sulfoxide residues (Carp et al. 1982).

In addition to the numerous oxidizing agents present in cigarette smoke, byproducts of smoke-stimulated phagocyte metabolism represent another potential source of oxidants capable of inactivating lung protease inhibitors. Carp and Janoff (1979) demonstrated that phagocytosing human PMNs produce activated oxygen species that diminish the elastase inhibitory capacity of human serum and pure α_1Pi in vitro. These workers presented evidence to show that hydroxyl radicals resulting from the reaction between superoxide anions and H_2O_2 were responsible for this effect. The inactivation of α_1Pi by a myeloperoxidase-mediated reaction was also described in the study, which concurs with other studies demonstrating that purified myeloperoxidase, in conjunction with H_2O_2 and a halide ion, can inactivate α_1Pi in vitro (Matheson et al. 1979, 1981). Further

work has shown that activation of human blood monocytes, PMNs, and PAMs by use of a membrane-perturbing agent (as opposed to phagocytosis) results in the release of superoxide anions and H_2O_2 and the suppression of serum elastase inhibitory capacity (Carp and Janoff 1980b). Clark and colleagues (1981) have demonstrated that the myeloperoxidase-H_2O_2-halide system from chemically stimulated PMNs oxidizes α_1Pi in vitro. Similar evidence ascribing inactivation of BMPi to the myeloperoxidase-H_2O_2-halide system has been reported (Carp and Janoff 1980a). In the studies noted above, phagocyte-derived oxidants were shown to be capable of inactivating α_1Pi when porcine pancreatic elastase was used as the substrate. These findings were recently extended to include the more pathophysiologically relevant protease, human neutrophil elastase (Zaslow et al. 1983). Little is known about in vivo inactivation of protease inhibitors by phagocyte-derived oxidants, other than that inactive α_1Pi (in the oxidized state) has been found in the synovial fluid of patients with inflamed joints (Wong and Travis 1980). The extent to which oxidants from stimulated phagocytes play a role in the suppression of lung α_1Pi activity in smokers is at present unknown.

Animal Studies

Although most of what is known about cigarette-smoke-induced oxidant injury to lung protease inhibitors has been derived from human studies, some work has gone into the effects of cigarette smoke on lung protease inhibitors in laboratory animals. It has been demonstrated that very brief exposure of rats to cigarette smoke can cause a significant reduction in the elastase inhibitory capacity of α_1Pi obtained from lung lavage fluid (Janoff et al. 1979). Very likely this toxic effect of cigarette smoke is caused by oxidant damage to protease inhibitors, because treatment of the lavage fluid with a reducing agent partially restored normal elastase inhibitory capacity and because animals rendered oxidant tolerant by preexposure to ozone did not exhibit a significant reduction in α_1Pi activity following exposure to cigarette smoke.

Effects on Lung Tissue Repair Mechanisms

A preponderance of the research to elucidate mechanisms by which cigarette smoking induces emphysema has focused on the factors that initiate lung tissue degradation. Recent studies suggest, however, that the increased risk of emphysema associated with cigarette smoking may be due partially to the effects of smoke on lung repair mechanisms.

Human Studies

For the most part, work concerning the effects of cigarette smoke on lung repair mechanisms has been conducted in experimental animals. It has been shown, however, that cigarette smoke contains an inhibitor that can prevent the cross-linking of human fibrin polymers and thereby impede normal tissue repair (Galanakis et al. 1982). Smoke and smoke constituents have also been shown to induce membrane damage in human lung fibroblasts (Thelestam et al. 1980). Of 464 smoke constituents tested, approximately 25 percent caused membrane damage. The most active constituents were amines, strong acids, and alkylated phenols; nitriles and polycyclic aromatic hydrocarbons were inactive.

Animal Studies

Cigarette smoke has been shown to affect elastin synthesis in vitro and elastin repair in vivo. Laurent and coworkers (1983) determined the effect of solutions of smoke condensate on elastogenesis in vitro by measuring the formation of desmosine (one of the major cross-linking amino acids of elastin) during conversion of tropoelastin to elastin. Using a cell-free system of purified tropoelastin from chick embryo aorta or porcine aorta and lysyl oxidase purified from chick embryo or bovine lung, these investigators found that desmosine synthesis was inhibited from 80 to 90 percent in the presence of an aqueous solution of the gas phase of cigarette smoke. Elastin repair in vivo has been reported to be retarded by tobacco smoke. Osman and colleagues (1982) showed that hamsters with elastase-induced lung injury resynthesized elastin at a reduced rate if they were exposed to six or seven puffs of whole cigarette smoke hourly for 8 hours per day during the repair period.

Summary and Conclusions

1. The mass median aerodynamic diameter of the particles in cigarette smoke has been measured to average approximately 0.46 μm, and particulate concentrations have been shown to range from 0.3×10^9 to 3.3×10^9 per milliliter.
2. The particulate concentration of the smoke increases as the cigarette is more completely smoked.
3. Particles in the size range of cigarette smoke will deposit both in the airways and in alveoli; models predict that 30 to 40 percent of the particles within the size range present in cigarette smoke will deposit in alveolar regions and 5 to 10 percent will deposit in the tracheobronchial region.
4. Acute exposure to cigarette smoke results in an increase in airway resistance in both animals and humans.

5. Exposure to cigarette smoke results in an increase in pulmonary epithelial permeability in both humans and animals.
6. Cigarette smoke has been shown to impair elastin synthesis in vitro and elastin repair in vivo in experimental animals (elastin is a vital structural element of pulmonary tissue).

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CHAPTER 9. ROLE OF THE PHYSICIAN IN SMOKING CESSATION

CONTENTS

Introduction

Although a variety of health care providers have attempted to change the smoking behavior of the groups with whom they work (USDHEW 1979), most of the research in this area, and this review, is confined to patient populations or patient groups who provide opportunities for physician intervention. The nature and extent of the relationship between patient and physician enhances the opportunity for long-term behavior change. Major international studies on utilization of health care reveal that 70 percent or more of North Americans see a physician at least once a year (Kohn and White 1976; National Center for Health Services Research 1983; Pacific Mutual 1978; National Center for Health Statistics 1982). Given this frequency of contact between smokers and their physicians, some 38 million of the 54 million adults in the United States who smoke could be reached annually with a smoking cessation message. Even if only 5 to 10 percent quit on a long-term basis, the potential impact of such contact is enormous. A recent study comparing free medical care to insurance plans requiring shared cost by participants did not show a beneficial impact on smoking (or other health habits associated with coronary heart disease and some types of cancer) from the average of one to two more encounters per year for several years (Brook et al. 1983). The authors comment that "these health habits, especially smoking, were at levels at which substantial health benefit from behavior change was possible" (p. 1432). Thus, physician contact alone does not increase smoking behavior change. Rather, a mix of physician, motivation, educational, and training efforts are doubtless called for.

Many techniques have been described in the literature to assist physicians in treating cigarette smoking in their patients (Allaire 1983; Best 1978; Bohm and Powell 1982; Danaher et al. 1980; Fowler 1983; Hochbaum 1975; Hymowitz 1977; Indyke and Ellis 1980; Luban-Plozza 1977; Pechacek and Grimm 1983; Pechacek and McAlister 1980; Pomerleau 1976; Rose 1975/76; Rosser 1977; Russell 1971; Secker-Walker and Flynn 1983; Sherin 1982; Shipley and Orleans 1982; Windsor et al. 1979). These range from supplying information about smoking and health with advice to quit smoking to implementing complex behavior modification techniques with routine monitoring and long-term followups.

Lichtenstein and Danaher (1978) have described a hypothetical model for the various roles that the physician can perform. According to their formulation, the physician can "(1) act as a model of a healthy lifestyle by not smoking, (2) provide information clarifying the risks associated with smoking and the risk reduction if the patient stops, (3) encourage abstinence by direct advice and suggestions, (4) refer the patient to a smoking cessation program, and (5) prescribe and follow up the use of specific cessation and

maintenance strategies in his or her own office management" (p. 233). This scheme is a hierarchical one, with each role subsuming the behavior of the ones that precede it. Other roles such as political lobbyist and researcher are related only indirectly to patient care (Rosen and Ashley 1978).

In addition to advising their patients to quit, an overwhelming majority of physicians have quit smoking; the prevalence of smoking among physicians has most recently been estimated at 10 percent or less in the United States, considerably below that of the general population (Enstrom 1983; Fletcher and Doll 1969; Garfinkel 1976; USDHEW 1976; Sachs 1983). Physicians are, therefore, carrying out their role as exemplars. In a major national survey, over 90 percent agreed that it was their responsibility to set a good example for patients by not smoking cigarettes (USDHEW 1976). With regard to other roles, the majority of reports (both research and advisory) indicate that physicians usually function as information providers and advice givers. However, evaluations of treatment procedures that can be used for referral or in-depth treatment have also been carried out. It is expected that as results become known and more referral agencies are available, more physicians will be expanding their roles.

The literature on rates at which physicians advise patients to quit smoking shows a disparity between physician estimates and patient reports. Over time, the proportion of physicians recommending cessation has increased dramatically. A mid-1960s survey revealed that 38 percent of physicians claimed that they advised "all" or "almost all" (95 to 100 percent) of their patients who did not have smoking-related disorders to quit or cut down (Green and Horn 1968). Eighty-eight percent of physicians claimed they gave this advice to patients with lung and pulmonary conditions. In 1979, 85 to 92 percent of physicians participating in the evaluation of a quit smoking kit said they had spoken to smoking patients in the past few weeks, advising quitting to 6 to 7 out of the last 10 smoking patients seen (American Cancer Society 1981). In a 1981 survey of primary care practitioners in Massachusetts, 90 percent of all physicians who responded said they routinely asked about smoking; however, only 58 percent felt "very prepared" to counsel patients, and a mere 3 percent felt they were currently "very successful" in helping patients to change their smoking behavior (Wechsler et al. 1983). Ninety-eight percent of a Canadian sample of primary care physicians surveyed in late 1981–1982 reported advising patients who smoke to stop, with 45 percent claiming some success (Battista 1983; Battista and Spitzer 1983). There is evidence that smoking physicians feel less comfortable in dispensing advice to quit smoking and, therefore, do it less forcefully (American Cancer Society 1981).

The majority of persons who smoke feel that physician advice to quit or cut down on smoking would be influential (American Cancer Society 1977; Pacific Mutual 1978). In a 1978 survey of the public, doctor's advice was perceived to be the most effective means of prompting cessation or reduction among six alternatives considered, the other five being prohibition of smoking at work and in public places; urging by children, spouse, or relatives; higher taxes on tobacco; antismoking informational campaigns at work; and antismoking advertising on television (Pacific Mutual 1978). In this survey, 76 percent of smokers reported that doctor's advice would be "very" or "somewhat" effective in this regard. Given this general level of enthusiasm and confidence in physician-delivered messages, actual rates of reported advice are quite low. In the survey just reported, only 8 percent of former smokers spontaneously mentioned a doctor's recommendation as a cause of their cessation, although 51 percent cited health reasons (Pacific Mutual 1978). In the 1975 Adult Use of Tobacco survey, a full 64.6 percent of male and 60.8 percent of female current smokers claimed they had never received advice from any doctor about quitting, cutting down, or continuing smoking (USPHS 1976). About 20 percent of current smokers had been advised to quit. Combining advice to quit or cut down, the percentage rose to approximately 35 percent. A somewhat lower estimate of physician advice was obtained from a nationwide study of approximately 8,000 people (Stewart et al. 1979). Advice to quit or cut down was reported by 22.4 percent, and lack of advice by 77.6 percent. However, patient recall for the details of a physician visit may be flawed. In one study, almost complete recall of cessation advice was reported 1 year later (Mausner 1970), but in a second study only 50 percent of patients recalled cessation advice 2 months after it was given (Rose and Udechuku 1971).

It seems quite likely that physicians do offer varying degrees of advice and guidance to their patients (Fowler and Jamrozik 1983; Wechsler et al. 1983), and in view of the decrease in social acceptability given to the smoker, more physicians will be spending more of their time and energy in this way in the future. A growing number of editorials in medical journals have been devoted to the importance of primary prevention and to motivating physicians to this task (Check 1979; Yankauer 1983).

This chapter reviews and summarizes studies of smoking cessation in various groups of patients, with a special focus on physician intervention. Four classes of patients are considered: general practice, obstetric, pulmonary disease, and cardiovascular disease. Reviews of this literature show a positive relationship between severity of disease and the likelihood of quitting smoking (USDHEW 1979, 1980; Lichtenstein and Danaher 1978; Pederson 1982). However, Pederson cautions that a causal interpretation of this relationship

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may not be warranted, as physician involvement may be greater and the effect of physician advice more salient or intense with sicker patients. In addition, a section on research using nicotine chewing gum as a treatment is included. Suggestions regarding future research and treatment are also presented.

Patient Groups

General Practice Patients

Unlike the physician whose practice involves mainly patients with pulmonary or cardiac disease, a large proportion of the general practitioner's time may be spent in lifestyle modification of a preventive nature with patients who are not experiencing smoking-related problems. It may be that compliance among these patients is dependent upon diagnosis, but no available studies have related the reason for the office visit to success or failure in quitting, although most counseling is said to take place during regular checkups or during visits for respiratory problems, much less often than during visits for unrelated major medical problems or minor problems (Battista 1983).

Nine studies have dealt specifically with general practice patients. Mausner et al. (1968) followed 157 smoking patients of two physicians sharing an office. One physician advised all the smokers in his practice who came to his office over a 2-month period to quit (n=121). Patients were told that smoking was harmful, and were given written information on quitting techniques as well as lobeline, a nicotine substitute. The other physician made no special mention of smoking (n=36 patients). At a 6-month followup, 33 percent of those who were told to quit had reduced the amount they smoked, compared with 9 percent in the group without such cessation advice. Reduction was defined as a decrease of at least 10 cigarettes per day. There was no validation of self-report. The factors found to be related to decrement in smoking were higher initial consumption and number of pack-years; a marginally significant relationship with being male was noted, and for both sexes it was the heavier smokers who changed.

Porter and McCullough (1972) compared the smoking behavior of 101 randomly selected patients who were counseled by one general practitioner about their smoking with 90 patients who were not counseled. Counseling consisted of advice, discussion, and a leaflet. There was no significant difference in quit rate after 6 months between the two groups: 2.5 percent in the counseled group and 4.4 percent in the not counseled group quit. No validation was performed.

Handel (1973) followed for 1 year a group of 100 patients whom she had advised in 1- to 7-minute messages to quit smoking. The advice

was followed by 38 percent of the men and 11 percent of the women. Eighteen percent of the remaining male smokers and 22 percent of the female smokers reported reducing consumption by more than 50 percent. No control group was included in this study.

Pincherle and Wright (1970) reported a smoking intervention in a clinic that provided health examinations of business executives on an annual or biannual basis. Physicians were encouraged to deliver a strong antismoking message, and a booklet was made available. Results varied among the 10 participating physicians; between 17 and 35 percent of the 1,493 smokers seen at a followup visit at approximately 18 months had stopped smoking cigarettes or had reduced their smoking more than 30 percent. There were no controls or validation of self-report. The doctor's own past or present smoking habits only partially accounted for the variation in success rates (cf. American Cancer Society 1981). The quit rate of 19 percent reported by Richmond (1977) in a similar setting is consistent with their findings. In preliminary findings, Rosser (1979) reported that 10 percent of smokers counseled by family physicians about cardiovascular risk reduction report smoking cessation 1 or 2 years later.

In a large-scale study of 2,138 patients of 28 London physicians in five practices, Russell et al. (1979) assessed the effectiveness of physician smoking advice in comparison with no advice. Assignment to group was by day of attendance at practice. Four groups were used: a nonintervention control, a questionnaire-only control, an advice-only group, and an advice group receiving a two-page pamphlet and a warning of subsequent followup. Advice was delivered in the physician's own style in a 1- or 2-minute message. At 1-year followup, the overall quit rate was 14.4 percent—respectively for each group, 10.3, 14.0, 16.7, and 19.1 percent. The percentages of patients who stopped within 1 month of the initial visit and who were still abstinent at followup were 0.3, 1.6, 3.3, and 5.1 percent, respectively. These results were statistically significant, indicating that advice to quit was effective and enhanced by written material and information about a subsequent followup. The major effect was to increase motivation in terms of the percentage of patients in each group attempting to quit but not the success rate of quit attempts, and to reduce relapse at the 1-year point compared with the initial 1-month assessment. One can interpret this as due to the limited scope of advice, focused on health education, and not to quitting skills. Quit rates differed markedly among physicians and were inversely related to the patient's initial consumption. Validation of the verbal report of abstinence on a very small subsample of patients, using a measure of nicotine concentration in saliva, revealed a low deception rate (7 percent), which may have been unreliable, owing to patient selection methods.

In an attempt to replicate findings of Russell et al. (1979) in a Canadian sample, Stewart and Rosser (1982) randomly assigned 691 patients to one of three groups: control, advice, and advice plus pamphlet. There were no differences between the groups; only 3 to 4 percent of patients had stopped smoking at the 5-month followup and were still abstinent at 1 year. At that later followup, the overall success rate was 11.7 percent; no objective measure of smoking status was included. The researchers note that the control group had a higher rate of long-term quitting (3.1 percent) than in the Russell group's 1979 study (0.3 and 1.6 percent).

A second study by Russell et al. (1983b) enrolled a sample of 1,938 cigarette smokers, aged 16 and older, who visited 34 general practitioners in six group practices in Kent and London in November 1980. All smokers were included and were assigned in balanced design by week of attendance to one of three groups; nonintervention controls, 1 to 2 minutes of advice in the physician's own style plus booklet and warning of followup, and similar advice plus booklet plus offer of a nicotine gum prescription. A questionnaire was mailed and a personal followup was performed after 4 months and 1 year. Patients who did not provide adequate data at both points were counted as smokers. Two-thirds of those who claimed to have quit at each time point were checked by measurement of expired air carbon monoxide. At 1 year, self-reported quit smoking rates in the three groups were 13.4, 10.8, and 16.2 percent ($p < 0.02$), respectively. For those patients not smoking at 4 months and at 1 year, the cessation rates were 6.0, 6.4, and 11.9 percent, respectively ($p < 0.02$). After correction for those who refused or failed chemical validation (22 percent) and for those who switched from cigarettes to pipes or cigars, the cessation rates were 3.9, 4.1, and 8.8 percent ($p < 0.001$). Compared with this group's earlier study (Russell et al. 1979), cessation rates in these nonintervention controls (also see Stewart and Rosser 1982) are much higher (3.9 versus 0.3 percent), but the rates are not directly comparable because the initial followups are not identical (1 month versus 4 months). However, cessation rates in the advice/booklet/warning groups are quite similar (5.1 versus 4.1 percent). Cessation rates in the nicotine gum group are discussed later in this chapter.

Wilson et al. (1982) reported that a simple followup procedure may enhance the effects of physician advice. A group of 211 smokers over 16 years of age attending two middle-class, university-based practices in Hamilton, Ontario, over a 6-month period were recruited. Nonsmokers, pregnant women who smoked, and smokers with communication disorders or terminal illness were excluded. All participating patients received brief (3 to 5 minute) intensive counseling to quit smoking and a pamphlet and, subsequently, were randomly assigned to one of two groups. The 106 smokers in the

treatment group were given followup appointments at 1, 3, and 6 months to review and discuss problems, while the control group of 105 smokers received followup appointments as needed for complaints, but no further smoking cessation counseling. In the treatment group, 23 percent reported cessation at 6 to 14 months, compared with 12 percent of the control condition ($p < 0.05$). When losses at followup were counted as continuing smokers, the success rates dropped to 19.8 and 10.5 percent, respectively. No objective validation was included. Success in quitting was significantly related to several factors: having made previous attempts to quit, judging that it would not be extremely difficult to quit, and smoking regular tar cigarettes (versus low tar).

Pregnant Patients

A number of studies concern smoking cessation and pregnant women, a group of patients who are not experiencing smoking-related disease, but for whom continued smoking has serious implications. It has been documented that smoking during pregnancy, especially in the last trimester, can result in such consequences as reduced birthweight and increased fetal and neonatal mortality (Landesman-Dwyer and Emanuel 1979; USDHHS 1980; USPHS 1973). Some evidence also suggests that lactation in smoking mothers is inhibited and that smoking during pregnancy may be related to childhood hyperkinesis (Denson et al. 1975) and developmental retardation (Landesman-Dwyer and Emanuel 1979). According to Fielding and Yankauer (1978), the pregnant woman has been largely ignored as a target for smoking cessation techniques because evidence concerning the dangers to the fetus is just beginning to emerge. Increasing concern is being expressed for the pregnant smoker (USDHHS 1980), and many smoking cessation strategies have been described to assist women (Gastrin 1983; King and Eiser 1981; Kretzschmar 1980).

The prevalence of smoking during pregnancy and rates of physician advice to quit or cut down have been previously summarized (USDHHS 1980). Almost 60 percent of physicians specializing in obstetrics and gynecology who participated in the 1975 CDC Survey of Physician Advice claimed that they advised most to all of their pregnant patients to quit or to cut down (Danaher 1978). As in the general population estimates of remembered physician advice cited earlier, fewer women report such advice given during pregnancy. About 24 percent of women last pregnant during the 5 years from 1970 to 1975 remembered such advice (Harris 1979).

Rates of cessation among regular smokers during pregnancy ranged from 0.9 to 35 percent, with a median of approximately 20 percent, in the 11 studies summarized in the 1980 Report of the Surgeon General *The Health Consequences of Smoking for Women*

(USDHHS 1980). Results of more recent studies were consistent with the median figure. Hackett (1979) interviewed 57 women at various stages of pregnancy, and 16 percent reported quitting at some time in the prenatal period. Fried et al. (1980) reported a similar quit rate in a group of 67 smokers. The 1980 National Natality Survey (NNS) examined changes in smoking and drinking behavior among 4,405 mothers during pregnancy (NCHSR 1983). Questionnaires were mailed 6 months after delivery to married mothers who delivered live-born infants. Nonmarried mothers were not included in the analysis because of problems with the State government requirement of confidentiality. Mothers were much more likely to stop drinking than to stop smoking during pregnancy. Of those who engaged in the behavior before pregnancy, 30 percent stopped drinking compared with almost 18 percent who stopped smoking. White mothers had the highest smoking rates before pregnancy (32.0 percent) when compared with blacks (24.8 percent), Hispanics (23.3 percent), and others (19.9 percent). No significant differences by age, race, or Hispanic origin were found in the proportion who stopped smoking, although blacks appeared to have slightly lower quit rates (13 percent) than either whites (18 percent), Hispanic (25 percent), or other mothers (21 percent). Educational attainment, however, was directly related to the tendency to stop smoking. Of white mothers who smoked, the proportion who stopped during pregnancy ranged from 10 percent for mothers with the least education (did not graduate from high school) to 24 percent of mothers with the most education (16 or more years education).

Three studies have combined observations of smoking discontinuance in pregnancy with some interventional tactic. Baric et al. (1976) found that their entire sample of 134 pregnant British women thought smoking could be harmful to the fetus, but only 16 percent received this information from a doctor; most had received it from the media. A total of 24 patients (18 percent of the sample) quit smoking on their own; 63 of the remaining women participated in an intervention program involving exposure to educational material by a "doctor," and 47 served as controls. Subsequent analysis revealed that while the groups did not differ significantly in the number of women who quit smoking 11 weeks following treatment (14 percent), significantly more in the intervention group modified their consumption.

Dalton et al. (1981) surveyed smoking behavior (using self-report only) in 282 pregnant British women, of whom 49 percent smoked at the beginning of pregnancy. Thirty-two percent of the smokers in the sample claimed they were given no medical advice to quit smoking. Ten percent reported quitting smoking during pregnancy. A local and a national poster and leaflet campaign designed to increase smoking cessation rates at a prenatal clinic had no effect. The advice

to curtail smoking was given in a minimal fashion, and rarely by general practitioners. Knowledge of the hazards of smoking was higher among those who acknowledged receiving advice than among those not acknowledging advice. Also, those who quit were better informed about fetal hazards than those who continued to smoke.

Using a breath test for carbon monoxide to validate self-report, smoking status was assessed in 179 pregnant women of moderate to low socioeconomic status in Pittsburgh (Hughes et al. 1982). Most women (61 percent) were in the third trimester of pregnancy. At the beginning of pregnancy, 55 percent of the women reported smoking; of these, 19 percent reported that they had quit and 37 percent reported that they had reduced their smoking rate during pregnancy. The rate of false positive results among self-reported nonsmokers was 12 percent, and the rate of false negative results among self-reported smokers was 12.5 percent. Both continuing smokers who reduced consumption and quitters made those changes in the first trimester, and gave pregnancy-related reasons for changing their smoking behavior. However, none of the pregnancy-related factors examined were statistically associated with quitting or cutting down. Most of the continuing smokers expressed a desire to quit or to cut down and wished to receive treatment, but only 1 woman (of 80) attended a free cessation program nearby. The authors note that interventions scheduled early in pregnancy during prenatal outpatient visits would be optimal for such a group.

A fourth test of an intervention designed for pregnant smokers was reported by Danaher et al. (1978). Eleven women participated in a 6-week program delivered by behavioral scientists that included instruction in behavior modification, deep muscle relaxation, and educational information. Of the eight women who completed the program, four quit smoking and another three markedly reduced consumption. At a 9-month followup, three women were completely abstinent, and one women was smoking less than one cigarette daily. No control group was included in this study, so it is not possible to evaluate the relative effectiveness of the treatment package.

Finally, three randomized trials of smoking cessation interventions with pregnant women have been reported. Donovan (1977) and co-workers (Donovan et al. 1975) randomly assigned 588 pregnant British women to a control or an intervention group receiving intensive antismoking information. Unfortunately, the number of patients achieving abstinence at least for the duration of their pregnancies was not reported. There was a significantly larger reduction in amount smoked by the intervention group than by controls, however. Almost one-third of a group of women who voluntarily quit resumed smoking before the end of pregnancy, a finding not replicated in U.S. women by Sexton and Hebel (1984).

Bauman et al. (1983) reasoned that exposure to alveolar carbon monoxide (CO) levels in pregnancy would provide a concrete demonstration of a current and personal consequence of smoking. All pregnant women attending a public prenatal clinic over a 6-month period were randomized to experimental and control groups; 47 percent of the 170 women were smokers. Experimental subjects, both smokers and nonsmokers, observed their CO levels in a group setting. Control subjects did not have the CO intervention. All subjects were read a script on smoking, CO, and adverse effects of smoking during pregnancy; health educators implemented all procedures. In the experimental group, there were 36 women smokers exposed to their own CO; the control group contained 43 smokers. Six weeks after the intervention, there was no difference in quit rates between the two groups (7 percent of experimental subjects and 13 percent of control subjects had quit) or on five other measures of smoking behavior. After adjusting for covariates used in assessing attrition effects and comparison group equivalence, CO levels were significantly lower in the treatment group. The authors concluded that the intervention had either a small or no influence on cigarette smoking.

The first prospective, randomized, controlled clinical trial demonstrating that a reduction of smoking produces a favorable change in infant birthweight contained an effective smoking intervention (Sexton and Hebel 1984). Pregnant women who smoked at least 10 cigarettes per day at the beginning of pregnancy and who had not passed their 18th week of gestation were eligible for entry into the trial. A total of 935 women were recruited from the practices of 52 private obstetricians and a university hospital's obstetric clinic in a large metropolitan area; subjects were randomly assigned to experimental and control groups. Subjects in both groups reported smoking an average of a pack a day at the beginning of pregnancy, but to have reduced their smoking to about 11 cigarettes per day by the time of randomization. The smoking intervention was delivered by health educators, and consisted of encouragement and assistance to stop smoking through informational and behavioral strategies. Each woman received a minimum of one personal visit, supplemented by telephone and mail contacts. The control subjects received no contact until followup. A questionnaire and saliva sample (for thiocyanate analysis) were obtained at randomization and during the followup in the eighth month of pregnancy. At followup, 43 percent of women in the treatment group and 20 percent of women in the control group reported quitting smoking. Overall, there was a significantly greater reduction of smoking in the treatment group; group means for number of cigarettes smoked per day were 6.4 for experimental subjects and 12.8 for control subjects, respectively. Mean thiocyanate levels were significantly lower in the experimental group than in the

control group, verifying self-report on a group level. Cessation results in the control group, contrary to the findings of Donovan (1977), showed that very few women who quit smoking in the first trimester resumed smoking during the pregnancy; also, very few who had not quit in the first trimester quit on their own later in the pregnancy. This study clearly demonstrated that an "antismoking intervention is feasible to conduct, accepted by pregnant women, and effective in producing a reduction in smoking, and most important of all, that cessation even during pregnancy improves the birthweight of the baby" (Sexton and Hebel 1984, p. 915). These are important results, obtained in a relatively high risk study group, and deserve to be followed up.

Patients With Pulmonary Disease

A large proportion of the patients seen by a pulmonary specialist are experiencing, firsthand, the health problems resulting from continued smoking (Pederson 1982; Windsor et al. 1979). The literature cited below demonstrates that the presence of serious illness adds credence to the physician's message and is related to increased compliance (Cooperstock and Thom 1982; Daughton et al. 1980; Davison and Duffy 1982; Hall et al. 1983; Pederson and Baskerville 1983; Pederson et al. 1982). The evidence continues to accumulate that smoking cessation is followed by favorable changes in cardiopulmonary functioning (Ball and Turner 1974; Buist et al. 1976, 1979; Peterson et al. 1968; Schuman 1971; World Health Organization 1975) and in morbidity and mortality (Hammond 1965, 1966; Kuller et al. 1982; USDHHS 1981; UUSDHEW 1979; Weinblatt et al. 1971; Wilson 1973).

A number of studies (Baker et al. 1970; Burns 1969; Burnum 1974; Dudley et al. 1977; Guzman 1978; Mausner 1970; Peabody 1972; Pederson et al. 1980; Raw 1976; Rose and Hamilton 1978; Rose and Udechuku 1971; Williams 1969) have investigated smoking cessation among patients with respiratory disease. Table 1 summarizes these studies, including data on subject groups, sample sizes, quit rates, and duration of followup.

Eleven studies have investigated quit rates among pulmonary disease patients following physician advice (Baker et al. 1970; Burns 1969; Burnum 1974; Cooperstock and Thom 1982; Daughton et al. 1980; Davison and Duffy 1982; Guzman 1978; Mausner 1970; Peabody 1971; Trahair 1967; Williams 1969). Compliance rates vary from 15 percent to 51 percent, but none of these studies included no-advice control groups as a test of the effectiveness of physician counseling. A trend toward lower quit rates has occurred in the more recent studies.

None of the investigations attempted to identify patient characteristics associated with compliance, although some results suggest that

TABLE 1.—Studies assessing smoking cessation rates among patients with pulmonary disease

Study	Groups	Quit rate (percent)	Duration of followup	Comments[1]
Baker et al. (*1970*)	Multidimensional treatment, N=134	34	6 months	No control group
Burns (*1969*)	Private, N=94	47	3 months	No control group; success related to less withdrawal, lower neuroticism, and being male
Burnum (*1974*)	Private	25	Average, 5 years	No control group
Cooperstock and Thom (*1982*)	Respiratory, N=33	36	Cross-sectional	Quit rates compared with circulatory and musculoskeletal groups
Daughton et al. (*1980*)	Hospitalized, N=107	63	Cross-sectional	No control groups, retrospective; ex-smokers and smokers differed in psychosocial factors, pack years
Davison and Duffy (*1982*)	Lung or cancer, N=52	25	5 years	No control group
Dudley et al. (*1977*)	Chest clinic Never smokers, N=66 Smokers, N=42 Quitters, N=132	76	Cross-sectional	No control group, retrospective; ex-smokers and smokers differed in psychosocial assets, stability, and expression of depression
Guzman (*1978*)	Chest clinic, N=123	20	3 to 24 months	No control group
Hall et al. (*1983*)	Cardiopulmonary Health motivation, N=19 Aversion condition, N=16	 10 30	6 months	No significant difference in quit rate; mood states related to reduction; objective verification
Mausner (*1970*)	Private Eight physicians, N=136	51	3 to 12 months	No control group; ex-smokers and smokers differed in severity of disease

TABLE 1.—Continued

Study	Groups	Quit rate (percent)	Duration of followup	Comments[1]
Peabody (*1972*)	Not given	25	Not given	Only quit rate reported
Pederson et al. (*1980*)	Private, N=117	27.4	Retrospective 6 months to 7 years	No control group; multivariate analysis; ex-smokers and smokers differ on diagnosis, age, and sex
Pederson et al. (*1982*)	Newly diagnosed pulmonary, N=308	12.9	6 months	No control group; multivariate predictive model developed, 92 percent accuracy
Raw (*1976*)	Motivating advice—"white coat" Motivating advice—"no white coat" Interview—"white coat" Interview—"no white coat," N=10 per group	Overall 12.5	3 months	Results not presented for individual groups
Rose and Hamilton (*1978*)	Normal case, N=731 Intervention, N=714	14 36	3 years	High risk for cardiorespiratory disease
Rose and Udechuku (*1971*)	Hospitalized with chronic bronchitis, N=29	25	Not given	No control group
Williams (*1969*)	Chest clinic, N=204	23	6 months	No control group

[1] Objective validation of self-report of smoking abstinence was performed only in those studies so indicated.

such relationships may exist (Burns 1969; Mausner 1970). Two retrospective studies (Dudley et al. 1977; Pederson et al. 1980) used multivariate techniques to determine the sociodemographic, physiological, and psychological variables that are related to quitting. Dudley et al. (1977) found that "good psychosocial assets, psychological stability, and the ability to express depression openly" (p. 367) discriminated between quitters and nonquitters. Since their measurements were made cross-sectionally, the question remains whether these variables are causes or effects of smoking cessation. In a sample of 117 pulmonary patients, 27 percent of whom quit after physician advice, Pederson et al. (1980) found that abstinence was related to primary diagnosis (those with COLD were more likely to quit), age (older or younger versus middle-aged), and sex (women were more likely to quit) in order of predictive power. These results could have been biased, however, because a number of patients were lost to followup and no objective verification of smoking status was used.

Pederson et al. (1982) conducted a prospective study of 308 newly diagnosed respiratory patients, and using multivariate statistical models, accurately categorized 92 percent of the samples as continuing smokers or quitters, following physician advice. This model was subsequently validated in a second group of similar patients with 89 percent accuracy. In both groups, cessation rates (self-report only) were approximately 15 percent (Pederson and Baskerville 1983). The variables from entry questionnaires useful for discriminating smokers from quitters at followup were prediction of the patient as to smoking status at followup, age, addiction as the major reason for smoking, desire to quit, educational level, socioeconomic status, number of children at home, and being married. Prediction of quitting, increasing age, desire for quitting, socioeconomic status, and being married were positively associated with quitting. Addiction, having children at home, and middle educational level were negatively associated.

Three investigators (Hall et al. 1983; Raw 1976; Rose and Hamilton 1978) tried to vary the type of advice given in order to increase compliance. Raw (1976) found that increasing the motivating information about the risks of smoking and the benefits of cessation by a psychologist subsequent to physician advice to quit did not have a positive effect on compliance, but donning a white coat did. The physician advice itself reduced smoking significantly among advised patients compared with among nonadvised patients. Additionally, the group for whom the psychologist wore the white coat during the interview (motivating or placebo) reduced smoking significantly more than the no-white-coat group did. The dependent variable was the percent reduction in smoking level (number of cigarettes smoked) at 3-month followup by self-report alone. Unfor-

tunately, the sample was small (n=40), and abstinence rates were not reported. The author suggests that the white coat is an advisor characteristic that can increase effectiveness of advice.

Hall et al. (1983) found no difference in 6-month abstinence rates between two groups of cardiopulmonary patients (n=35) randomly assigned to a health motivation and self-management treatment (26 percent abstinence) or to an aversive smoking treatment (6 percent abstinence), both led by nonphysician health professionals. Results summarizing attrition rate and outcome (post-treatment and at 6-month followup) generally favored the health motivation group, however.

The London Civil Servants Smoking Trial (Rose and Hamilton 1978) was a randomized controlled trial of 1,445 men at high risk for cardiorespiratory disease. Following a screening examination, 714 men were randomized to an intervention group and 731 to a normal care group. For the normal care group, the results of the examination were forwarded to the general practitioner, leaving further action to him. The men were not aware they were in the trial. They were invited to return for the 1-year and 3-year examinations as part of the research. Men in the intervention group were invited by letter to discuss the results of their examination with a physician (all accepted). The 15-minute appointment consisted of strong advice to quit smoking, risk appraisal (oriented to fitness and well-being more than to disease), benefits of cessation, and the practicalities of stopping—choice and personalized motivation. Two booklets were provided, prepared especially for the study. Three further interviews were scheduled at 1-week, 10-week, and 6-month points. All men (intervention and control) who attended the 1-year and 3-year examinations completed a self-administered questionnaire; some were completed by mail. No validation of self-report was made. At the 1-year examination, 51 percent of intervention subjects and 10 percent of control subjects reported cessation of cigarette smoking; excluding those men who had switched to pipes or cigars, rates of tobacco abstinence drop to 38 and 8 percent, respectively. Of all the men who stopped within the first year, 80 percent did so immediately after the first interview. At 3 years, 36 percent of intervention subjects and 14 percent of control subjects were not smoking cigarettes; total tobacco abstinence rates were 23 and 10 percent, respectively. A number of personal characteristics assessed at entry were associated with increased probability of cessation: smoking less than 20 cigarettes per day, not inhaling, use of filter tips, prior attempts to stop, marital status "other than married," professional or executive employment category, and neuroticism (Eysenck Personality Inventory). The level of abstinence achieved in the treatment group is comparable to several other studies with similar

patients (Baker et al. 1970; Burns 1969; Mausner 1970; Pederson et al. 1980) and is closer to the remainder than control group results.

Patients With Cardiac Disease

The studies concerned with smoking cessation among cardiac patients further support the notion that presence of disease may be an important precursor of compliance. The occurrence of a myocardial infarction (MI) is a dramatic event that, in many patients, should add credence to the physician's admonishments. Evidence demonstrates that reduction or cessation of smoking is positively related to survival in MI patients (Hickey et al. 1983; Mulcahy et al. 1975, 1977; Pentecost 1980; Salonen 1980; Sparrow et al. 1978; USDHHS 1983) and is negatively related to a coronary event following uncomplicated angina (Hubert et al. 1982). It appears that smoking cessation decreases mortality among post-MI patients, so that attempts to increase compliance among this group could have life-or-death ramifications.

Table 2 summarizes the studies on this patient group. Successful smoking cessation is relatively high among survivors of MI (Baile et al. 1982; Burnum 1974; Burt et al. 1974; Cooperstock and Thom 1982; Croog and Richards 1977; Halhuber 1978; Hay and Turbott 1970; Kirk et al. 1980; Kornfeld et al. 1982; Lloyd and Cawley 1980; Mallaghan and Pemberton 1977; Mayou et al. 1978; Ronan et al. 1981; Sillett et al. 1978; Weinblatt et al. 1971; Wilhelmsson et al. 1975). Cessation rates range from 22 to 94 percent, with the majority of studies falling in the 40 to 60 percent range. The discrepancies in rates are partially attributable to sample size variations or duration of followup. A trend is apparent, however, with more recent studies reporting lower rates.

In a recent review of the literature on smoking following myocardial infarction, Burling et al. (1984) discuss four major methodological limitations in these studies. First, the definition of abstinence varies among studies, ranging from zero to five cigarettes per day; also, the period over which abstinence is measured, from the MI continuously tc followup, should be specified.

Second, self-report of smoking status is rarely verified; a few studies have used biochemical validation Baile et al. 1982; Burling et al. 1982; Kirk et al. 1980; Ronan et al. 1981; Sillett et al. 1978; Wilcox et al. 1979). Rates of deception have varied from approximately 25 percent of patients claiming abstinence (Sillett et al. 1978; Wilcox et al. 1979) to much lower estimates of discrepancy between self-report and objective measure (Baile et al. 1982; Burling et al. 1982; Kirk et al. 1980; Ronan et al. 1981).

Third, specification of the treatment—the time and amount of antismoking advice delivered—is not always explicit. Advice can be verbal or verbal plus written, and the intensity of the message has

TABLE 2.—Studies assessing smoking cessation rates among patients with cardiac disease

Study	Groups	Quit rate (percent)	Duration of followup	Comments[1]
Baile et al. (*1982*)	Post-MI	62	Approximately 10 days	In-hospital relapse among patients receiving standard advice, no control group; probability of relapse inversely related to severity of MI; objective validation (breath CO) on a parallel series of patients (unpublished), 9.2% deception rate
Burnum (*1974*)	Private, N=52	42	Average, 5 years	No control group
Burt et al. (*1974*)	Post-MI Strong advice, N=125 Conventional advice, N=85	62 27.5	1 to 3 years	
Cooper et al. (*1982*)	High risk, N=519	24	2 years	No control group
Cooperstock and Thom (*1982*)	Patients with circulatory problems, N=377	73	Cross-sectional	Quit rates compared with respiratory and musculoskeletal groups
Croog et al. (*1977*)	Post-MI, N=205	51	8 or 9 years	No control group; no differences between ex-smokers and smokers for health beliefs or sociodemographic characteristics
Hay and Turbott (*1970*)	Post-MI, N=137 Coronary insufficiency, N=44	29 11	6 months to 2 years	Control for severity of disease
Halhuber (*1978*)	CHD, N=935	94	4 weeks	No control group

TABLE 2.—Continued

Study	Groups	Quit rate (percent)	Duration of followup	Comments[1]
Kirk et al. (*1980*)	Arterial disease, N=39	49 reported 44 verified	9 months	Objective validation (serum SCN); possible deception rate, 10.5 percent
Kornfeld et al. (*1982*)	Patients after coronary bypass surgery, N=100 (39 smokers)	67	9 months	No control group
Lloyd and Cawley (*1980*)	Post-MI, N=105 (64 smokers)	36	4 months	No control group
Mallaghan and Pemberton (*1977*)	Post-MI, N=321	22	1 year	No control group; differences between ex-smokers for perceived severity and memory of advice
Malotte et al. (*1981*)	High risk, N=43	53	6 months	No control group; residential program
Mayou et al. (*1978*)	Post-MI, N=100	45	1 year	No control group
Meyer and Henderson (*1974*)	Behavior modification, N=5 Individual counseling, N=4 Physician counseling, N=6	20 25 33	3 months	High risk patients; no significant difference between groups
Ockene et al. (1982b)	High risk group Special intervention, N=4,103 Usual care, N=4,091	 40 reported 35 verified 21 reported 19 verified	4 years	MRFIT; objective validation (SCN)

TABLE 2.—Continued

Study	Groups	Quit rate (percent)	Duration of followup	Comments[1]
Powell and Arnold (*1982*)	High risk, N=42	50 verified	1 year	Objective validation (SCN); hard core smokers
Rahe et al. (*1979*)	Post-MI		4 years	No significant difference
	Group therapy, N=22	33		
	Control, N=22	42		
Ronan et al. (*1981*)	Post-MI, N=117 (111 smokers)	51 reported 47 verified	4 to 18 years	Objective validation (COHb); possible deception rate, 8.8 percent
Rose and Hamilton (*1978*)	Normal care, N=731	14	3 years	High risk for cardiorespiratory disease
	Intervention, N=714	36		
Rose et al. (*1982*)	Normal care, N=731	Not reported	9 years	Followup of Rose and Hamilton (*1978*)
	Intervention, N=714	36		
Rose and Udechuku (*1971*)	Hospitalized with atherosclerotic disease, N=56	44	Not given	No control group
Rose et al. (*1980*)	High risk, N=736	29	4 years	Part of WHO trial
Sillett et al. (*1978*)	Post-MI, N=91	65 reported 51 verified	1 year	Objective validation; possible deception rate, 23 percent
Sivarajan et al. (*1983*)	Post-MI		6 months	No significant differences
	Exercise, N=88	31		
	Exercise and counseling, N=86,	34		
	Control, N=84	41		
Sparrow et al. (*1978*)	Post-MI, N=202 smokers	28	Variable 2 to 6 years	Followup of smokers developing MI in the Framingham study; no control group

TABLE 2.—Continued

Study	Groups	Quit rate (percent)	Duration of followup	Comments[1]
Weinblatt et al. (*1971*)	Post-MI, N=283 Angina, N=146 Non-CHD, N=432	50 50 19	4.5 years	Control for severity of disease
WHO European Collaborative Group (*1982*)	High risk, N=4,770	6	4 years	No control condition
Wilhelmsson et al. (*1975*)	Post-MI, N=564	53	3 months	Differences between ex-smokers and smokers for increasing age and severity of disease

[1] Objective validation of self-report of smoking abstinence was performed only in those studies so indicated.

varied from routine to strong. Results have generally been better when stronger advice was delivered (Burling et al. 1982).

For example, in an experimental test of the effect of intense advice on post-MI cessation, Burt et al. (1974) routinely assigned 210 male patients to intense or to routine advice conditions. Abstinence rates were higher in the intense advice condition, 62 versus 27.5 percent. The intense intervention consisted of telling the patient repeatedly—in the critical care unit, during convalescence, and during followup—never to smoke again in his lifetime, plus giving him a pamphlet. However, other attempts to increase cessation rates by using group counseling (Rahe et al. 1979) or exercise with or without counseling (Sivarajan et al. 1983) showed no differences in abstention rates for treatment groups and control groups.

Fourth, a variety of subject and environmental factors that may influence cessation have rarely been systematically examined or controlled. These include age, sex, race, severity of the MI, and personality and environmental factors. Age is not found to be related to cessation in most studies (e.g., Baile et al. 1982; Croog and Richards 1977; Salonen 1980; Sparrow et al. 1978; Weinblatt et al. 1971). Both of the studies presenting data on sex differences in post-MI cessation have noted somewhat higher cessation rates among males; however, sample sizes were small and the differences were not statistically significant (Baile et al. 1982, Sparrow et al. 1978). Racial data have not been available for nonwhite populations. Greater severity of an MI has been associated with higher smoking cessation rates (Baile et al. 1982, Wilhelmsson et al. 1975). Personality and environmental factors are complex, and only a few relationships have been explored. For example, neither Baile et al. (1982) nor Croog and Richards (1977) found associations with any of the sociodemographic or Health Belief Model variables measured, but Baile et al. (1982) did identify an environmental factor—being offered cigarettes by visitors—that influenced resumption of smoking among hospitalized post-MI patients.

The descriptive study by Baile et al. (1982) provided several suggestions for intervention with post-MI patients—introducing the intervention prior to hospital discharge and as early in the hospitalization as is feasible, even in the critical care unit, and involving family members and visitors in the effort to prevent resumption of smoking. This study was not designed to assess the mechanism by which relapse was negatively associated with severity of the MI, but the authors offered several possibilities: the presence of subjective factors such as specific illness symptoms, general malaise or level of fear, communications from the medical staff regarding severity of heart attack, intense and specific advice to quit smoking, or differential medical treatment that might have affected the patients' smoking behavior. These factors should be considered in the design

of future experimental evaluation of post-MI smoking cessation interventions.

Moving on from the patient with established cardiovascular disease to people classified as "at risk," it is found that a number of large controlled trials of risk reduction have demonstrated that counseling on individual specific risk factors and exposure to smoking cessation techniques can be effective. These trials have been discussed in detail in the 1983 Report of the Surgeon General *The Health Consequences of Smoking* (USDHHS 1983). Rose and Hamilton and their colleagues (Rose 1977; Rose and Hamilton 1978; Rose et al. 1982) have found higher abstinence levels in a group given intense advice and education as compared with a control group. The Multiple Risk Intervention Trial (MRFIT) (Ockene et al. 1982b), with 12,866 high risk men, reported 40 percent abstinence in the special intervention group and 21 percent in the usual care group. Similar results were found in Britain (Rose et al. 1980) as part of the WHO multifactorial trial (WHO European Collaborative Group 1982). Other smaller scale studies have generally found that high risk men are susceptible to risk-reduction interventions (Cooper et al. 1982; Malotte et al. 1981; Powell and Arnold 1982). For the most part, these studies have been well designed and many have included objective validation of verbal reports.

The Use of Nicotine Chewing Gum

A pharmacological aid to smoking cessation designed to decrease the smoker's desire for nicotine and to relieve withdrawal symptoms has recently become available as a prescription product in the United States after development in Europe; current information and research has been summarized (Grabowski and Hall, in press; Hughes and Miller, unpublished manuscript). The new aid is a chewing gum containing 2 mg nicotine bound to an ion exchange resin for controlled release and buffered for rapid absorption through the buccal mucosa. Compared with the rapid elevation of blood nicotine levels achieved after smoking a cigarette, peak blood levels with 2 mg gum are lower and are achieved more slowly (Russell et al. 1976a; McNabb et al. 1982). Although blood levels may peak within minutes following smoking, peak levels occur after 20 to 30 minutes of chewing the gum, presumably not reproducing the pleasure of smoking because of the slower, nonbolus release of nicotine (Russell et al. 1980). Nicotine chewing gum is indicated as a temporary aid to the cigarette smoker seeking to give up his or her smoking habit while participating in a behavioral modification program under medical supervision. The efficacy of nicotine chewing gum use without concomitant participation in a behavioral modification program has not been established. Thus, nicotine gum could aid

in the cessation process by allowing the smoker to break the smoking habit with abrupt cigarette cessation, while gradually withdrawing from nicotine. In controlled studies, evidence has been offered that nicotine gum can relieve withdrawal symptoms (Jarvis et al. 1982; Schneider and Jarvik 1984; Schneider et al. 1983; Hughes et al. 1984; West et al. 1984).

According to Hughes and Miller (unpublished manuscript), contraindications include recent MIs or life-threatening arrythmias, severe or worsening angina, or active temporomandibular joint disease. Nicotine may aggravate coronary heart disease, vasospastic diseases, hypertension, diabetes, and hyperthyroidism. Because nicotine is swallowed during use of the gum, people with peptic ulcer or esophagitis may be particularly at risk. These contraindications are based on known or presumed relationships between nicotine and these conditions, and not upon direct tests of nicotine gum use. Women who are pregnant or nursing should also avoid gum use because nicotine decreases fetal breathing movements and is secreted in maternal milk (USDHHS 1980).

Common side effects of use include air swallowing, belching, jaw ache, sore mouth or throat, upset stomach, hiccups, nausea, and mouth ulceration (Fagerstrom 1982; Jarvis et al. 1982; Russell et al. 1980; Schneider et al. 1983). Most side effects can be diminished by proper instruction on mode of chewing. The percentage of subjects who may become dependent upon gum use is not well known. In two studies, 3 to 7 percent of all subjects were considered dependent by the investigators (Jarvis et al. 1982; Raw et al. 1980).

Given that nicotine gum does appear to alleviate withdrawal symptoms, to what extent has it been efficacious in cessation? Early studies of cessation were confounded by allowing smokers to simultaneously smoke and chew the gum (Brantmark et al. 1973; Puska et al. 1979; Russell et al. 1976b). More recently, controlled clinic-support studies have shown enhancement of both short- and long-term success rates with nicotine gum (Fagerstrom 1982; Jarvis et al. 1982; Schneider et al. 1983). Success has been attributed to an interaction between the active gum and the support systems in ways not yet understood. Schneider et al. (1983) compared nicotine and placebo gum in both dispensary and clinic settings. There was no effect of active gum in the dispensary setting; subjects chewed the gum for a very short time period and resumed smoking quickly. In the clinic conditions, the nicotine gum produced significantly higher success rates than placebo, with a peak difference achieved at 6 months (48 percent versus 20 percent). In other studies with followups of from 3 to 12 months, cessation rates were higher for groups receiving active gum than for placebo gum groups or groups receiving other treatments (Fee and Stewart 1982; Hjalmarson 1983; Jarvis 1983; Malcolm et al. 1980; Raw et al. 1980). Fagerstrom's

(1982) work suggests that highly nicotine-dependent smokers may be the best candidates for gum use.

Studies conducted in physicians' offices have produced mixed results. In a study using over 1,500 patients with smoking-related diseases attending a hospital or chest clinic, there was no reported superiority of nicotine gum compared with several conditions involving usual physician advice to quit and a booklet (British Thoracic Society 1983). Overall, 9.7 percent of patients were abstinent at 1 year, but approximately one-fourth of patients claiming abstinence had carboxyhemoglobin and plasma thiocyanate concentrations typical of smokers. This study has been criticized for the manner in which the gum was administered to the patients (Jarvis and Russell 1983). On the other hand, Fagerstrom (1983) found nicotine gum use to be statistically superior to a no-gum condition at 1-year followup in a 13-physician study involving 145 patients. Similarly, Russell and his colleagues (Russell et al. 1983a,b), in a well-designed study involving 1,938 general practice patients, observed a difference for the same time period. Success rates in the nicotine gum plus advice group were about double those in the nonintervention and advice-only groups (8.8 percent versus 4 percent not smoking at 4 months and at 1 year). These results are based on all smokers who saw their physician regardless of desire to quit. The higher success rate of the group offered the nicotine gum was achieved even though only 53 percent tried the gum. The self-selected subgroup who used more than one box of gum (105 pieces) had an adjusted long-term success rate of 24 percent.

Reasons for the inconsistent results may relate to differences in (1) instructions on gum use given to the patient, (2) distribution of the gum (whether it was provided directly to the patient or offered in the form of a prescription), (3) patient personality characteristics or motivation for smoking, (4) support or followup in addition to providing the gum, and (5) sample sizes and duration of followup. The first four of these factors can all affect compliance, which is deemed critical for effective use of the gum in physician practice. Key questions remaining to be systematically tested relate to what constitutes optimal gum use, such as dose, frequency, and duration (Schneider et al. 1983). Future research should resolve the general usefulness of this pharmacologic treatment as well as the appropriate adjunct treatment strategies.

Discussion and Synthesis

Methodological Considerations

There is marked variation in the methodology and presentation of results from the studies included in this review, posing problems for comparison. To begin with, interventions are not always well

specified, making it difficult to categorize or to evaluate any given technique. This is particularly true in studies in which the intervention consisted of a very brief warning to quit delivered in the physician's own style. Any accompanying written material is often only vaguely described. There are, of course, studies in which interventions are well detailed, such as the MRFIT trial (Ockene et al. 1982b). In this relatively new area of smoking cessation research, it is particularly important to researchers to report as much detail as possible on their intervention and control methods.

In evaluating the success of interventions, standard definitions of outcome need to be agreed upon. These include total abstinence from tobacco use, not just cessation of cigarette smoking or reduction in total amount smoked. If multiple measures are preferred, abstinence should always be reported. Objective validation of self-report is critically important, especially when at-risk or patently ill patients may be biased to report abstinence. Followup periods should optimally be at least 1 year. When subjects are lost to followup, the method of calculating success rates should be clearly specified. For example, the most conservative criterion would dictate classifying as smokers subjects who refuse measurement. Other problems may include incomplete data because of nonsurvivors, especially in medical populations. If results are based only on those successfully followed, as much information on lost subjects as is possible should be provided. In retrospective studies, memory bias may also influence results. Other problems common to smoking cessation research include inadequate sample sizes, which reduce statistical power; lack of comparison or control groups; and the failure to select an appropriate design, such as randomization or a quasi-experimental model. Design, methodology, and interpretation issues in smoking research have been treated in other sources in greater detail (Pederson 1982; USDHEW 1979; USDHHS 1982, 1983).

Trends in the Literature

When considering quit rates among the various patient groups discussed in this review, it is important to keep two considerations in mind. First, quit rates can vary as a function of the type of intervention, not only by patient group. For example, the highest quit rate among controlled pregnancy interventions (Sexton and Hebel 1984) was found in the study with the largest subject sample and strongest design, and consisted of a multiple contact intervention. Second, of the four classes of patient considered, persons with pulmonary and cardiac disease differ qualitatively from general practice and pregnant patients. The first two categories of patients have diseases directly related to their smoking behavior; risks and consequences of continued smoking can be personalized and detailed. On the other hand, general practice patients may not be coming in

for a problem directly related to their smoking. Battista (1983) reported that antismoking counseling was delivered by 99 percent of primary care physicians in his survey sample when the reason for the medical visit was related to smoking, but by only 52 percent when the medical problem was unrelated and a mere 11 percent when the visit was for a minor problem. Finally, pregnant patients seen routinely for prenatal care are usually not ill, and may have difficulty personalizing the risks to the fetus and to themselves, especially if they have smoked through previous pregnancies and borne healthy babies.

Notwithstanding these limitations, some trends are evident in the literature: the quit rates in recent research appear lower than in older studies, and a positive association between severity of disease and quit rate can be noted. There are exceptions to these generalizations, but the intention in presenting them is to bring some order to the results.

The series of studies examining quit rates among pulmonary patients indicate a decrease in success over time, with more recent studies reporting lower rates. The same general trend appears among post-MI patient groups when data from groups receiving treatment in addition to physician advice are excluded. This apparent decline in effectiveness may be attributable to higher spontaneous quit rates in the population of smokers. Because more people are quitting on their own, fewer current smokers and more ex-smokers are presenting themselves to physicians. Included in the group of ex-smokers are those who a decade or two ago would have stopped on the advice of their physician, but who have quit because of media educational campaigns. Physicians specializing in pulmonary or cardiac disease are then left to deal with the more recalcitrant, hard-core group. In addition, current patients may be more honest in reporting failure to quit, and there are measures for objectively verifying verbal reports (e.g., expired air carbon monoxide, carboxyhemoglobin, saliva or blood thiocyanate, saliva or blood cotinine).

Although there are comparatively few studies with general practice patients and pregnant women, these two groups show fairly low abstinence rates. As mentioned above, when attending for routine visits, these patients are generally healthier than those with chronic pulmonary disease or cardiac disease. They are also less likely to be visiting the physician for an illness related to smoking. When treated with a powerful intervention, however, high cessation rates (over 40 percent) have been reported (Sexton and Hebel 1984). The quit rates among patients with pulmonary disease vary from 12.5 to 76 percent. The highest rates are found in studies including patients who have ever smoked in the past, as well as those who are smoking at the time of treatment (Daughton et al. 1980; Dudley et al.

1977; Mausner 1970). When these studies are excluded, the between-study rates cluster more closely between 20 and 40 percent. In general, it appears that patients with MI, especially those receiving strong advice, are much more likely to quit smoking than are other patient groups, with 40 to 50 percent abstinence levels being the rule rather than the exception. This finding matches the most successful behavioral interventions reported in the general smoking cessation literature—those programs with strong maintenance as well as cessation components (USDHHS 1982). The potential effect of continued smoking on future health status for cardiac patients has an immediacy that appears to motivate positive action. Six studies investigating severity of diagnosis (Baile et al. 1982; Campbell et al. 1983; Dudley et al. 1977; Mausner et al. 1970; Sillett et al. 1978; Wilhelmsson et al. 1975) support this relationship; one does not (Weinblatt et al. 1971). It is possible that the health benefits of cessation have been underestimated to date, if the most severely ill patients are the most likely to quit.

Although this discussion implies a causal relationship between severity of disease and compliance, other explanations are possible. Factors such as personality characteristics that are differentially related to diagnosis and ease of quitting may influence results. In addition, physician involvement may be much more intense with patients who have more severe diagnoses and may be causally related to differential outcome.

Patient Variables Related to Abstinence

There have been a number of attempts to relate variables to successful quitting among patient groups. The underlying rationale of these attempts can be conceived as a search for possible causal factors. Multivariate statistical procedures have been used to generate predictive models, which may serve as the basis for theorizing about mechanics involved in explaining why some patients quit smoking and others do not. The results with respiratory patients of Dudley et al. (1977) and Pederson and her colleagues (Pederson et al. 1980, 1982; Pederson and Baskerville 1983) were described earlier. Examining the psychological and behavioral variables, the retrospective study of Dudley et al. (1977) identified good adjustment variables as predictors of success, and the prospective studies (Pederson et al. 1982; Pederson and Baskerville 1983) found that prediction of quitting and desire for quitting were positively associated with success, but addiction was negatively associated. In the MRFIT program (Ockene et al. 1982a), men at high risk for CHD who were classified as Continuing Successes (stopped smoking and maintained abstinence) were characterized as having, in combination (and in decreasing order of importance), a high expectation of success, few cigarettes smoked upon entry, low stress,

ease of prior cessation attempts, a long period of prior abstinence, and a high degree of personal security. Together, the combination of high stress and low psychosocial assets acted as barriers to long-term smoking cessation, characterizing the "problem smokers" (the combined group of nonstoppers and recidivists). The congruency of these findings suggests the need to "develop systematic and convenient ways to collect and use data regarding a participant's experiences of stress and psychological assets," according to Ockene et al. (1982a, p. 26). As studies of self-attribution of change related to positive outcome (self-efficacy) in smoking ceesation have shown (USDHHS 1982), these and related psychosocial variables may be critical predictors for all persons attempting smoking cessation. Thus, this approach should be expanded and tested on other patient populations.

Physician Variables Related to Effectiveness

Success rates in physician intervention studies have been shown to vary as a function of the participating physicians as well as of the interventions they employ (Ewart et al. 1983; Pincherle and Wright 1970; Rose and Hamilton 1978; Russell et al. 1979). While most smoking cessation studies using behavior modification techniques attempt to standardize the intervention and to eliminate differences among those delivering it, physician intervention studies often involve advice delivered in the doctor's own style and hope to capitalize on the personal interaction with the patient, e.g., Russell et al. (1979). As this stage of research it is sometimes difficult to separate out the various factors contributing to the degree of success of a particular intervention.

Both types of intervention and physician factors were found to be important in determining success rates in two studies reported by Ewart et al. (1983), using two very different patient populations, asbestos-exposed shipyard workers (n=871) and low-income women attending family planning clinics (n=1,179). Physicians saw all patients only once; assignment to group was random in the shipyard study and controlled by clinic in the family planning population (quasi-experimental design). In both studies, the more detailed advice effort consisted of a physician's warning to stop smoking with up to 5 minutes of individually focused cessation counseling. The comparison technique consisted of a simple warning by the physician (shipyard workers) or viewing an educational film (low-income women). Cessation rates at 1 year in the detailed advice group were double those in the comparison group in both studies. Mean quit rates were not reported, but variability in physician success was examined. In the shipyard study, success rates were defined as the proportion of patients counseled by the physician who quit smoking

within 3 months. Among the four participating physicians, success rates ranged from 6 to 14 percent at the 1-year followup.

Success rates were examined by types of patients assigned to each physician and by differences in physician behavior. Patient characteristics did not explain the variable rates of success between different physicians. These included medical symptoms, demographics, physiological characteristics, and a number of behavioral variables that have been found to predict smoking cessation (number of cigarettes smoked daily, motivation to quit, and length of past nonsmoking periods). On the other hand, physician motivation and effort in patient counseling emerged as important factors. When physician success rates were examined as a function of time since the continuing medical education (CME) training program over a 9-month period, all physicians were shown to become less effective as time passed, but two of the four had dramatic drop-offs in effectiveness. Declining rates of success were associated with lack of compliance with the protocol by failing to have the patient select a target date for quitting smoking. (Both patient and physician had been asked specifically about this in an exit interview. The proportion of patients who reported agreeing on such a target date was treated as an indirect marker of compliance.) Target date setting in noncompliant physicians decreased from 23 percent of patients counseled in the first 3-month period to 3 percent in the final 3-month period, with a concomitant decrease in success from 15 to 2.0 percent. In comparison, the two more successful physicians set target dates with 57 and 49 percent of their patients in the first and final 3-month study periods, and achieved 15 and 9 percent success rates, respectively. Furthermore, with the passage of time, the two less compliant physicians altered their pattern of target date setting with patients, providing such advice to many fewer lighter smokers (under 20 cigarettes per day) but maintaining the rate of advice with heavier smokers. The authors interpreted this as a selective shift of effort, but it can be seen also as a simple diminution of effort with the former group of patients because the proportion of heavy smokers advised did not actually increase over time.

In the family planning clinic study, maintenance of physician performance was influenced by a feedback intervention. Performance was monitored by asking patients who had just seen the physician whether they had been counseled to quit smoking; when the percentage of patients reporting advice declined, a private personal communication was made with the physician. For both physicians involved in this study, the percentage of patients counseled to quit smoking rose after each feedback session. Although physicians may adequately learn antismoking interventions with training, these two studies show that their application of such skills may decline with time and their own modifications of the interven-

tions, two sources of variability that are potentially controllable with regular feedback sessions. Ewart et al. (1983) suggest that experimental designs include collecting continuous time series data that can be analyzed for individual and group performance trends. Such analyses will also provide a means of testing the generalizability of these findings.

Conclusions

Recommendations for Physicians

Patients, particularly those who are not experiencing life and death decisions in which continuation of smoking is relevant, find it difficult to comply with their physicians' advice to quit. Griffiths has observed, however, "Physicians frequently get discouraged with their rate of success, about one out of five, in helping patients to stop smoking. They forget, however, that their rate of success in curing lung cancer is much lower" (Griffiths 1981). As we have seen, a 20 percent cure rate would indeed be high for a truly minimal intervention. What are some of the actions that the physician who is interested in preventive action can take to assist his or her patients to stop smoking?

Some suggestions come from a theoretical formulation known as the Health Belief Model (Becker 1974, 1976; Becker et al. 1979). According to the model, the following elements are hypothesized to determine behavior: the individual's readiness to take action, determined by perceived susceptibility to the illness and perceived severity of the consequences of the illness; the individual's evaluation of the feasibility and efficacy of health behavior; the individual's evaluation of barriers to the health behavior; and a cue to action that triggers the behavior. On several of these elements, patients who are experiencing respiratory and cardiac problems have much more clearly defined reasons to be compliant with the request to quit smoking than patients seen in general practice. Thus, they would be seen as having stronger health beliefs. Women who are pregnant fall somewhere in between, depending on just how harmful they perceive their smoking to be to themselves and the fetus (Dalton et al. 1981). The clinician may succeed in motivating the members of the latter two groups by intensifying the message. Support for this position is found in studies that have compared more intense with less intense advice (Burt 1974; Ockene et al. 1982b; Raw 1976; Rose 1977).

Other models with a more social learning and social psychological orientation pose as central concepts the belief in personal control (Bandura 1973) and the need for relearning to change the conditioned emotional schema that contribute to maintaining smoking (Leventhal and Cleary 1980). Social support has also been raised as an important theoretical variable (Ockene et al. 1982a; USDHHS

1980). Practical applications of such approaches might be assessing and bolstering the self-confidence of a patient wishing to quit smoking and involving a spouse in the cessation effort.

The physician's message must be tempered with other factors, such as the strength of already existing beliefs and the mechanisms for continued smoking. Work by Leventhal (1968, 1970) on the communication of fear messages suggests that such messages may interfere with adoption of a recommended health-facilitating behavior. For example, he found that smokers are less likely to undergo a chest X-ray after viewing a filmed lung cancer operation than smokers who do not view the film, because the experience produces an increased fear that interferes with the goal of the advice. The extent of the interference is probably related to the purpose that smoking serves for the person (whether it is arousal reducing or habitual).

Physicians should also appreciate the importance of both physiological and personality variables that lead to the initiation and maintenance of smoking (USDHEW 1979; USDHHS 1982). Likewise, they should consider both the habitual and the addictive components of smoking behavior and the consequent difficulty in producing extinction (APA 1980; NIDA 1979). When these factors are considered, it is not surprising that a brief warning to a "healthy" patient is not effective. In this context, "healthy" relates to the lack of current major symptoms that the smoker relates to smoking.

Physicians do not need to assume full responsibility for helping patients quit smoking, however. Lichtenstein and Danaher's (1978) model suggests that the physician can become involved with patients at a variety of levels, although Wilson et al. (1982) indicate that continuing contact with the patient can be useful. Chu and Day (1981), Ewart et al. (1983), and Spencer (1983) have shown that awareness of smoking and providing antismoking materials for clinical use can motivate physicians toward increased effort with smoking patients. Wechsler et al. (1983) found that 81 percent of primary care physicians surveyed personally provided patient education as opposed to having a nurse or other health professional deliver it. They were more likely to want to learn about a specific area (e.g., smoking cessation techniques) in CME classes if they believed in the importance of changing behavior in that area and had confidence in their chances of success in helping patients. Thus, physician self-efficacy is an important concept in delivering smoking cessation advice. The most valuable types of assistance identified by the physicians in this study were information on referral sources, financial reimbursement for health-promotion services and staffing, literature for distribution to patients, and training for physicians, support staff, or both. The direct provider role, as well as other roles for the physician (such as referral to treatment), has been described,

and practical guides that cover the physician's involvement on a number of levels do exist (Pechacek and Grimm 1983; Shipley and Orleans 1982). Smoking cessation materials prepared especially for the physician are available from the National Cancer Institute—the Helping Smokers Quit Kit—and from the American Cancer Society—the Physician's Help Quit Kit. These kits have not yet been formally evaluated for efficacy.

Future Research

A number of salient issues for future research in the area of physician intervention emerge from this review. First of all, the interventions that will work best for physician providers have yet to be identified. For example, is a minimal intervention like simple advice to quit the optimal use of a physician's time, or can physicians successfully integrate a multicomponent or multistage intervention into their practice and achieve substantially higher quit rates? What techniques supplementary to physician advice will yield maximum return in cessation? What are the differential effects of advice alone and of the offer of treatment on the likelihood of cessation? How does one improve the communication skills of physicians practicing health education with patients?

Second, will different interventions work best for different patients classified according to disease status? Will tailoring treatments according to patient group or to individual patient characteristics be useful (Best 1975; Best and Steffy 1975; Eiser 1982)? Can the physician employ a sequential model of smoking behavior (Prochaska and DiClemente 1983) so that interventions can be staged according to the patient's readiness to quit smoking?

Third, what kind of training in smoking cessation will be most effective for physicians? Training formats range from noninteractive materials such as printed matter and audio or video cassettes to formal programs such as CME classes or other instructor-led workshops or programs. Should role modeling and direct practice under supervision be used to help teach skills? What educational (or other) efforts will be needed to sustain physician counseling efforts and success?

Fourth, what are the variables controlling differential success rates among physicians? Are they personal variables, like smoking status (American Cancer Society 1981; Danaher 1978), or training-influenced performance factors such as consistency of applied effort over time (Ewart et al. 1983)? How can physician motivation to counsel patients be increased and maintained? How can physicians best be delivered feedback about their counseling performance as well as the efficacy of their efforts?

Fifth, future research needs to pay closer attention to methodological considerations that will facilitate testing hypotheses and evaluat-

ing outcomes. These have been summarized earlier and involve design considerations, assignment of patients to groups, followup of outcome, and objective verification of self-report.

Sufficient evidence has been presented here to support an effective role for the physician, as the leading and most credible figure in the health care world, in smoking cessation efforts. As Cullen and Gritz (1983) stated, "The most effective technique to be employed, as well as when and with what specific group, can await further research. But given the importance of smoking as the most potent, preventable pathogen still responsible for a substantial amount of premature mortality, morbidity, and health care costs, there is no longer an excuse for physicians to leave this effort solely to other health professionals" (p. 224).

Summary and Conclusions

1. At least 70 percent of North Americans see a physician once a year. Thus, an estimated 38 million of the 54 million adults in the United States who smoke cigarettes could be reached annually with a smoking cessation message by their physician.
2. Current smoking prevalence among physicians in the United States is estimated at 10 percent.
3. While the majority of persons who smoke feel that physician advice to quit or cut down would be influential, there is a disparity between physicians' and patients' estimates of cessation counseling, with physician advice being reported by only approximately 25 percent of current smokers.
4. Studies of routine (minimal) advice to quit smoking delivered by general practitioners have shown sustained quit rates of approximately 5 percent. Followup discussions enhance the effects of physician advice.
5. A median of 20 percent of pregnant women who smoke quit spontaneously during pregnancy. That proportion can be doubled by an intervention consisting of health education, behavioral strategies, and multiple contacts.
6. Large controlled trials of cardiovascular risk reduction have demonstrated that counseling on individual specific risk factors, including smoking cessation techniques, can be effective.
7. Studies of pulmonary and cardiac patients indicate that severity of illness is positively related to increased compliance in smoking cessation. Survivors of a myocardial infarction have smoking cessation rates averaging 50 percent.
8. Nicotine chewing gum has been developed as a pharmacological aid to smoking cessation, primarily to alleviate withdrawal symptoms. Cessation studies conducted in offices of physicians who prescribe the gum have produced mixed results, however,

with outcome depending on motivation and intensity of adjunctive support or followup.

9. Physician-assisted intervention quit rates vary according to the type of intervention, provider performance, and patient group. In general, quit rates in recent research appear to be lower than in older studies.

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CHAPTER 10. COMMUNITY STUDIES OF SMOKING CESSATION AND PREVENTION

CONTENTS

Introduction

Community studies of smoking cessation and prevention are defined as research in which geographically defined populations or age cohorts are selected for experimental intervention or as control or comparison groups. In this chapter, four major studies of cessation are described, and related research findings are briefly considered. Three major studies of prevention are also reviewed, with less extensive presentations of other recent research. The theoretical background for these studies is outlined, methodological issues are discussed, and directions for future research are suggested. It is concluded that community studies represent a significant emerging paradigm for public health research.

The first public health "revolution," the recently achieved control of major infectious disease, evolved in two phases: (1) recognition that certain aspects of the environment are associated with disease, and (2) establishment of sanitation facilities and services, such as refuse collection and plumbing systems, for entire communities of people. Basic public health engineering that was revolutionary a century ago is now taken for granted by society. Today we emphasize the second public health "revolution," the current efforts to control chronic disease through behavior change. This development has also evolved in two stages: (1) recognition of behaviors, such as cigarette smoking, as being associated with disease, and (2) development of new services to change those behaviors (Wynder and Hoffman 1979). As might be expected, this most recent history of public health is no less turbulent than that which preceded it.

Various factors have hindered progress. After the basic causes of smoking-related diseases were recognized, there has been a tendency to invest scarce resources in increasingly intricate studies of disease causation processes. In addition, once funding is secured for intervention to reduce smoking, efforts often focus on individual-level, clinically oriented interventions (Lichtenstein 1982). If these interventions do not succeed, society is inclined to "blame the victim," much as the poor were held responsible for the microbes in their water by 19th century social conservatives. The socioeconomic gradient in rates of smoking and smoking-related disease may also slow society's response at a community level to this modern, noncommunicable disease epidemic. The greatest factor inhibiting progress, however, is the cost of prevention. Such costs are compounded by political obstacles stemming from the tremendous influence of the tobacco industry, which employs thousands of people and regularly delivers a substantial portion of tax revenues (Breslow 1982; Fritschler 1975; Sapolsky 1980). On a national scale, dramatic changes in tobacco consumption have occurred in response to successive measures (Warner 1977; Warner and Murt 1982), but these have been limited largely to higher income groups. Few

examples of bold community or regional efforts comparable to those involved in the control of infectious disease have been witnessed, and the prevalence of smoking has declined much less dramatically among women and has even increased in some minorities.

Characteristics of a Controlled Community Study

For this discussion, a controlled community study is defined according to the scope of intervention and quality of research design, with the essential feature being identification of natural, location-based aggregations of individuals as well as formal and informal social systems. In a community study, the entire population of a geographic area is considered, so that a church or worksite is not a community itself, but one of many systems constituting the total network of interactions. The term "community" originally referred to small systems numbering no more than several thousand persons. This discussion, however, includes research on towns, counties, or other relatively independent zones with up to several hundred thousand inhabitants. Because educational systems represent all age cohorts of youth, school-based studies are also reported. Studies of entire States or nations are only briefly considered.

Because the population size to be addressed is a limiting factor in any social program, the large numbers of people involved in a community study dictate selection of intervention methods. Clinical or other people-oriented approaches that typify behavioral research on smoking cessation and prevention (Bernstein 1969; Bernstein and McAlister 1976; Pechacek and McAlister 1980; Lando and McGovern 1982; Lichtenstein 1982) are not feasible for programs directed toward many thousands of people. Community studies instead emphasize large-scale delivery systems such as the mass communication media. Because community participation is now considered essential for success, such studies also include community organization programs seeking to stimulate interpersonal communication in ways that are feasible on a large-scale basis. Community studies also may involve environmental change, such as programs to modify the purchase price or availability of consumer products or to sanction public behaviors.

Because the emphasis herein is on controlled community research, attention is limited to studies in which valid inferences can be made concerning the effects of intervention on smoking rates in an entire population. The essential elements are use of adequate measures of smoking behavior applied over time in order to estimate long-term trends, and equally important, the inclusion of control or reference areas for the purpose of comparison. There are, of course, many questions and controversies regarding the usefulness and validity of large-scale experimental or quasi-experimental research (Campbell

and Cook 1979). Social policies such as those needed to sharply reduce smoking are not likely to be introduced without experimental trials, however, and the studies reported herein probably represent the best currently attainable compromise between external and internal validity. Given the very small number of studies meeting even the minimal methodological criteria, it would be unwise to restrict this review to the standards required by laboratory or clinical studies.

Theoretical Background

Effective mass communication, community organization, and environmental change require a theoretical basis for planning. Most community studies of health promotion and disease prevention are based on fundamental theories and concepts from the behavioral sciences. The most important of these are briefly outlined below.

Mass Communication

Theories on mass media effect have changed during the recent history of communication research, and several clear stages have been identified (Klapper 1960; Griffiths and Knutson 1960; Atkin 1979; Flay et al. 1980; Wallack 1981). Media were initially considered nearly omnipotent in directly altering behavior, but it was later discovered that they are incapable of producing effects independent of other, more powerful social forces. The most recent view is that mass media may have effects, but that they are small and largely dependent on facilitation from interpersonal influences and favorable environmental circumstances. Notwithstanding these limitations, shifts of a few percentage points in consumer preferences may be very significant in product marketing, while similar reductions in chronic disease-promoting behaviors may have enormous absolute significance in a population of several millions. One mass media effect that is agreed upon by most communication scientists is termed the "agenda-setting function" (McCombs and Shaw 1972), in which the media powerfully influence topics generated in formal and informal social gatherings. Media communication can also inform and teach simple skills (Bandura 1977). But the manner in which people actually behave with regard to a particular topic of discussion, and whether or not information or skills are actually used, depends more upon interpersonal forces than upon the media messages themselves.

Community Organization

The theories and concepts that underlie community organization are less well developed than those applied to media planning. Although there is broad agreement that the effects of the media are

enhanced by interpersonal factors, there is no clear consensus on the exact identity of those factors or how they can be feasibly modified in entire communities. A useful principle is derived from Bandura's (1977) distinction between factors influencing acquisition of new behaviors and those influencing performance of new behaviors. Media communications can model new behaviors so that they are learned (acquired) on a cognitive level (the person knows how to perform the behavior). However, cueing and feedback (direct social reinforcement) are usually needed for behavioral learning, or actual performance of the new behavior. Numerous studies of learning via media communication show that when a complex behavior is being learned, effectiveness is sharply enhanced by providing supplementary interpersonal communication for encouragement, feedback, and reinforcement (Bandura 1977). To create feedback and reinforcement in a community setting, organizations must be involved to provide roles and structure for interpersonal communication. Where formal social networks are not involved, communication and influence will be diffused through families and other informal systems (Meyer et al. 1977). The effectiveness of interpersonal communication can be greatly enhanced, however, by organizing formal or semiformal structures, such as learning groups using leaders trained to lead discussions, answer questions, and provide encouragement and followup. Various campaigns in agricultural development illustrate these principles (Green 1970; Rogers and Shoemaker 1971).

A related factor is the notion of generalized social support (Caplan et al. 1975), which refers not to the differential social reinforcement of specific behaviors, but to the general extent and quality of interpersonal relationships. Social relations appear to be generally helpful, probably because of their "stress-buffering" effects. Social ties within the family probably enhance cessation and prevention of tobacco use. For example, spousal support leads to higher successful quit rates (West et al. 1977; Mermelstein et al. 1983), and lower rates of teenage smoking occur in families in which neither parent smokes (National Institute on Education 1979). The general enhancement of interpersonal support networks is, of course, a primary objective of religious groups and social work and most other helping professions.

Environmental Change

There are also theories and concepts from which environmental changes can be planned (Bandura 1977; Craik 1973), the basic principle of which is to modify the availability and cost of products or behaviors (such as by limiting supply or prohibiting behaviors in public settings). Not all such measures can be applied by communities as defined herein. For example, regulations on mass media advertising can probably be controlled in most cases only at the Federal level, although billboard advertising may be amenable to

more local control. Other promising interventions such as taxation (Lewit et al. 1981; Fugi 1980) can be applied within fairly small localities, but the risk of "black market" competition is lessened when economic controls are fairly uniform across larger geographic units. Product availability and regulation of behavior can be achieved by towns or countries, but restrictive regulations almost invariably arouse opposition unless the public is willing to self-enforce the restrictions. Therefore, it is legitimate to favor voluntary restraints over those that require formal policing. Syme and Alcalay (1982) call for intervention and prevention efforts at the community level using a public education agenda. Such programs will seek to increase public awareness of the health consequences of smoking, create an atmosphere in which smoking is recognized as a minority behavior, influence public policy, and increase antismoking advertisements.

Breslow (1982) has recently reviewed the environmental and public policy approaches to smoking control and calls for a "comprehensive strategy that will mobilize all available resources most effectively" (p. 149). He advocates Federal, State, and local legislation as the most important forms of social action directed toward action alternatives as well as research. He states that "protection and advancement of economic interests will generally follow prevailing ideology. Finding ways of cutting through the economic barriers, as always, will pose a challenge to public health. While compromises will be necessary, the objective of steady movement toward the goal now seems attainable" (p. 149).

Cessation Studies

Controlled community studies on smoking cessation are still relatively scarce. However, community trials for cardiovascular disease prevention, in which cigarette smoking is the major risk factor, are providing some of the best examples of research in this area. These studies have tended to focus on cessation among adults because primary outcomes of the trials include possible short-term (5- to 10-year) effects on cardiovascular mortality and morbidity rates that could hypothetically result from widespread adult cessation. These studies were reviewed in depth in the 1983 Report of the Surgeon General *The Health Consequences of Smoking* (USDHHS 1983).

Stanford Three-Community Study

The most well known U.S. cardiovascular community study was conducted in California by Farquhar, Maccoby, and colleagues at Stanford University (Farquhar et al. 1977; Maccoby and Alexander 1980; Meyer et al. 1980). Beginning in 1972 and ending in 1976, the

study was supported through the National Institutes of Health research grant program and involved three small communities (population of each was approximately 20,000) nonrandomly assigned to control, media-only, or media and face-to-face programs. The three towns are all within 100 miles of Stanford University. The control town, Tracy, is located in an inner valley and not exposed to media sources common to the other two towns, Gilroy and Watsonville. Gilroy, assigned to the media-only condition, is situated in a coastal valley, and Watsonville, receiving a small additional interpersonal communication program, is on the coast. In Watsonville, a cardiovascular high risk group including many smokers ($n = 169$) was identified, and 113 cases were randomly assigned at a 2:1 ratio for face-to-face intervention. The three towns are demographically similar, although the proximity of Watsonville and Gilroy to the larger cities of Santa Cruz and San Jose gives them more cosmopolitan features than Tracy. Nevertheless, the research design was probably the best balance of feasibility and external and internal validity that could have been achieved in that setting given the limited available resources.

In each town, multistage probability samples of households were contacted and invited to a survey station where questionnaires and physiological measures were administered. These surveys were applied in the autumn months, beginning in Watsonville in September and ending in Tracy in November. Approximately 600 persons aged 35 to 59 were sampled at each location. The measurements included questions about smoking, and serum samples from high risk participants were analyzed to estimate thiocyanate concentrations as a check on inaccurate reporting of smoking status (Meyer et al. 1980). These measurements were taken annually for 4 years, yielding a picture of 3-year smoking trends among the survey participants in the three communities.

The program of media communication was conducted over 3 years (1973 to 1975), with greatest intensity in the first and second years of work. Television, newspapers, radio, billboards, and direct mail advertising were designed to provide information and to model attitudes and skills that would promote behavioral changes associated with lowered cardiovascular risk, such as weight reduction, lowered fat consumption, and increased exercise. To encourage cessation of smoking, information about its harmful effects was given, along with advice on how to stop smoking. In booklets mailed to the sampled households in Gilroy and Watsonville, instructions were provided for simple self-control skills (Meyer et al. 1980). In brief television and radio communications, actors were shown recommending or modeling cessation of smoking in a variety of authoritative and entertaining ways.

The face-to-face, intensive instruction program was provided for 113 randomly assigned high risk participants in Watsonville, of whom 107 started treatment, and 77 continued for the second annual examination. Activities were based on principles of behavioral psychology and group dynamics and were designed to reinforce and train skills for behavior change (Meyer et al. 1980). The first-year program consisted of classes and home visits, mostly during the summer of 1973. During the summer of the following year, aggressive followup activities were conducted to reinforce smokers who reported cessation and to encourage and train those who were not yet able to quit. This maintenance program included training in stress management and other intensive, individual counseling for those who consented to continuing contact. In the third year, the activities were gradually reduced to telephone contacts and a small "reunion" in the summer of 1975.

The results of the program among high risk participants in each of the four surveys are displayed in Figure 1. Over the 3 years of study, the prevalence of smoking decreased markedly among the group receiving media and face-to-face communication. The group receiving media intervention showed an initial decline as compared with the control group, but the change did not differ from the modest reduction observed in Tracy over the entire 3-year period. Because the high risk samples included most of the older smokers in the survey samples from each community, the data on cessation in the complete samples corresponded closely to that of the high risk group. The serum thiocyanate tests indicated very slight overreporting of cessation (Farquhar et al. 1977), but self-reported cessation rates were not adjusted for thiocyanate findings (Kasl 1980). There was some attrition in this longitudinal study, but not enough to account for the clear differences in cessation rates between the intensively instructed and the other participants. Adjusting for attrition, 32 percent reported sustained cessation in the intensive intervention group (Meyer et al. 1980). This research supports the hypothesis that face-to-face communication is a necessary part of a successful community program to reduce smoking. Farquhar and his colleagues (Farquhar et al. 1981) conclude that the question of how such communication can be feasibly and cost-effectively provided on a widespread basis remains to be answered by further studies, and this conclusion will be noted in a later section. A number of critical comments can be made in regard to the Stanford three-community study, and these have been thoroughly discussed in numerous publications (Leventhal and Cleary 1980; Meyer et al. 1980). The primary shortcomings concern the quasi-experimental research design and the inability to generalize from the longitudinally followed study group to the entire community.

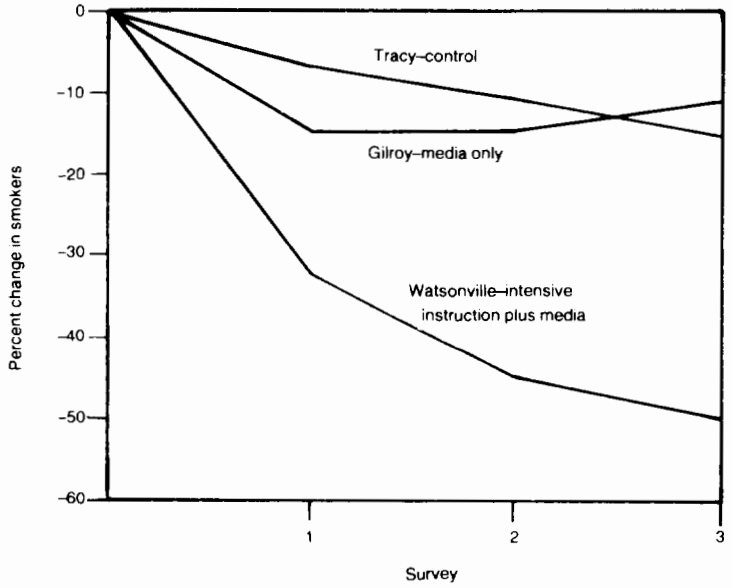

FIGURE 1.—Comparison of cessation rates among smokers in communities subjected to varied intensities of education, the Stanford three-community study

SOURCE: Farquhar et al. (1981).

Australian North Coast Program

A trial very similar to the Stanford three-community study was conducted by the regional Health Department of New South Wales, Australia (Egger et al. 1983), beginning in 1978 and, as in the Stanford study, using small community populations of 12,000 to 27,000 persons. The towns of Tamworth, Coff's Harbor, and Lismore were assigned to one of three conditions: control, media only, or combined media and community programs. The three towns were all between 300 and 400 miles from the research center in Sydney. Coff's Harbor, the media-only town, was approximately half the size of the other two communities. Tamworth was not served by the regional administrative center in Sydney.

In each town, a series of random sample surveys was conducted. Interviews and physiological examinations were requested from up to two adults in randomly sampled households. Those who refused appointments were given self-report questionnaires to be completed at home. Separate samples were drawn in 1978, 1980, and 1981 with the objective of measuring 600, 1,200, and 1,200 different persons in the 3 respective years. Smoking behavior, attitudes, and knowledge

regarding smoking were measured, and in 1980 and 1981, serum thiocyanate values were determined for a randomly selected 5 percent subsample. Measures were also made of other cardiovascular disease risk factors in accordance with the program's primary goal.

The media program included output from a television station, a radio station, and several small newspapers, supplemented by other materials such as stickers, posters, T-shirts, and balloons. The three stages of the media campaign were designed to sequentially raise awareness, provide information, and stimulate action. Advertising time was purchased to insure presentation of television commercials during peak viewing periods. Beginning in October 1979, the print advertisements were suspended for several months because of a complaint to the Media Council of Australia. The overall campaign continued for approximately 1 year. The community program that was applied in Lismore was varied. Several different kinds of groups, clinics, workshops, and other interpersonal support systems were organized; physicians were also involved. A total of 386 smokers participated in these activities, most (150) joining a 1-day workshop. The 3-month success rate in smoking cessation, measured by telephone interview, was 16 percent for the workshop participants. The highest success rate (48 percent) was found for the 40 persons who received help kits from physicians. The community program also included other programs (e.g., for physical fitness and stress management), which may have facilitated the cessation of smoking.

The results of the project were based on the three independent sample surveys. The authors point out that "there was substantial confounding owing to age and sex differences between towns" (p. 1127). Analyzing results according to a multiple logistic model controlling for age and sex differences, a significant treatment effect ($p=0.05$) was observed. Thiocyanate analyses showed no difference between towns in the small estimated invalidity of self-reports (3 percent). Among men and women in various age groups, consistently different rates of change in prevalence of smoking were found. In Lismore, absolute percentage reductions ranged from 6 to 15 percent. In the media-only town (Coff's Harbor) absolute 6 to 11 percent reductions were estimated. In Tamworth (the control) absolute reductions of only 2 to 5 percent were found. The researchers found no evidence of effects on knowledge or attitudes.

Many criticisms can be made from the standpoint of a clinical scientist accustomed to dealing with individual subjects in highly controlled settings. If limitations to inference are clearly acknowledged, however, the Australian study provides a practical illustration of what may be achieved through community intervention. The findings are based on independent samples, and thus represent changes that seem to have occurred on a communitywide basis. The magnitude of the apparent effect was particularly encouraging

among the youngest age groups (18 to 25) where absolute reductions in prevalence of smoking showed a threefold difference between the maximum intervention (15.6 percent) and control towns (5.0 percent). The most significant limitation arises out of the nonrandom assignment of communities and problems with their comparability.

Swiss National Research Program

Another important community study was conducted in Switzerland (Autorengruppe Nationales Forschungsprogramm 1984; Gutzwiller and Schweizer 1983). Four communities of 12,000 to 16,000 inhabitants were selected, two each from the German-speaking and the French-speaking parts of the country. A fifth community in the Italian-speaking region was also studied, but only for epidemiological purposes. French-speaking and German-speaking pairs were randomly assigned to intervention (Nyon) or regular care (Solothurn and Vevey) conditions. This project was conducted over a 4-year period with research support from the Swiss National Science Foundation. A baseline assessment was made in late 1977 and early 1978 by stratified random sampling and examination of 2,000 persons aged 16 to 69 in each community. With attrition of approximately 30 percent, this sample was resurveyed at the end of 1980, at which time another independent sample was drawn and surveyed. A questionnaire was used to determine smoking behavior, and plasma thiocyanate was measured on a subsample of respondents. Other health-related factors such as blood pressure, lipid fractions, exercise tolerance, and psychosocial adjustment were also measured.

The community interventions were conducted over 2.5 years in Nyon, with guiding principles of "active local participation" and "integration into existing local health and social services." The central feature was the establishment of a Citizen Health Action Committee in each of the two towns, with a coordinator assigned to guide local planning and implementation. Media and community organizations were combined to promote a variety of programs in each location, including classes, self-help groups, and meetings to discuss topics such as environmental regulation via public nonsmoking areas.

The results of this study are moderately encouraging. Within the sample population surveyed at baseline and followup, 26 percent of the regular smokers in the intervention communities reported cessation. In the control areas, 13 percent of the corresponding group reported cessation. The investigators also report effects on other cardiovascular disease risk factors, although plasma cholesterol reductions were significant only for women in the German-speaking region. A cost-benefit estimation model has been applied to the data and results indicate a twofold cost-benefit ratio. The use of indepen-

dent surveys and the random assignment of communities represent significant methodological strengths as compared with the Stanford and Australian studies. However, the rural communities in this study were very small, and only four were included. The final report has been presented to formal decisionmakers to determine whether broader national efforts are warranted.

The North Karelia Project

The best documented long-term community study is being conducted in Finland by Puska and colleagues (Puska et al. 1979, 1981, 1983a; Puska and Koskela 1983; McAlister et al. 1982). Also beginning in 1972 and continuing to the present, the research is comparing changes in cardiovascular disease risk factors in two neighboring counties of eastern Finland, Kuopio and North Karelia. Both are large rural areas with numerous small farming, lumber, or mining communities and a single major town. North Karelia is representative of eastern Finland as a whole in having one of the world's highest rates of cardiovascular disease (Pyörälä 1974; World Health Organization 1975). Financial support for the intervention came from the Finnish Ministry of Health, following a formal request from leaders in North Karelia for help in reducing the high mortality and morbidity levels. Research funds were awarded by the Academy of Finland. The neighboring county of Kuopio was selected as a reference or control location. In North Karelia, a broad program was implemented to provide new services, education, and training through community health centers, the mass media, and a variety of community organizations. During the second 5 years of the project, media programs were carried out on a national level, with special organizing and support for activities in North Karelia.

In both counties, independent samples of households were drawn in 1972, 1977, and 1982, with approximately 5,000 persons aged 25 to 59 in 1972 sampled in each area in the first two surveys and about 4,000 aged 25 to 64 sampled in the 1982 measurement. Response rates were generally excellent, and nearly 90 percent of the sample participated by attending local survey centers in the spring of each of the survey years (1972, 1977, 1982). Self-reported cigarette-smoking behavior was measured in all three surveys. In the 1977 survey, serum thiocyanate values were estimated for a subsample, and in the 1982 survey, for all participants. For the 1977 sample, there was 99 percent agreement in smoking status (smoker/nonsmoker), and when classified by intervals of 5 or 10 cigarettes, the agreement between results was 93 and 97 percent, respectively (Puska et al. 1979). The age-adjusted partial correlation between daily reported number of cigarettes and serum thiocyanate in 1982 was approximately 0.7 among men and women in both areas. In the years when the larger surveys were not conducted, smaller samples (1,200 to

3,500) were selected yearly for a postal survey of North Karelia. Together, these measurements provide a comparative view of trends over 10 years in the populations of both counties and a year-to-year picture of the changes in North Karelia.

The program of service, education, and training was very broad in scope. Initially, an intensive educational campaign was conducted for reduction of cigarette smoking with cooperation from the news media. Physicians and public health nurses staffing community health centers were provided special training and were encouraged to recommend cessation to all patients visiting the centers. Tens of thousands of leaflets and posters were distributed to encourage nonsmoking. With assistance from Heart Association volunteers in each small community, informal restrictions on smoking and point-of-purchase advertising were adopted. During 1976 and 1977, these measures became part of a package of national legislation that increased cigarette tax revenue, directed health services to provide information services, limited public smoking, and banned tobacco advertising.

During the second 5-year period, an effort was made to provide nationwide applications, while maintaining intensive community work in North Karelia. A series of programs was broadcast nationally on television to demonstration how "average" people stop smoking (Puska et al. 1981). In association with these broadcasts, special organizing campaigns were conducted in North Karelia to increase social support for people attempting to quit. These activities occurred in the winters of 1978, 1979, 1980, and 1982 and were seen nationally by a majority of the population, with higher viewership in North Karelia. During the first broadcast series, an effort was made to encourage the formation of informal volunteer-led self-help groups to view the broadcasts together. Very few volunteers succeeded in establishing groups, however, and focus in subsequent years has been on training volunteers to provide even less formal cueing, reinforcement, and support in their incidental, day-to-day contacts with cigarette smokers (Puska et al. 1981).

The results to date (Puska and Koskela 1983) are presented in Table 1. Over the 10-year period, self-reported numbers of cigarettes smoked per day fell by more than one-third among men in North Karelia. In the control or reference area, a less than 10 percent reduction was observed. Changes in prevalence of smoking account for most of this difference. No evidence of an effect occurred among women, with rates of smoking going up in both areas. In Figure 2, the year-to-year data for 25- to 29-year-old men and women in North Karelia show an interesting pattern, with the sharpest declines among men associated with the first year of work and with the television broadcasts and associated activities in 1978 to 1980 and in 1982. Since 1978, when new antismoking laws were passed, the

proportion of male smokers aged 15 to 64 has changed from 44 to 31 percent in North Karelia, and from 39 to 35 percent in the rest of the country, a difference of 9 percent in absolute rates of change over that 4-year period. Although the effect of changes in smoking cannot be separated from the effects of new hypertension services and other measures to prevent cardiovascular disease, there is some early indication that mortality rates may have been influenced by the program: a 24 percent decline in cardiovascular deaths has been observed in North Karelia, compared with a 12 percent decline nationally in Finland (Puska et al. 1983a, b).

The North Karelia Project has received much attention, and various points of controversy have been widely discussed. The methodology of the study does not compare with that achieved in controlled clinical trials, but it may have been the optimal design that was feasible in the circumstances. Puska and his colleagues point out that "it is easy to say that the North Karelia Project was successful because of the unique historical background and because the conditions in North Karelia were favorable for the program. However, at the planning stage, great concern was expressed because the area was rural, of low socioeconomic status with high unemployment, and so forth." Because a large number of independent units were not randomly assigned to experimental and control conditions, the Finnish study cannot be taken as a conclusive test of the effects of community programs, but it does provide a promising illustration and evaluation of what can be achieved through broad and vigorous intervention to reduce smoking behavior. Its major strengths are the relatively large number of different communities that were studied and the 10-year followup interval.

Other Large-Scale Studies

There have been a number of other large-scale controlled studies, single and multifactor clinical trials, and worksite trials that provide a context for the consideration of the community-level intervention studies described above. These studies were discussed in the 1983 Report of the Surgeon General *The Health Consequences of Smoking* and include the London Civil Servants Smoking Trial (Rose and Hamilton 1978; Rose et al. 1980, 1982), the Göteborg (Sweden) study (Werko 1979; Wilhelmsen 1981; Wilhelmsen et al. 1972), the Oslo (Norway) study (Hjermann et al. 1981; Holme et al. 1981), the World Health Organization European Collaborative Trials (WHO European Collaborative Group 1974; Kornitzer et al. 1980a, b) and the Multiple Risk Factor Intervention Trial (MRFIT) (Hughes et al. 1981; MRFIRG 1982). In the sole American study (MRFIT), 12,866 men, 35 to 57 years old and at high risk for coronary heart disease (CHD), were entered into a randomized clinical trial designed to test the effect of a multifactor intervention program on CHD morbidity and

TABLE 1.—Mean amount of reported daily smoking (±SD) in North Karelia and the reference area, in independent baseline (1972) and 5-year (1977) and 10-year (1982) followup survey samples, by sex and age

Sex and age (years)	North Karelia			Reference area			Net difference, percentage[1]	
	1972	1977	1982	1972	1977	1982	1972–1977	1972–1982
Men								
30–39	10.6 ± 11.7	9.0 ± 12.5	7.2 ± 10.7	8.5 ± 11.0	9.0 ± 11.9	8.6 ± 11.5	16	33
40–49	10.2 ± 11.2	8.5 ± 11.6	7.0 ± 10.3	9.0 ± 10.7	8.6 ± 11.4	8.0 ± 11.7	10	21
50–59	9.0 ± 10.7	7.9 ± 11.5	5.7 ± 9.7	7.7 ± 9.9	7.7 ± 10.5	6.5 ± 9.6	16	23
Total	10.0 ± 11.3	8.5 ± 11.9	6.6 ± 10.2	8.5 ± 10.6	8.5 ± 11.4	7.8 ± 11.1	13	28
Women								
30–39	1.4 ± 4.2	1.6 ± 5.1	2.6 ± 5.8	1.5 ± 4.5	2.0 ± 4.8	2.8 ± 6.2	15	2
40–49	1.2 ± 4.0	1.1 ± 4.0	1.5 ± 4.4	1.0 ± 3.2	1.2 ± 5.0	1.7 ± 4.9	23	36
50–59	0.7 ± 3.2	0.7 ± 3.4	0.9 ± 3.6	1.0 ± 3.6	0.8 ± 3.2	1.2 ± 4.0	43	41
Total	1.1 ± 3.8	1.1 ± 4.2	1.7 ± 4.7	1.2 ± 3.8	1.3 ± 4.4	1.9 ± 5.1	8	14

Four-way ANOVA[2]	1972–1977	1972–1982
Area	$p<0.05$	n.s.
Time	n.s.	$p<0.001$
Area–time	$p<0.01$	$p<0.001$
Area–time–sex	$p<0.05$	$p<0.001$

ANOVA for linear trend 1972, 1977, 1982	North Karelia	Reference area
Men	$p<0.001$	n.s.
Women	$p<0.001$	$p<0.001$

[1] (North Karelia, 1982/1977–1972) – (Reference area, 1982/1977–1972).

[2] ANOVA = Analysis of variance.

SOURCE: Puska and Koskela (*1983*).

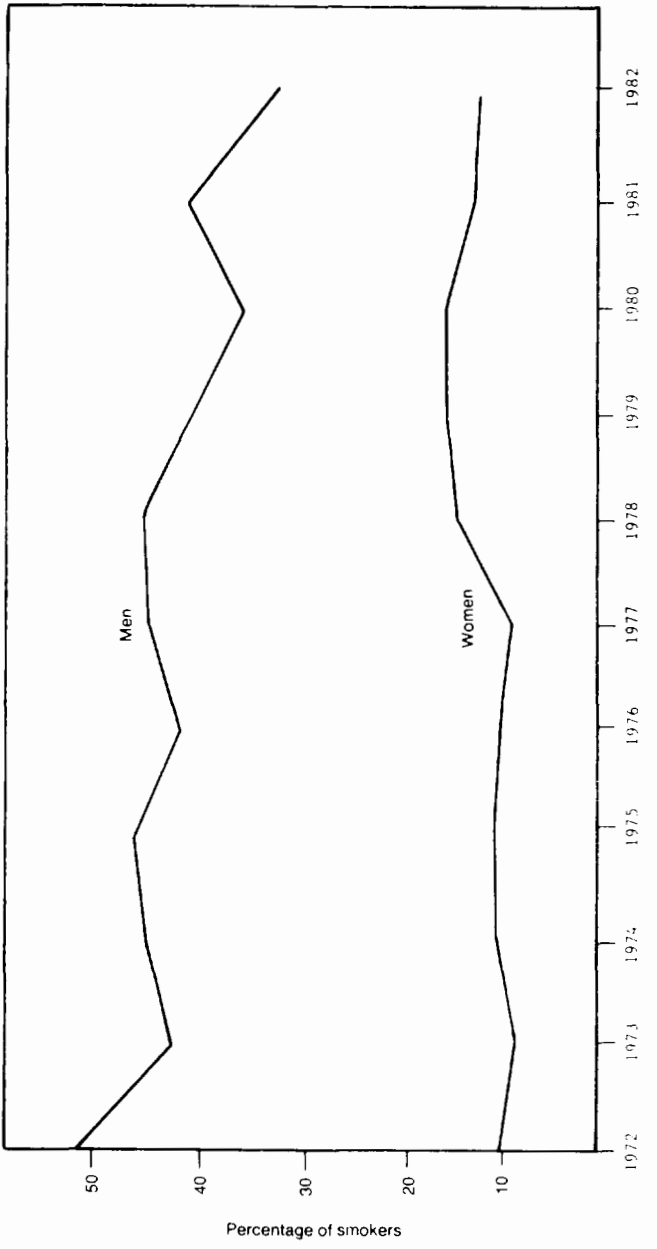

FIGURE 2.—Prevalence of smoking among men and women, aged 25–29, North Karelia, 1972–1982

SOURCE: Puska and Koskela (1983).

mortality. They were followed for an average of 7 years. At intake,

TABLE 2.—Results of community studies compared with other large-scale studies

Study	Years of study	Net percent reduction in smoking[1]	Strengths	Weaknesses
Stanford Three-Community study	3	15–20	Matched communities	Panel study only
Australian North Coast study	3	15	Independent samples	Problems with comparability of groups
Swiss National Research program	3	8	Randomization, independent samples	Small size and number of study sites
North Karelia project	10	25[2]	Numerous communities, independent samples	Nonrandom assignment
Other large-scale studies[3]	2–10	5–25	Internal validity	External validity

[1] Difference between percent reduction in proportion of smokers in the maximum intervention versus control conditions.

[2] Difference between percent reduction in the mean number of cigarettes smoked per day among men.

[3] Clinical and work-site trials: the London Civil Servants Smoking Trial, the Göteborg study, the Oslo study, the WHO Collaborative Trial, and the Multiple Risk Factor Intervention Trial.

the self-reported prevalence of smoking was 64 percent. The 6,428 men randomized into the Special Intervention (SI) group received intensive group sessions, personal instruction, and other followup to encourage and support cessation of smoking, as well as intensive assistance to alter other CHD risk factors. There were 6,438 men in the group randomly assigned to Usual Care (UC). At 6-year followup, self-reported cessation rates were 43 percent in the SI group and 25 percent in the UC group. Thiocyanate analyses showed a necessity for small adjustments in these figures to 42 percent and 24 percent, respectively, a statistically significant difference ($p < 0.01$). Comparison of the results from the four community studies with those from the large-scale studies, as shown in Table 2, indicates distinct similarities. The individual studies each have somewhat different weaknesses, but all indicate that absolute reductions in smoking prevalence in intervention communities are about 12 percent greater than reductions in comparison communities.

Several ambitious community studies of cardiovascular disease prevention are currently in progress with support from the National Heart, Lung, and Blood Institute, but no additional data on community-level intervention are available. At Stanford University, a large study of two intervention and three control towns with several hundred thousand residents has been in progress since 1978 and is projected to continue for at least 10 years (Farquhar 1978). A

similar study, with three matched pairs of variously-sized towns and cities, has been in progress in Minnesota since 1979 (Blackburn et al., in press; Blackburn, in press; Blackburn and Pechacek, in press). A smaller study of one Rhode Island town and one town in a neighboring State began in 1980 (Lasater 1983). Because it has become clear that community studies are the most natural and cost-effective method for testing new public health services to reduce chronic disease (Farquhar 1978; Puska et al. 1983a, b), more of these efforts may be useful, particularly if costs can be reduced and, where possible, absorbed into existing services.

Related Studies of Cessation

A number of recent efforts have increased understanding of and confidence in the methods employed in large-scale community studies. Research on methods of stimulating interpersonal support for mass media programming is particularly relevant (Colletti and Brownell 1982). In quasi-experimental studies, McAlister et al. (1980) and Puska et al. (1981) have reported methods for facilitating the effectiveness of televised smoking cessation classes in Finland. Formal self-help groups appear difficult to organize, but reorganization of less formal social reinforcement in natural interaction settings appears feasible and effective. Related studies of television and other media-based methods are described by Danaher et al. (1983), Best (1980), Leathar (1981), and others. Dubren (1977a, b), Brengelmann (1976), and the American Cancer Society (1981) found that effects of media programs may be enhanced if a telephone hotline is offered. Flay et al. (1983b) used a school-based, family-oriented prevention program that included a five-segment television component to be aired the following week to encourage participation of cigarette-smoking parents. Overall, parents of students in experimental groups were over three times more likely to view the cessation segment than parents of control students, with similar differences observed for the proportions of successful parental attempts to quit. Within the experimental groups, teacher training had a significant effect ($p<.01$) on raising participation rates by parents of program students. Considering only homes with smokers, 51 percent of the students with trained teachers reported that at least one cigarette smoking adult viewed one or more cessation segments, compared with 37 percent of students with untrained teachers. Furthermore, 38 percent of parents with trained teachers attempted to quit smoking, compared with 24 percent of parents of students with untrained teachers ($p<.001$). At 1-year followup, the cessation rates in the two groups were 19 and 13 percent, respectively, according to children's reports of parental behavior. The validity of the indicators of adult smoking behavior is at issue; student reports could contain bias, which will be estimated in further

analyses. Nevertheless, these results suggest that children can enhance the effectiveness of a media program in encouraging parents to stop smoking, and that organized social reinforcement is important in mass media smoking cessation programming (Flay et al. 1983b). More research is needed on these and other methods of large-scale social reinforcement and support for cessation of smoking.

Some attention has been given to environmental changes that might contribute to the cessation of cigarette smoking. Evidence indicates that smoking can be regulated by counteradvertising, restrictions on advertising, warning labels, and symbolic or governmental actions such as the Surgeon General's Report of 1964 (Warner 1977). Complete prohibition of smoking is not an acceptable alternative, but restrictions on smoking locations may be helpful for people attempting to quit voluntarily (Horwitz et al. 1982). Taxation of cigarettes has provided an effective deterrent in some population groups, particularly among younger men (Lewit et al. 1981). In Finland, cigarette taxes have been increased and a portion (0.5 percent) of the funds are dedicated to support services to reduce the prevalence of smoking (Puska and Koskela 1983). Similarly, integrated environmental and educational interventions may be useful in further large-scale efforts.

Prevention Studies

Although evidence increasingly indicates that it is more cost effective to prevent the onset of smoking among young people than to change the dependent behavior of adults, smoking prevention has received far less attention than cessation in controlled community research. This can be attributed to the complex processes involved in the onset of smoking (e.g., Evans 1976; Leventhal and Cleary 1980), to the extended timespan required for proper evaluation of prevention studies, and to the overall tendency of the health sciences to focus more on individual-level research than on primary prevention studies in which whole populations must be followed. Research on the prevention of smoking onset was considered in detail in the 1982 Report of the Surgeon General *The Health Consequences of Smoking: Cancer* (USDHHS 1982), and only selective studies are reviewed herein. Although there are no currently available published reports on controlled community studies of smoking onset prevention in whole populations, a number of school-based studies have been conducted recently that involve large proportions of particular age-grade cohorts in discrete communities.

Stanford Study

In one such study McAlister et al. (1979, 1980b) assigned the 1978 seventh grade cohorts in two similar suburban California towns to control (receiving Usual Care health education) or to a special peer prevention program to deter the onset of smoking. The special intervention program consisted of 7 classroom hours distributed over the school year in which 15- to 17-year-old peer leaders led Socratic dialogues, role plays, and simple contests to reinforce smoking avoidance behavior among 12-year-old students and to promote the social desirability of nonsmoking. Role plays and simple contests were used to help students learn assertive ways of declining offers to smoke, emphasizing counterarguments to the kinds of perceived peer social pressures that may be associated with the onset of smoking (McAlister et al. 1979). Several followup sessions were conducted when the study cohort reached the eighth grade.

At baseline and three followup points, students in the control and the environmental groups provided anonymous self-reports of smoking through classroom surveys. Participation rates were close to 100 percent in all surveys, and the measures were supplemented by collecting samples of exhaled breath at followup. These repeated surveys provided good measures of smoking prevalence in the age-grades studied in the two similar suburban communities, and although attrition and replacement may have threatened inference, the findings in Figure 3 indicate that the special intervention may have had a preventive effect. Note that the dependent variable is the percentage of participants who reported smoking during the previous week. Definitions of smoking in adolescents often differ, making results difficult to compare. Over 2 years of initial followup, the rate of self-reported smoking onset diverged sharply in the two age-grade cohorts, and differences persisted over an additional year of followup (Telch et al. 1982).

The North Karelia Youth Project

Stemming from the North Karelian project described in an early section, a youth program was initiated in six rural communities in eastern Finland (Vartiainen et al. 1983). Two urban and two rural communities were assigned to intensive (direct contact with the experimenter) or countywide (teacher-led) intervention programs in North Karelia. Two matched communities were selected as controls in the neighboring province of Kuopio, and subjects were seventh grade students (average age of 13 years) in the autumn of 1978. From a population of 897 available students, nearly all participated in the baseline survey; 95 percent participated in a 2-year followup; and 88 percent participated in a second followup 30 months after the program began. The survey included measurements of self-reported smoking and related variables as well as serum thiocyanate levels.

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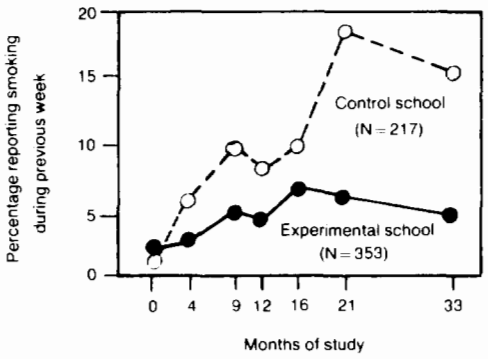

FIGURE 3.—Long-term effects of a peer group training course on smoking behavior of 13-year-old students

SOURCE: Telch et al. (1981).

The special intervention spanned the seventh and eighth grade years and included 10 hours of instruction in the intensive program and 5 hours in the countywide program. The methods were based on those employed by McAlister et al. (1980), as reported in the preceding study. Peer leaders, students 1 to 2 years older than the subjects, were the primary agents used to deliver the antismoking message. The program used role play and other active learning techniques to teach skills for resisting the social and psychological pressures to smoke and to reinforce negative attitudes toward smoking.

The results indicated a preventive effect from the special intervention, as shown in Figure 4. Among boys, the followup rates of smoking at least once a month were significantly lower in the four intervention schools (21 to 24 percent) than in the reference area communities (39 percent). Results for girls were less conclusive, but the overall difference between groups at followup was significant: a 17 percent rate of smoking at followup in intervention schools and a 24 percent rate in control schools. Analysis of the serum thiocyanate samples showed that 2 to 3 percent of the professed nonsmokers gave inaccurate self-reports, but the slight underreporting was greater in the control schools—indicating that inferences from the reported findings were not significantly threatened by self-report biases.

Other Prevention Studies

In a more rigorous study, Flay et al. (1983a) assigned 22 schools in Canada, some randomly, to receive special interventions or to serve as controls. The smoking prevention curriculum consisted of three major components, using the social psychological model delivered in

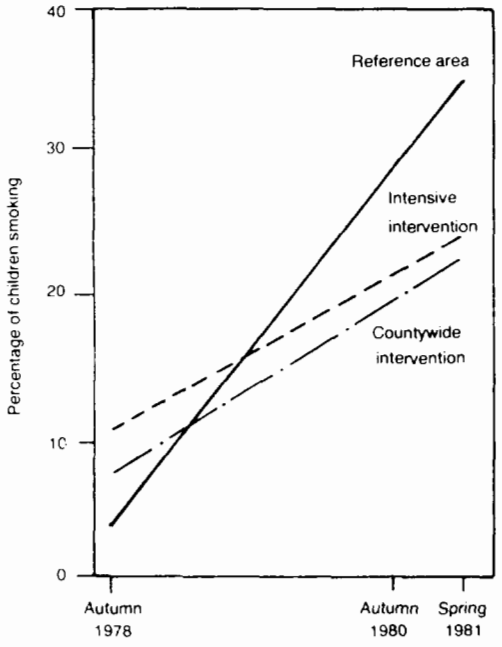

FIGURE 4.—Percentage of children who reported smoking at least once a month in baseline survey (1978) and two followup surveys (1980 and 1981)

SOURCE: Vartiainen et al. (1983).

six 1-hour weekly sessions during grade six. The social psychological model aims at developing future attitude and behavior changes and acquiring social skills, and involves eliciting information from children rather than providing it for them. The three components focused on smoking consequences and reasons for smoking, social influences promoting smoking, and decisionmaking and public commitment. Two booster sessions were delivered in both grades seven and eight. Short-term findings show a preventive effect, manifested in grade seven by an increased level of experimental smoking in the control group compared with the experimental group. In another study, Worden et al. (1983) tracked changes in smoking rates in two towns receiving a mass media campaign and a high-intensity program of adult communication skills related to adolescent smoking prevention. Over 1 year of followup, onset rates were markedly greater among a set of comparison towns receiving only the media campaign and some low-intensity community intervention.

McAlister (1983) randomly assigned members of five matched pairs of community and neighborhood schools to serve as controls or to receive an experimental prevention program. The study included students in the first year of secondary school (sixth or seventh grade) in 1979 in coastal and inland California towns and inner-city and suburban locations near Boston, Massachusetts. Over 2 school years of initial followup, sharply lower smoking onset rates were observed in some of the schools receiving the experimental programs. The findings are difficult to interpret and suggest that variability among highly diverse community age-grade cohorts, inconsistent implementation, and other related factors threaten inferences that may be drawn from studies of relatively small numbers of unique age-grade cohorts. Preventive effects on smoking onset have been reported by other investigators in Houston (Evans 1976), Minnesota (Hurd et al. 1980), New York (Botvin et al. 1980), and elsewhere; they were reviewed extensively in the 1982 Report of the Surgeon General *The Health Consequences of Smoking* (USDHHS 1982). These studies have tended to show positive results for the nontraditional health education methods, particularly those using peer teaching and role plays of saying no or resisting social pressures toward smoking. Currently, large-scale research on the prevention of smoking is in progress in the community studies of cardiovascular disease prevention that were cited in a previous section, as well as in other research centers in the United States and abroad. Internationally, Sweden has declared the creation of a "Smoke-Free Generation," and other countries have taken various steps to deter the onset of smoking (Wake et al. 1982).

Although studies were not sufficient to confirm the hypothesis, it is probable that young people not strongly dependent on tobacco are most sensitive to the various "environmental" policy options for smoking reduction. For example, the price elasticity of decisions to smoke regularly (smoking status) is –1.4 for males aged 20 to 25, but lower for older men (Lewit et al. 1981). **This indicates that a 9 percent increase in the price of cigarettes might yield a 15 percent decrease in the proportion of male smokers in the younger age group.** Environmental changes related to the marketing, price, or availability of cigarettes tend to be implemented in whole States or nations and are not amenable to controlled demonstration research. However, as local authorities play an increasing role in various matters, opportunities for innovative community level research may be available.

Methodological Issues

In view of the high costs of clinical trials, such as those incurred by the Multiple Risk Factor Intervention Trial, a strong argument can

be made for the cost effectiveness and generalizability of community studies of chronic disease prevention (e.g., Farquhar 1978). However, there are methodological problems with the community studies that deserve careful consideration. In order to ensure strict adherence to assumptions of the statistical theories supporting experimental inference, independent units of observation must be sampled. Because the behavior and disease rates of people within a community are obviously not independent, the data from geographic units must be aggregated at various levels, such as family, neighborhood, community, and region. Thus, for example, smoking rates in three communities assigned to three different experimental conditions must be treated as three discrete observations, but having only one observation per condition does not permit use of traditional statistical procedures for hypothesis testing. By assigning more than one community to each condition, between-community variance can be estimated to provide more valid tests of program effect. As the statistical theory guiding community studies becomes more developed (Flay and Cook 1981), future research may be expected to involve more sites, with fewer cases sampled in each site.

Another problem concerns the comparability of groups. Unless a large number of communities are randomly assigned to conditions, the strict methodologist can identify obvious threats to experimental validity. For example, it might be natural to expect a bias toward the application of experimental programs in settings favorable to the adoption of innovation, while using "less interested" communities for the control group. This inevitably raises questions about the comparability of communities with regard to socioeconomic status, cosmopolitan features, or other hard-to-measure social characteristics. If the experimental group has a favorable predisposition at baseline, inferences about changes in health-related variables are severely threatened. When a high degree of demographic similarity between communities can be demonstrated, confidence in inferential statistics is enhanced. If possible, the communities to be compared should be assigned randomly to experimental groups or to control groups.

Problems with comparability are also introduced by the possibilities of experimental contamination or confounding effects of competing experimental programs. This issue must be thoroughly analyzed with respect to the North Karelia Project, where it appears that program results for dietary change and control of hypertension have been diluted by program spillover and the establishment of new health services in the reference (control) area.

Related to the issue of comparability of groups within a study is the problem of generalization to broader populations. For example, some groups that fall into the lower socioeconomic strata have not followed the general population trend toward smoking cessation and

may also be at increased risk for smoking-related disease from concurrent industrial exposures. Results of trials involving such populations (WHO European Collaborative Trials) should be examined for overall outcome as well as evaluation of programmatic elements wherever possible. Differential effectiveness of intervention techniques with varying populations remains to be established.

Another methodological question is raised by studies that rely primarily on self-reports that may be biased by intervention programs (Evans et al. 1977; Benfari et al. 1977; Pechacek et al., in press). Physiological indicators of cigarette smoking are expensive in studies involving large numbers of individual measurements. Most researchers take physiological measurements from a subsample of the group providing self-reports. If there is no evidence of self-report bias between groups, experimental comparisons can be based on the self-report data. However, the usefulness of this procedure depends upon the statistical power of the test comparing relationships between self-reports and physiological measures in the different experimental groups. Tests based on very small subsamples will almost certainly show no statistically significant evidence of self-report bias, but only because they lack the statistical power to detect the relatively small differences that might confound inference. Numerous other methodological points are pertinent to the review of community studies. For example, cohort studies that track individuals over time may be much less generalizable than those that involve repeated independent surveys, but are critical for studying development of certain behaviors, such as smoking onset. A great need exists, therefore, for more focused awareness on the various methodological concerns that limit the interpretation of community studies.

Directions for Future Studies

There is a clear need for further research on community-level intervention to reduce smoking. The challenge is to develop relatively inexpensive methods that can be easily implemented on a large-scale basis. This will involve refinements in three broad activity categories: (1) education and instruction related to smoking, smoking cessation, and smoking prevention; (2) social reinforcement in support for nonsmoking behavior; and (3) environmental changes related to cigarettes and cigarette smoking.

Education and instruction methods are needed to convey information, attitudes, and skills more effectively as they relate to the cessation and prevention of smoking. For example, as the factors contributing to the process of smoking cessation and prevention are identified (DiClemente and Prochaska 1982; McAlister 1983; Leventhal et al. 1980), they can be modeled via television or other forms of mass communication. Although the schools have an obvious role in

smoking prevention, the kinds of educational activities that appear to produce results are not easily adopted by traditional educators. Innovative education and training programs can be marketed to those willing to pay for therapeutic or consultative services related to smoking cessation and prevention, but less costly methods need to be developed for communitywide application. The establishment of smoking cessation programs within existing health services and the integration of chronic disease prevention with mental health promotion are also needed to effect broad-scale societal education and change.

Growing evidence indicates that the social reinforcement and support provided in formal therapies can be effectively evoked at far less expense by self-help groups and natural helping networks. In the North Karelia Project, community volunteers were taught to reinforce learning of smoking cessation skills from television (Puska et al. 1981). Children may also be powerful, natural sources of social reinforcement (Flay et al. 1983b). Related methods are being applied in other ongoing community studies to harness the influence of natural social networks for antismoking campaigns (Pechacek et al., in press). In addition to reinforcing specific behaviors and attitudes related to smoking prevention and cessation, social environments can give more general support and assistance to people trying to cope with stress, strain, and conflict. Given the relationship between chronic smoking, stress, and alienation, it is reasonable to expect a positive effect from interventions that reduce stress, improve coping, and increase social support (Colletti and Brownell 1982).

Other community efforts are being made in noncontrolled contexts, as in the following examples. First, the American Cancer Society has introduced an "Adopt A Smoker" program to involve ex-smokers in the annual Great American Smokeout Day. Second, community physicians are being urged to increase the frequency and intensity of cessation advice given to smokers. Finally, the television and newspaper media have become involved in the antismoking campaign, frequently including programming and articles that feature behavioral scientists discussing smoking behavior and the techniques of quitting.

Options for environmental change and public policy are varied and complex (Farquhar et al. 1981). The outright prohibition of smoking is not feasible, but limited prohibitions on smoking in public and some private places can have desirable effects in shifting negative attitudes. Restrictions on marketing are difficult on a local level, but constraints on advertising or availability may have a powerful effect. As indicated in a previous section, new taxes or other broad environmental changes are more likely to affect young smokers among whom dependence is not firmly established. Thus, they may be expected to have cumulative, long-term effects on future smoking

rates. There is a role for research in clarifying optimal forms of restriction, but is has not been implemented, even in worksites where the effects of restrictions could be evaluated (Orleans and Shipley 1982).

Future studies must also develop an integrated model for combining cessation and prevention activities. Although the processes involved in the adoption of smoking are clearly different from those involved in its discontinuance, there are commonalities to be explored to find more efficient strategies for smoking reduction. The research of Flay et al. (1983a) is particularly promising in this regard. Any program that changes perceptions of social norms or other environmental factors may influence nonadoption or discontinuance of cigarette smoking, but effects will probably be greatest on young people not dependent on tobacco or on older age groups where the adverse health effects of smoking are already becoming apparent.

Summary and Conclusions

1. Community studies of smoking cessation and prevention are becoming an established paradigm for public health action research. Such studies emphasize large-scale delivery systems, such as the mass media, and include community organization programs seeking to stimulate interpersonal communication in ways that are feasible on a large-scale basis.
2. Although there are methodological limitations to nearly all communitywide studies, the results yield fairly consistent positive results, indicating that large-scale programs to reduce smoking can be effective in whole populations. Person-to-person communication appears to be a necessary part of a successful community program to reduce smoking.
3. Further research is needed, with both improved methodology and more emphasis on low socioeconomic status groups that have not yet shown population trends toward reduced smoking.
4. Several promising directions for research are clear, but the most important future trends will be toward the establishment of smoking reduction programs within existing health services, the combination of chronic disease prevention with mental health promotion via mass media and community intervention, and the development of social policy to establish integrated strategies for smoking cessation and prevention.

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